Drug Class Review

Newer Diabetes Medications, TZDs, and Combinations

Final Original Evidence Tables

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The Agency for Healthcare Research and
Quality has not yet seen or approved this report

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Abbreviations used in evidence tables

Abbreviation	Meaning
ACE	Angiotensin-converting enzyme
ACT	Active-control trial
AE	Adverse event
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
ARB	Angiotensin receptor blockers
AST	Aspartate aminotransferase
BiAsp	Biphasic insulin aspart
bid	Twice daily
BMI	Body mass index
CCT	Controlled clinical trial
CHF	Congestive heart failure
CI	Confidence interval
CND	Cannot determine
CNS	Central nervous system
CPK	Creatine phosphokinase
CR	Controlled release
CrCl	Creatinine clearance
CV	Cardiovascular
CVD	Cardiovascular disease
CVS	Cardiovascular system
d	Day
DB	Double-blind
dL	Deciliter
DM	Diabetes mellitus
DPP-IV	Dipeptidyl peptidase IV
ECG	Electrocardiogram
EEG	Electroencephalogram
EF	Ejection fraction
ER	Extended release
FDA	US Food and Drug Administration
FU	Follow-up
g	Gram

Abbreviation	Meaning
GI	Gastrointestinal
GLP-1	Glucogon like peptide-1
GP	General practitioner
h	Hour
HbA1c	Glycosylated hemoglobin
HbA1c	Glycosylated hemoglobin
HDL	High-density lipoprotein
HDL-C	High density lipoprotein cholesterol
Hg	Mercury
HMO	Health maintenance organization
HR	Hazard ratio
HRQOL	Health-related quality of life
ICD-10	International Classification of Diseases, Tenth Revision
ICD-9	International Classification of Diseases, Ninth Revision
IR	Immediate release
ITT	Intention-to-treat
L	Liter
LA	Long acting
LDL	Low-density lipoprotein
LDL-C	Low-density lipoprotein cholesterol
LOCF	Last Observation Carried Forward
LS means	Least squares means
MANCOVA	Multivariate analysis of covariance
mcg	Microgram
mg	Milligram
MI	Myocardial Infarction
min	Minute
mL	Milliliter
mo	Month
N	Sample size (entire sample)
n	Subgroup sample size
NA	Not applicable
NR	Not reported
NS	Not significant
NSD	No significant difference

Abbreviation	Meaning
OAD	Oral antidiabetic
OR	Odds ratio
P	*P* value
P	Placebo
PCT	Placebo-controlled trial
PPY	Per person year
qd	Once daily
QOL	Quality of life
RCT	Randomized controlled trial
RR	Relative risk
SB	Single-blind
SCr	Serum creatinine
SD	Standard deviation
SE	Standard error
SR	Sustained release
T1D	Type 1 diabetes
T1DM	Type 1 diabetes mellitus
T2D	Type 2 diabetes
T2DM	Type 2 diabetes mellitus
TC	Total cholesterol
TG	Triglycerides
tid	Three times daily
TZD	Thiazolidinedione
VAS	Visual analog scale
vs.	Compared with (versus)
WD	Withdrawal
XR	Extended release
y	Year

Evidence Table 1. Key Question 1: Studies of pramlintide

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Inclusion and Exclusion Criteria	Overall Sample Size Interventions Group Sizes	Baseline Population Characteristics Mean Age, years Race/Ethnicity % Female
Active-control studies			
Riddle, 2009 24 weeks US Amylin Pharmaceuticals Fair	Inclusion: 18 - 75 years of age, type 2 diabetes, HbA1c > 7% and < 10%, with or without use of any combination of metformin, thiazolidinedione, or sulfonylurea OADs, pramlintide naïve and either insulin naïve or had used <50 units.day of basal insulin for < 6 months, BMI > 25 and < 50 kg/m2, female patients were not pregnant nor lactating and were postmenopausal or using birth control. Exclusion: Poor adherence to diabetes management recommendations, recurrent svere hypoglycemia within the last 6 months, or had a history of hypoglycemia unawareness, gastroparesis, use of exenatide, sitagliptin, antiobesity medications, systemic glucocorticoids, or investigational medications	N=113 (112 analyzed) G1: (pramlintide 120 ug before major meals - two participants reduced dose to 60ug) n=56 G2: (rapid-acting insulin analog 5 units before each meal, titrated every 3-7 days to maintain >70 and <100 before next meal/bedtime) n=56	G1: 55 (11); Race NR; Female 39.3% G2: 54 (10); Race NR; Female 34%

Evidence Table 1. Key Question 1: Studies of pramlintide

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Background Medications	Intermediate Outcomes HbA1c Weight (kg)	Health and Utilization Outcomes Microvascular Disease Macrovascular Disease Lower Extremity Ulcers All-Cause Mortality Quality of Life Hospitalization Medical Visits (diabetes) Other
Active-control studies			
Riddle, 2009 24 weeks US Amylin Pharmaceuticals Fair	Insulin glargine or detemir, some participants were also taking oral antihyperglycemic drugs	Mean (SE) change from baseline, HbA1c: G1: -1.1 (0.2) G2: -1.3 (0.2) P=0.46 Mean (SE) change from baseline, weight: G1: 0.0 (0.7) G2: +4.7 (0.7) P<0.0001	NR

Evidence Table 2. Key Question 1: Studies of sitagliptin and saxagliptin

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Inclusion and Exclusion Criteria	Overall Sample Size Interventions Group Sizes	Baseline Population Characteristics Mean Age, years Race/Ethnicity % Female	Background Medications
Active-control studies				
Williams-Herman, 2009 54 weeks Multinational Merck Fair Williams-Herman, 2010 104 weeks	Inclusion: T2DM (18–78 years of age) who were on or not on an oral diabetes mellitus medication at the screening Exclusion: T1DM; unstable cardiac disease; significant renal impairment (glomerular filtration rate<60ml/min) AST, ALT ≥ 2x upper limit of normal	N=885 in 30 week continuation phase (1091 initially randomized) (#s for continuation phase) G1: (placebo/ metformin 1000 bid) n=23 G2: (sitagliptin 100mg QD): n=141 G3: (metformin 500mg bid): n=147 G4: (metformin 1000 bid): n=153 G5: (sitagliptin 50 bid + metformin 500 bid) n=160 G6: (sitagliptin 50mg bid + metformin 1000mg bid) n=161	G1: Age 53.6; Female 51% G2: Age 53.5; Female 48% G3: Age 53.7; Female 52% G4: Age 54.2; Female 55% G5: Age 53.7; Female 47% G6: Age 53.6; Female 59% Race NR	None

Evidence Table 2. Key Question 1: Studies of sitagliptin and saxagliptin

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Intermediate Outcomes HbA1c Weight (kg)	Health and Utilization Outcomes Microvascular Disease Macrovascular Disease Lower Extremity Ulcers All-Cause Mortality Quality of Life Hospitalization Medical Visits (diabetes) Other
Active-control studies		
Williams-Herman, 2009 54 weeks Multinational Merck Fair Williams-Herman, 2010 104 weeks	HbA1c mean change from baseline (95% CI): G1: NR G2: -0.8 (-1 to -0.6) G3: -1.0 (-1.2 to -0.8) G4: -1.3 (-1.5 to -1.2) G5: -1.4 (-1.6 to -1.3) G6: -1.8 (-2.0 to -1.7) Weight mean change from baseline (95% CI) G1: NR G2: -0 (-0.2 to 1.4) G3: -1.0 (-1.7 to -0.3) G4: -1.5 ((-2.2 to -0.8) G5: -0.7 (-1.3 to 0.0) G6: -1.7 (-2.4 to -1.1)	All cause mortality: G1: 1 G6: 1

Evidence Table 2. Key Question 1: Studies of sitagliptin and saxagliptin

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Inclusion and Exclusion Criteria	Overall Sample Size Interventions Group Sizes	Baseline Population Characteristics Mean Age, years Race/Ethnicity % Female	Background Medications
Williams-Herman, 2009 54 weeks Multinational Merck Fair Williams-Herman, 2010 104 weeks Cont'd		Entered extension: 685 original randomization: 1091 extension sizes: G1: 103 (sitagliptin 100) G2: 107 (met 500 BID) G3: 121 (met 1000 BID) G4: 134 (sit 50 BID + met 500 BID) G5: 122 (sit 50 BID + met 1000 BID)	(for those included in the efficacy analysis) Race NR G1: Age 54.1, female 42% G2: Age 55.9, female 54% G3: Age 54.3, female 56% G4: Age54.5, female 50% G5: Age 53.9, female 63%	
Aschner, 2010 24 weeks Multinational Merck Fair	Inclusion: Men and women with type 2 diabetes (18–78 years of age)who were treatment na¨ıve (i.e. not taking an antihyperglycaemic agent for at least 16 weeks prior to study entry) with HbA1c 6.5–9.0% Exclusion: Patients with type 1 diabetes, fasting plasma glucose (FPG) <120 mg/dl (6.7 mmol/l) or >250 mg/dl (13.9 mmol/l), unstable cardiac disease, significant renal impairment (creatinine ≥1.4 mg/dl for males or ≥1.3 mg/dl for females or creatinine clearance <60 ml/min), elevated alanine aminotransferase, aspartate aminotransferase, or creatine phosphokinase (more than 2 times upper limit of normal) or triglycerides >600 mg/dl	1050 randomized G1: sita 100mg N= 528 G2:metformin N= 522	G1: Age 56.3, race NR, female 52% G2: Age 55.7, race NR, female 56%	NR

Evidence Table 2. Key Question 1: Studies of sitagliptin and saxagliptin

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Intermediate Outcomes HbA1c Weight (kg)	Health and Utilization Outcomes Microvascular Disease Macrovascular Disease Lower Extremity Ulcers All-Cause Mortality Quality of Life Hospitalization Medical Visits (diabetes) Other
Williams-Herman, 2009 54 weeks Multinational Merck Fair Williams-Herman, 2010 104 weeks Cont'd	For Extension study: HbA1c (mean change from baseline) G1: -1.2 G2: -1.1 G3: -1.3 G4: -1.4 G5: -1.7 Weight (mean change from baseline) G1: +0.5kg G2: -0.8 kg G3: -2.4kg G4: 0 kg G5: -1.2kg	For Extension study: All-cause mortality G1: 0 G2: 1 (cancer) G3: 0 G4: 1 (CAD) G5: 0
Aschner, 2010 24 weeks Multinational Merck Fair	HbA1c: G1: -0.43% G2: -0.57% Change in Weight G1: -0.6kg G2: -1.9kg	All cause mortality G1: 1 (lung cancer) G2: 0

Evidence Table 2. Key Question 1: Studies of sitagliptin and saxagliptin

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Inclusion and Exclusion Criteria	Overall Sample Size Interventions Group Sizes	Baseline Population Characteristics Mean Age, years Race/Ethnicity % Female	Background Medications
Dersoa, 2010 52 weeks Italy University of Pavia Fair	Inclusion: White T2DM patients aged at least 18 years of either sex with uncontrolled T2DM (HbA1c 7.5% or greater) in therapy with pioglitazone. All the patients were not well controlled with diet, physical activity, and pioglitazone at the dosage of 30 mg/d. Exclusion: History of ketoacidosis or had unstable or rapidly progressive diabetic retinopathy, nephropathy, or neuropathy, impaired hepatic function , impaired renal function or severe anemia; serious cardiovascular disease or cerebrovascular conditions within 6 months before study enrollment ; Women who were pregnant or breastfeeding or of childbearing potential and not taking adequate contraceptive precautions	N = 151 G1: (sitagliptin) n=75 G2: (metformin) n=76	Age: G1: 57; G2: 58 Ethnicity: G1: 100% white; G2: 100% white % Female: G1: 51; G2: 49	Pioglitazone
Chan, 2008 54 weeks Multinational Merck Fair	Inclusion: T2DM; moderate to severe renal insufficiency (CrCl <50); ages 18+ Exclusion: T1DM; acute renal disease, renal transplant; liver disease; cardiovascular event within 6 months; hepatic transaminase or creatine phosphokinase levels >= two times the upper limit of normal; repeated fasting plasma glucose >15mmol/l or trigycerides >6.8mmol/l	N=91 G1: (25mg or 50mg sitagliptin) n=65 G2 (placebo/5mg-20mg glipizide) n=26	G1 Age: 68.9 (9.8); White 34%; Black 6%; Hispanic 26%; Asian 31% Other = 3%; Female 52%; G2 Age: 65.3 (9.7); White 31%; Black 4%; Hispanic 35%; Asian 27% Other = 4%; Female 38%	Insulin

Evidence Table 2. Key Question 1: Studies of sitagliptin and saxagliptin

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Intermediate Outcomes HbA1c Weight (kg)	Health and Utilization Outcomes Microvascular Disease Macrovascular Disease Lower Extremity Ulcers All-Cause Mortality Quality of Life Hospitalization Medical Visits (diabetes) Other
Dersoa, 2010 52 weeks Italy University of Pavia Fair	HbA1c: 12 months G1: 7.1 (0.3) G2: 7.0 (0.2) Weight: 12 months G1: -1.6 G2: -2.8	
Chan, 2008 54 weeks Multinational Merck Fair	HbA1c mean change from baseline at week 12 (95% CI): (sitagliptin vs placebo): G1: -0.6% (-0.8 to -0.4) G2: -0.2% (-0.4 to 0.1) at week 54 (sitagliptin + placebo/glipizide): G1: -0.7% (-0.9 to -0.4) G2: -1.0% (-1.6 to -0.3) Weight: mean change (SE) from baseline at week 12 (sitagliptin vs placebo) G1: 0.0 (0.3); G2: -0.6 (0.4) at week 54 (sitagliptin + placebo/glipizide): G1: -0.9 (0.6) G2: 0.0k(0.5)	Macrovascular disease: G1: n=3 (4.6%) G2: n=0 All cause mortality: 6 deaths during double-blind period: G1: n=5 (7.7%) G2: n=1 (3.8%)

Evidence Table 2. Key Question 1: Studies of sitagliptin and saxagliptin

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Inclusion and Exclusion Criteria	Overall Sample Size Interventions Group Sizes	Baseline Population Characteristics Mean Age, years Race/Ethnicity % Female	Background Medications
Placebo-controlled studies				
Chacra, 2009 CV181-040 24 weeks Multinational Bristol-Myers Squibb and AstraZeneca Fair	Inclusion: Age 18-77 with inadequate glycemic control of T2DM (HbA1c between 7.5% and 10%, inclusive); on a submaximal sulphonylurea dose for at least 2 months; fasting C-peptide >=1.0ng/ml; BMI <= 40kg/m^2 Exclusion: Symptoms of poorly controlled diabetes, history of diabetic ketoacidosis or hyperosmolar non-ketotic coma; insulin therapy within 1 year; cardiovascular event within 6 months of or stage III/IV congestive heart failure and/or known left ventricular ejection fraction <=40%; significant history of renal or liver disease; psychiatric disorder; alcohol or drug abuse within last year; treatment with potent CYP 3A4 inhibitors or inducers; immunocompromised individuals; active liver disease or clinically significant abnormal hepatic, renal, endocrine, metabolic or hematological screening.	N=768 G1: (2.5 mg saxagliptin + 7.4mg (final mean) open-label glyburide) n=248 G2: (5mg saxagliptin + 7.4mg (final mean) open-label glyburide) n=253 G3: (placebo + 2.5mg blinded glyburide + 7.5mgopen-label glyburide; final mean total daily dose = 14.6mg) n=267 Note: glyburide doses were uptitrated in placebo plus glyburide group	Age: G1 = 55.4 (9.6); G2 = 54.9 (10.0); G3 = 55.1 (10.7) Race (%): White: G1 = 59.7%; G2 = 59.7%; G3 = 56.9% Black: G1 = 2.0%; G2 = 2.8%; G3 = 2.6% Asian: G1 = 16.9%; G2 = 18.2%; G3 = 19.1% Other: G1 = 21.4%; G2 = 19.4%; G3 = 21.3% % Female: G1 = 54.4; G2 = 56.5; G3 = 53.9	NR

Evidence Table 2. Key Question 1: Studies of sitagliptin and saxagliptin

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Intermediate Outcomes HbA1c Weight (kg)	Health and Utilization Outcomes Microvascular Disease Macrovascular Disease Lower Extremity Ulcers All-Cause Mortality Quality of Life Hospitalization Medical Visits (diabetes) Other
Placebo-controlled studies		
Chacra, 2009 CV181-040 24 weeks Multinational Bristol-Myers Squibb and AstraZeneca Fair	Mean change at 24 weeks, HbA1c: G1 = -0.54%; G2 = -0.64%; G3 = +0.08% P < 0.0001 for G1 and G2 v G3 Mean change at 24 weeks, weight: G1 = +0.7kg; G2 = +0.8kg; G3 = +0.3kg	All-cause mortality: Cardiac death: G3 = 1

Evidence Table 2. Key Question 1: Studies of sitagliptin and saxagliptin

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Inclusion and Exclusion Criteria	Overall Sample Size Interventions Group Sizes	Baseline Population Characteristics Mean Age, years Race/Ethnicity % Female	Background Medications
Rosenstock, 2009 CV181-011 Study 24 weeks US Bristol-Myers Squibb and Astra Zeneca Fair	Inclusion: 18 -77 years of age, T2DM inadequately controlled with diet and exercise (HbA1c ≥7 and ≤10% at screening visit), treatment naïve (see comments for definition), fasting C-peptide ≥ 1 ng.mL (≥0.33 nmol/L), and a BMI of < 40 kg/m2. Exclusion: symptoms of poorly controlled diabetes, history of diabetic ketoacidosis or hyperosmolar nonketotic coma, cardiovascular event within 6 months prior to study entry or New York Heart Association stage III/IV congestive heart failure and/or known left ventricular ejection fraction of <40%, significant renal, liver, or psychiatric history, history of alcohol or drug abuse within the previous year, immunocompromised, active liver disease or clinically significant abnormalities on screening tests of hepatic, renal, endocrine, metabolic, or hematologic function.	N=403 (401 analyzed) G1: (saxagliptin 2.5 mg) n=102 G2: (saxagliptin 5 mg) n=106 G3: (saxagliptin 10 mg) n=98 G4: (placebo) n=95	G1: Age: 53.27 (10.06); White 87.3%, Black 4.9%, Asian 4.9%, Other 2.9%; Female 43.1% G2: Age: 53.91 (11.57); White 87.7%, Black 4.7%, Asian 3.8%, Other 3.8%; Female 49.1% G3: Age: 52.72 (11.27); White 81.6%, Black 6.1%, Asian 6.1; Other 6.1; Female 54.1% G4: Age: 53.91 (12.32); White 83.2%, Black 6.3%, Asian 3.2%, Other 7.4%; Female 50.5%	None

Evidence Table 2. Key Question 1: Studies of sitagliptin and saxagliptin

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Intermediate Outcomes HbA1c Weight (kg)	Health and Utilization Outcomes Microvascular Disease Macrovascular Disease Lower Extremity Ulcers All-Cause Mortality Quality of Life Hospitalization Medical Visits (diabetes) Other
Rosenstock, 2009 CV181-011 Study 24 weeks US Bristol-Myers Squibb and Astra Zeneca Fair	HbA1c: Note: The adjusted mean change for each group was calculated from a mean baseline of 7.9%, although the actual mean baseline for each group was not 7.9%. The actual mean baseline values were: G1: 7.9%, G2: 8.0%, G3: 7.8%, G4: 7.9% At week 24, mean change from 7.9% G1: -0.43% G2: -0.46% G3: -0.54% G4: +0.19% Weight: At week 24, mean changes from baseline G1: -1.2 kg G2: -0.1 kg G3: -0.1 kg G4: -1.4 kg	NR

Evidence Table 2. Key Question 1: Studies of sitagliptin and saxagliptin

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Inclusion and Exclusion Criteria	Overall Sample Size Interventions Group Sizes	Baseline Population Characteristics Mean Age, years Race/Ethnicity % Female	Background Medications
Rosenstock, 2008 12 weeks Multinational Bristol-Myers Squibb Fair	Inclusion: drug-naïve patients; men and non-breastfeeding, non-pregnant women; age 21-70; T2DM; HbA1c 6.8-9.7; BMI<37; screening fasting or random C-peptide >0.5ng/ml; patients aged <35 had to test negative for anti-glutamic acid decardoxylate antibodies Exclusion: T1DM; symptoms of poorly controlled diabetes or a history of ketoacidosis or hyperosmolar coma; congestive heart failure; a history of significant gastrointestinal disease, cardiovascular illness, rapidly progressive renal disease, malignancy, immunodeficiency, asthma or atopic skin disorder; clinically significant abnormalities on screening tests of hepatic, renal, endocrine, metabolic or hematologic function or on chest x-ray or electrocardiogram, use of systemic corticosteroids and cytochrome p450 3A4 inhibitors	N=338 G1 (saxagliptin 2.5mg/day): n=55 G2 (saxagliptin 5mg/day): n=47 G3 (saxagliptin 10mg)/day): n=63 G4 (saxagliptin 20mg/day): n=54 G5 (saxagliptin 40mg/day): n=52 G6 (placebo): n=67	G1: Age: 52.5; White 85%, Black 11%, Other 4%; Female 60% G2: Age: 53.7; White 87%, Black 13%, Other 0%; Female 47% G3: Age: 54.5; White 84%, Black 8%, Other 8%; Female 37% G4: Age: 53.6; White 87%, Black 7%, Other 6%; Female 30% G5: Age: 54.1%; White 92%, Black 4%, Other 4%; Female 42% G6: Age: 55.2; White 87%, Black 10%, Other 3%; Female 37%	None

Evidence Table 2. Key Question 1: Studies of sitagliptin and saxagliptin

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Intermediate Outcomes HbA1c Weight (kg)	Health and Utilization Outcomes Microvascular Disease Macrovascular Disease Lower Extremity Ulcers All-Cause Mortality Quality of Life Hospitalization Medical Visits (diabetes) Other
Rosenstock, 2008 12 weeks Multinational Bristol-Myers Squibb Fair	HbA1c Adjusted change from baseline (95% CI): G1: -0.72 (-0.97 to -0.48) G1 vs. G6: -0.45 (-0.78 to -0.13) G2: -0.90 (-1.17,-0.63) G2 vs. G6: -0.63 (-0.97 to -0.29) G3: -0.81 (-1.03 to -0.58) G3 vs. G6: -0.54 (-0.85 to -0.23 G4: -0.74 (-0.98 to -0.50) G4 vs. G6: -0.47 (-0.80 to -0.14) G5: -0.80 (-1.04 to -0.56) G5 vs. G6: -0.53 (-0.86 to -0.20) G6: -0.27 (-0.49 to -0.05) Weight Mean change from baseline (95% CI): G1: -0.94 (-1.64 to -0.23) G2: -0.23 (-1.07 to 0.60) G3: -1.28 (-2.09 to -0.47) G4: -0.11 (-0.81 to 0.59) G5: 0.51 (-0.41 to 1.42) G6: -1.03 (-1.80 to -0.27)	NR

Evidence Table 2. Key Question 1: Studies of sitagliptin and saxagliptin

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Inclusion and Exclusion Criteria	Overall Sample Size Interventions Group Sizes	Baseline Population Characteristics Mean Age, years Race/Ethnicity % Female	Background Medications
DeFronzo, 2009 Saxagliptin CV181-014 Study 24 weeks Multinational Bristol-Myers Squibb & AstraZeneca Fair	Inclusion: T2DM, inadequate glycemic control (HbA1c >=7.0 and <=10.0%), taking a stable dose of metformin (>=1,500mg but not >2,550mg) for at least 8 weeks before screening, fasting C-peptide concentration >=1.0ng/ml, age 18-77, BMI<=40kg/m^2 Exclusion: Symptoms of poorly controlled DM, history of diabetic ketoacidosis or hyperosmolar nonketonic coma, use of any other antihyperglycemic meds (8 weeks before) or insulin (1 year before), a cardiovascular event within 6 months of study entry, stage III/IV congestive heart failure and/or known left ventricular ejection fraction <=40%, chronic or repeated intermittent corticosteroid treatment, history of alcohol or drug abuse within 1 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, assessment of an immunocompromised state, pregnancy, breastfeeding	N=743 G1 (placebo): n=179 G2 (2.5mg saxagliptin): n=192 G3 (5mg saxagliptin): n=191 G3 (10mg saxagliptin): n=181	Age: G1=54.8 (10.2); G2=54.7 (10.1); G3=54.7 (9.6); G4=54.2 (10.1) Race: White: G1=83.8%; G2=79.7%; G3=83.2%; G4=79.6% Black: G1=3.9%; G2=4.2%; G3=5.8%; G4=7.7% Asian: G1=2.2%; G2=4.2%; G3=1.6%; G4=2.8% Other: G1=10.1%; G2=12.0% G3=9.4%; G4=9.9% Female: G1=46.4%; G2=56.8%; G3=46.1%; G4=47.5%	Metformin

Evidence Table 2. Key Question 1: Studies of sitagliptin and saxagliptin

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Intermediate Outcomes HbA1c Weight (kg)	Health and Utilization Outcomes Microvascular Disease Macrovascular Disease Lower Extremity Ulcers All-Cause Mortality Quality of Life Hospitalization Medical Visits (diabetes) Other
DeFronzo, 2009 Saxagliptin CV181-014 Study 24 weeks Multinational Bristol-Myers Squibb & AstraZeneca Fair	HbA1c mean change from baselineat week 24: G1: +0.13% (0.07) G2: -0.59% (0.07) G3: -0.69% (0.07) G4: -0.58 (0.07) all <0.0001 vs placebo Weight: Mean change from baseline at 24 weeks : G1: -0.92 G2: -1.43 G3: -0.87 G4: -0.53	NR

Evidence Table 2. Key Question 1: Studies of sitagliptin and saxagliptin

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Inclusion and Exclusion Criteria	Overall Sample Size Interventions Group Sizes	Baseline Population Characteristics Mean Age, years Race/Ethnicity % Female	Background Medications
Hollander, 2009 CV181-013 24 weeks US Bristol-Meyers Squibb and AstraZeneca Fair	Inclusion: 18-77 years old; T2DM treated with stable dose of TZD monotherapy for at least 12 weeks prior to screening; HbA1c 7-10.5; fasting C-peptide ≥ 0.3 nmol/L; BMI< 45 Exclusion: history of any anti-hyperglycemic therapy within 12 weeks other than TZD; history of diabetic ketoacidosis; history of hyperosmolar nonketotic coma; symptoms of poorly controlled diabetes; those receiving insulin within 1 year except during hospitalization or gestational diabetes; immunocompromised; treated with potent CYP3A4 inhibitors or inducers within 6 months; had a cardiovascular event; New York Heart Association class III/IV congestive heart failure; left ventricular ejection fraction < 40%; significant renal, liver or psychiatric history; significant alcohol or drug abuse in the past year; active liver disease; significant abnormalities on screening tests of hepatic, renal, endocrine, metabolic, or hematologic function	N=565 G1 (saxagliptin 2.5mg/day + open-label TZD): n=195 G2 (saxagliptin 5mg/day + open-label TZD): n=186 G3 (placebo + open-label TZD): n=184	G1: Age 54.9; White 55.9%, Black 2.6%, Asian 34.4%, Other 7.2%; Female 45.6% G2: Age 53.2; White 53.2%, Black 5.4%, Asian 35.5%, Other 5.9%; Female 52.2% G2: Age 54.0; White 54.9%, Black 3.8%, Asian 34.2%, Other 7.1%; Female 53.8%	TZD in all groups

Evidence Table 2. Key Question 1: Studies of sitagliptin and saxagliptin

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Intermediate Outcomes HbA1c Weight (kg)	Health and Utilization Outcomes Microvascular Disease Macrovascular Disease Lower Extremity Ulcers All-Cause Mortality Quality of Life Hospitalization Medical Visits (diabetes) Other
Hollander, 2009 CV181-013 24 weeks US Bristol-Meyers Squibb and AstraZeneca Fair	HbA1c Mean change at 24 weeks: G1: -0.66 G2: -0.94 G3: -0.30 p=0.0007, G1 vs. G3 p<0.0001, G2 vs. G3 Weight mean change at 24 weeks: G1: +1.3 G2: +1.4 G3: +0.9	All cause mortality G1: n=1 G2: n=0 G3: n=0

Evidence Table 2. Key Question 1: Studies of sitagliptin and saxagliptin

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Inclusion and Exclusion Criteria	Overall Sample Size Interventions Group Sizes	Baseline Population Characteristics Mean Age, years Race/Ethnicity % Female	Background Medications
Hanefeld, 2007 Sitagliptin Study 014 12 weeks Multinational Fair	Inclusion: 21-75 years old; T2DM; currently on monotherapy (except TZDs) with HbA1c 6-9 or not on an anti-diabetic agent with HbA1c 6.5-10 Exclusion: T1DM; unstable cardiac disease; AST, ALT or CPK ≥ 2x upper limit of normal	N=555 randomized, 552 analyzed G1 (placebo): n=111 G2 (sitagliptin 25 mg/day): n=111 G3 (sitagliptin 50 mg/day): n=112 G4 (sitaglitptin 100 mg/day): n=110 G5 (sitagliptin 50 mg bid): n=111	G1: Age: 55.9; White 78.4%, Asian 0.9%, Black 7.2%, Other 13.5%; Female 36.9% G2: Age: 55.1; White 88.3, Asian 0.9%, Black 3.6%, Other 7.2%; Female 48.6% G3: Age: 55.3; White 85.7%, Asian 0%, Black 8.0%, Other 6.3%; Female 54.5%; G4: Age: 56.0; White 88.2%, Asian 0%, Black 5.5%, Other 6.4%; Female 44.5% G4: Age: 55.2; White 81.1%, Asian 0.9%, Black 6.3%, Other 11.7%; Female 55.9%	None
Nonaka, 2008 12 weeks Japan Banyu Pharmaceuticals (Merck) Good	Inclusion: T2DM; ages 20-69; either not on treatment with an oral antihyperglycemic agent or only on a single agent over the 8 weks prior to the screening; HbA1c 6.5-10 in patient not on medication and fasting plasma glucose 126-240 Exclusion: T1DM; treatment with either insulin or pioglitzone in the 8 weeks prior to screening; unstable cardiac disease; elevated serum creatinine; elevations >2-fold the upper limit of normal of AST, ALT or CPK	N=152 G1 (sitagliptin 100mg/day): 75 G2 (placebo): 76	G1: Age: 55.6; Japanese 100%; Female 40% G2: Age: 55.0; Japanese 100%; Female 34%	NR

Evidence Table 2. Key Question 1: Studies of sitagliptin and saxagliptin

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Intermediate Outcomes HbA1c Weight (kg)	Health and Utilization Outcomes Microvascular Disease Macrovascular Disease Lower Extremity Ulcers All-Cause Mortality Quality of Life Hospitalization Medical Visits (diabetes) Other
Hanefeld, 2007 Sitagliptin Study 014 12 weeks Multinational Fair	HbA1c mean change (95% CI) at 12 weeks: G1: 0.12 (-0.02, 0.26) G2: -0.28 (-0.42, -0.14) G3: -0.44 (-0.58, -0.30) G4: -0.44 (-0.58,-0.30) G5: -0.43 (-0.56, -0.29) P<0.001, all groups vs. placebo Weight mean change at 12 weeks not reported for individual groups: G1: -0.5kg (SD NR) G2, G3, G4, G5): range of -0.5 to -0.8kg (SD NR) p<0.05, all groups vs. baseline NS, G1 vs. G2/G3/G3/G5	Macrovascular disease: N=0
Nonaka, 2008 12 weeks Japan Banyu Pharmaceuticals (Merck) Good	HbA1c mean change from baseline (95% CI): G1: -0.65 (-0.80 to -0.50) G2: 0.41 (0.26 to 0.56) G1 vs. G2: -1.05 (-1.27 to -0.84); P<0.001 Weight mean change from baseline (95% CI): G1: -0.1 (-0.4 to 0.3) G2: -0.7 (-1.0 to -0.4) G1 vs. G2: 0.7 (0.2, to1.1), P<0.01	NR

Evidence Table 2. Key Question 1: Studies of sitagliptin and saxagliptin

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Inclusion and Exclusion Criteria	Overall Sample Size Interventions Group Sizes	Baseline Population Characteristics Mean Age, years Race/Ethnicity % Female	Background Medications
Mohan, 2009 18 weeks China, India, Korea Merck Good	Inclusion: 18+ years; T2DM diagnosis within past 5 years; HbA1c >=7.5% and <=11.0% if not taking an oral antihyperglycemic agent, or HbA1c >=7.0% and <=10.0% if taking and OHA Exclusion: Receipt of insulin or TZD within 12 weeks; pregnant / breastfeeding; T1DM; unstable cardiac disease; moderate to severe renal insufficiency	N=530 G1 (placebo): n=178 G2 (100mg sitagliptin): n=352	G1 (placebo): Age=50.9 (9.3); Chinese=46%; Indian=35%; Korean=19%; Female=40% G2 (sitagliptin): Age=50.9 (9.3); Chinese=46%; Indian=36%; Korean=18%; Female=43%	None
Raz, 2008 30 weeks Multinational Merck Fair	Inclusion: 18 - 78 years of age, currently on metformin monotherapy or any other single oral hypoglycemic agent or being treated with metformin in combination with another oral hypoglycemic agent, and HbA1c was 8.0 - <11.0%. Exclusion: Received treatment with insulin within 8 weeks prior to screening, treatment with a TZD or exenatide within 12 weeks, had T1DM, a BMI < 20 kg/m2 or > 43 kg/m2, or fasting plasma glucose during run-in that was consistently < 7.2 mmol/L or > 15.6 mmol/L.	N=190 randomized, 187 analyzed G1: (placebo) n=94 G2: (sitagliptin 100mg QD) n=96	G1: 56.1 (9.5); White 47%, Hispanic 25%, Black 1%, Multiracial 25%, Other 2%; Female 58.5% G2: 53.6 (9.5); White 42%, Hispanic 32%, Black 3%, Multiracial 22%, Other 1%; Female 49%	Metformin
Seck, 2010 104 weeks Multinational Merck Fair Extension of Nauck, 2007	Inclusion: Men and women (aged 18–78 years) with T2DM who were either not taking an antihyperglycaemic agent, were taking any oral antihyperglycaemic agent as monotherapy or were taking metformin in combination with another oral antihyperglycaemic agent"	1172 randomized; 519 entered year 2 G1: (sitagliptin 100mg) n=248 G2: glipizide n=256	G1: Age 57.6, White 77.4%; Asian 9.3%, Black 3.6%, hispanic 5.6%, other 4%, female 42.7% G2: Age 57.0, White 78.5%; Asian 8.2%, Black 5.1%, hispanic 5.1% other 3.1%, female 37.1%	Metformin

Evidence Table 2. Key Question 1: Studies of sitagliptin and saxagliptin

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Intermediate Outcomes HbA1c Weight (kg)	Health and Utilization Outcomes Microvascular Disease Macrovascular Disease Lower Extremity Ulcers All-Cause Mortality Quality of Life Hospitalization Medical Visits (diabetes) Other
Mohan, 2009 18 weeks China, India, Korea Merck Good	HbA1c mean change (SE) from baseline: G1: 0.3 (0.1, 0.5) G2: -0.7 (-0.8, -0.6) P<0.001 Weight mean change (SE) from baseline: G1: 0.0 (0.2) G2: 0.6 (0.1)	Macrovascular disease: G1: n=0 G2: n=1 All cause mortality: G1: n=0 G2: n=1
Raz, 2008 30 weeks Multinational Merck Fair	HbA1c (LS mean and 95% CI) G1: Week 18, n=92 0.0 (-0.2 to 0.3) G2: Week 18, n=95 -1.0 (-1.2 to -0.8) G1: Week 30, n=92 0.0 (-0.2 to 0.3) G2: Week 30 n=95 -1.0 (-1.3 to -0.7) At 30 weeks P<0.001 Weight: At 30 weeks, a small decrease in body weight of 0.5 kg was seen in both groups, mean change NR	Macrovascular disease: G1: n=1 G2: n=0 All cause mortality: G1: n=1 G2: n=0
Seck, 2010 104 weeks Multinational Merck Fair Extension of Nauck, 2007	HbA1c (mean change from baseline) G1: -0.54% G2: -0.51% Weight (kg) (mean change from baseline) G1: -1.6kg G2: +0.7 kg	All Cause Mortality 9 deaths G1: 1 G2: 8

Evidence Table 2. Key Question 1: Studies of sitagliptin and saxagliptin

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Inclusion and Exclusion Criteria	Overall Sample Size Interventions Group Sizes	Baseline Population Characteristics Mean Age, years Race/Ethnicity % Female	Background Medications
Vilsboll, 2010 24 weeks Multinational Merck Fair	Inclusion: at least 21 years of age, had a body mass index (BMI) >20 kg/m2 and <43 kg/m2, were taking insulin (≥15 IU/day; long- or intermediate-acting or premixed insulin) alone or in ombination with metformin (at a dose of at least 1500 mg/day), and had inadequate glycaemic control (HbA1c 7.5–11% at screening) Exclusion: type 1 diabetes, fasting plasma glucose (FPG) <130 mg/dl, unstable cardiac disease (including new or worsening signs or symptoms of coronary heart disease within 3 months of study entry or any of the following within 6 months of study entry: acute coronary syndrome, stroke or ischaemic event; coronary artery intervention, or NYHA Class II-IV congestive heart failure), significant renal impairment (creatinine clearance<50 ml/min), elevated (more than twofold the upper limit of normal) alanine aminotransferase (ALT) or aspartate aminotransferase (AST), or elevated triglycerides (>600 mg/dl), treatment with oral antihyperglycaemic agents (except metformin) or exenatide within 8–12 weeks of study entry	N = 641 G1: (sitagliptin 100mg) N=322 G2: (placebo) N=319	G1: Age 58.3, white 71%, black 6%, asian 17%, other 6%, female 51% G2: Age 57.2, white 69%, black 7%, asian 19%, other 5%, female 47%	nsulin +/- metformin

Evidence Table 2. Key Question 1: Studies of sitagliptin and saxagliptin

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Intermediate Outcomes HbA1c Weight (kg)	Health and Utilization Outcomes Microvascular Disease Macrovascular Disease Lower Extremity Ulcers All-Cause Mortality Quality of Life Hospitalization Medical Visits (diabetes) Other
Vilsboll, 2010 24 weeks Multinational Merck Fair	HbA1c (mean change from baseline): G1: -0.6 G2: 0 Weight (mean change from baseline): G1: -0.1 kg G2: +0.1 kg	All cause mortality: G1: 0 G2: 0

Evidence Table 3. Key Question 1: Studies of exenatide and liraglutide

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Inclusion and Exclusion Criteria	Overall Sample Size Interventions Group Sizes	Baseline Population Characteristics Mean Age, years Race/Ethnicity % Female	Background Medications
Head-to-head studies				
Buse, 2009 LEAD-6 26 weeks Multinational Novo Nordisk Fair	Inclusion: Aged 18 - 80 with T2DM, HbA1c between 7 - 11 %, BMI ≤ 45kg, on stable treatment with maximally tolerated doses of metformin, sulfonylurea, or both for at least 3 months Exclusion: Previous insulin treatment (except short-term treatment for intercurrent illness), previous exposure to exenatide or liraglutide, impaired liver or renal function, clinically significant cardiovascular disease, retinopathy or maculopathy requiring acute treatment, hypertension (>180/100 mm Hg), or cancer	N=464 G1: (Liraglutide 1.8 mg qd) n=233 G2: (Exenatide 10 ug bid) n=231	G1: Age, 56.3; White 93%, Asian/ Pacific Islander <1%, Black (including African American) 6%, Hispanic or Latin American 14%, Other 1%; Female 51% G2: Age, 57.1; White 91%, Asian/ Pacific Islander 2%, Black (including African American) 5%, Hispanic or Latin American 11%, Other 2%; Female 45%	Metformin with or without sulfonylurea

Evidence Table 3. Key Question 1: Studies of exenatide and liraglutide

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Intermediate Outcomes HbA1c Weight (kg)	Health and Utilization Outcomes Microvascular Disease Macrovascular Disease Lower Extremity Ulcers All-Cause Mortality Quality of Life Hospitalization Medical Visits (diabetes) Other
Head-to-head studies		
Buse, 2009 LEAD-6 26 weeks Multinational Novo Nordisk Fair	Liraglutide vs. Exenatide HbA1c mean change at 26 weeks: -1.12% vs. -0.79% Estimated treatment difference = -0.33% 95% CI -0.47, -0.18 Weight mean change at 26 weeks (mean, SE) -3.24kg (0.33) vs. 2.87kg (0.33) 95% CI, -0.99 to 0.23	NR

Evidence Table 3. Key Question 1: Studies of exenatide and liraglutide

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Inclusion and Exclusion Criteria	Overall Sample Size Interventions Group Sizes	Baseline Population Characteristics Mean Age, years Race/Ethnicity % Female	Background Medications
Active-control studies				
Brodows, 2008 Duration NR Eli Lilly and Amylin Pharmaceuticals Poor	Inclusion: T2DM inadequately controlled on metofrmin and sulfonylurea Exclusion: NR	N=414 G1: (Exenatide) n=205 G2: (Insulin Glargine) n=209	G1: Age 59.4; Race/Ethnicity NR; Female 45% G2: Age 57.4; Race/Ethnicity NR; Female 45%	NR
Pratley, 2010 26 weeks Multinational Novo Nordisk Fair	Inclusion: 18-80 y; T2DM; HbA1c 7.5-10.0%;BMI ≤ 45.0 kg/m2; treatmed with metformin (≥1500 mg/d) for ≥ 3 mo Exclusion: Prior treatment with any antihperglycemic drug (except metformin) within 3 mo; Recurrent major hypoglycemia; hypoglycemic unawareness; present use of any drug that could affect glucose (except metformin); contraindication to trial drugs; cardiovascular disease; cancer	N = 665 G1: Liraglutide (1.2mg/d) n=225 G2: Liraglutide (1.8 mg/d) n=221 G3: Sitagliptin (100mg/d) n=219	G1: Age 55.9; Caucasian 82%, Hispanic/Latino 17%, Black 10%, Asian 3%, Other 5%; Female 48% G2: Age 55.0; Caucasian 91%, Hispanic/Latino 16%, Black 5%, Asian 1%, Other 4%; Female 48% G3: Age 55.0; Caucasian 87%, Hispanic/Latino 15%, Black 7%, Asian 2%, Other 4%; Female 45%	Metformin

Evidence Table 3. Key Question 1: Studies of exenatide and liraglutide

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Intermediate Outcomes HbA1c Weight (kg)	Health and Utilization Outcomes Microvascular Disease Macrovascular Disease Lower Extremity Ulcers All-Cause Mortality Quality of Life Hospitalization Medical Visits (diabetes) Other
Active-control studies		
Brodows, 2008 Duration NR Eli Lilly and Amylin Pharmaceuticals Poor	Exenatide vs. Insulin Mean HbA1c at 26 weeks: 7.1% vs. 7.1% Weight: NR	NR
Pratley, 2010 26 weeks Multinational Novo Nordisk Fair	HbA1c G1: -1.24% (-1.37 to -1.11) G2: -1.50% (-1.63 to -1.37) G3: -0.90% (-1.03 to -0.77) Mean treatment differences G1 vs. G3: -0.34% (-0.51 to -0.16) G1 vs. G2: -0.60% (-0.77 to -0.43) Weight: G1: -2.86 kg (-3.39 to -2.32) G2: -3.38 kg (-3.91 to -2.84) G3: -0.96 kg (-1.50 to -0.42) Mean treatment differences: G1 vs. G2: -1.90 kg (-2.61 to -1.18) G2 vs. G3: -2.42 kg (-3.14 to -1.70)	All Cause Mortality Deaths: G1: 0 G2: 1 (<1%) G3: 1 (<1%)

Evidence Table 3. Key Question 1: Studies of exenatide and liraglutide

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Inclusion and Exclusion Criteria	Overall Sample Size Interventions Group Sizes	Baseline Population Characteristics Mean Age, years Race/Ethnicity % Female	Background Medications
DeFronzo, 2010 20 weeks US Eli Lilly Fair	Inclusion: age 18 –75 years, BMI 25–40 kg/m2, stable body weight for at least 6 months prior to screening, A1C 6.8–10.0%, stable dose of metformin for at least 6 weeks prior to screening and no treatment with any other antidiabetic medication, and absence of islet cell autoantibodies. Exclusion: NR	N = 137 G1: Exenatide n=45 G2: Rosiglitazone + Exenatide n=47 G3: Rosiglitazone n=45	Mean age 56 yrs 61% white 49% female	Metformin

Evidence Table 3. Key Question 1: Studies of exenatide and liraglutide

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Intermediate Outcomes HbA1c Weight (kg)	Health and Utilization Outcomes Microvascular Disease Macrovascular Disease Lower Extremity Ulcers All-Cause Mortality Quality of Life Hospitalization Medical Visits (diabetes) Other
DeFronzo, 2010 20 weeks US Eli Lilly Fair	HbA1c Change from baseline, LS Mean (SE): G1: -0.9 (0.1) G2: -1.3 (0.1) G3: -1.0 (0.1) G1 vs. G2 P=0.016 G1 vs. G3 P=0.720 G3 vs. G2 P=0.039 Weight Change from baseline LS Mean (SE): G1: -2.8 (0.5) G2: -1.2 (0.5) G3: +1.5 (0.5) G1 vs. G2 P=0.038 G1 vs. G3 P<0.001 G3 vs. G2P<0.001	NR

Evidence Table 3. Key Question 1: Studies of exenatide and liraglutide

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Inclusion and Exclusion Criteria	Overall Sample Size Interventions Group Sizes	Baseline Population Characteristics Mean Age, years Race/Ethnicity % Female	Background Medications
Derosa, 2010 52 weeks Italy NR Fair	Inclusion: White, T2DM patients 18 years old of either sex, with poor glycemic control (expressed as HbA1c level >8.0%) and overweight (body mass index [BMI] 25 and <30 kg=m2) receiving therapy with metformin at the mean dosage of 1,500 500mg=day, intolerant to metformin at maximum dosage (3,000mg=day) with the onset of gastrointestinal disorders like diarrhea and significant meteorism when metformin was titrated to the maximum level. Exclusion: History of ketoacidosis or had unstable or rapidly progressive diabetic retinopathy, nephropathy, or neuropathy, impaired hepatic function , impaired renal function or severe anemia; serious cardiovascular disease or cerebrovascular conditions within 6 months before study enrollment ; Women who were pregnant or breastfeeding or of childbearing potential and not taking adequate contraceptive precautions	N = 128 G1: Exenatide n=63 G2: Sulfonylurea n=65	Age: G1: 57 G2: 56 Ethnicity: G1: 100% white G2: 100% white % Female: G1: 52 G2: 49	NR

Evidence Table 3. Key Question 1: Studies of exenatide and liraglutide

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Intermediate Outcomes HbA1c Weight (kg)	Health and Utilization Outcomes Microvascular Disease Macrovascular Disease Lower Extremity Ulcers All-Cause Mortality Quality of Life Hospitalization Medical Visits (diabetes) Other
Derosa, 2010 52 weeks Italy NR Fair	HbA1c Mean Change from baseline at 12 months: G1: -1.5 G2: -1.8 Weight Mean Change from baseline at 12 months: G1: -8.0 kg G2: +4.5 kg	NR

Evidence Table 3. Key Question 1: Studies of exenatide and liraglutide

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Inclusion and Exclusion Criteria	Overall Sample Size Interventions Group Sizes	Baseline Population Characteristics Mean Age, years Race/Ethnicity % Female	Background Medications
Bergenstal, 2009 Novo-Log Mix vs Exenatide Study Group 24 weeks United States Novo Nordisk Poor	Inclusion: T2DM >6 months, age >18 and <80 years, HbA1c >8%, insulin naïve (received no insulin for more than 2 weeks of daily use in the preceding 6 months), had received at least 1500 mg/day metformin and a sulfonylurea at at least half the maximum dose for 3 months before screening Exclusion: Significant cardiac disease within 12 months prior to the study, hepatic insufficiency, renal insufficiency, used thiazolidinediones, alpha-glucosidase inhibitors or meglitinides within 6 months before the study, had a history of an eating disorder or were receiving current treatment with a weight-reducing diet.	N=372 G1: (Exenatide 5ug bid increased to 10ug bid) n=124 G2: (BIAsp 30 qd started at 12 IU qd and adjusted as indicated) G3: (BIAsp 30 bid started at 12 IU divided in to two doses and adjusted as indicated)	G1: Age, 52.5 (10.62); American Indian/Alaska Native 10.5%, Asian 1.6%, Black 19.4%, White 63.7%, Other 4.8%; Female 51.6% G2: Age, 51.8 (10.90); American Indian/Alaska Native 8.1%, Asian 2.4%, Black 18.5%, White 67.7%, Other 3.2%; Female 51.6% G3: Age, 53.4 (9.96); American Indian/Alaska Native 8.9%, Asian 1.6%, Black 26.6%, White 59.7%, Other 3.2%; Female 52.4%	Metformin and sulfonylurea

Evidence Table 3. Key Question 1: Studies of exenatide and liraglutide

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Intermediate Outcomes HbA1c Weight (kg)	Health and Utilization Outcomes Microvascular Disease Macrovascular Disease Lower Extremity Ulcers All-Cause Mortality Quality of Life Hospitalization Medical Visits (diabetes) Other
Bergenstal, 2009 Novo-Log Mix vs Exenatide Study Group 24 weeks United States Novo Nordisk Poor	Exenatide vs. BiAsp 30 qd vs. BiAsp 30 bid Data based on Per-protocol population, the N in each group varies for each week a measurement was taken, and last observation carried forward was used for missing data. HbA1C change from Baseline (mean +/- SD) -1.75 (1.57) vs. -2.34 (1.51) vs. -2.76 (1.79) P<0.0001 for G3 v G1 P<0.0001 for G2 v G1	

Evidence Table 3. Key Question 1: Studies of exenatide and liraglutide

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Inclusion and Exclusion Criteria	Overall Sample Size Interventions Group Sizes	Baseline Population Characteristics Mean Age, years Race/Ethnicity % Female	Background Medications
Russel-Jones, 2009 LEAD-5 26 weeks Multinational Novo Nordisk Good	Inclusion: 18–80 years old, with T2DM treated with oral glucose-lowering drugs (OGLAs) (94–95% combination therapy) for at least 3 months ; HbA1c level of 7.5–10% if on OGLA monotherapy or 7–10% if on OGLA combination therapy, and BMI ≤ 45kg/m2. Exclusion: Insulin within 3 months prior to the trial (except for short-term treatment for intercurrent illness); impaired hepatic or renal function, clinically significant cardiovascular disease, proliferative retinopathy or maculopathy, hypertension (≥180/100 mmHg) or cancer; pregnant; experienced recurrent hypoglycaemia or hypoglycaemia unawareness; were seropositive for hepatitis B antigen or hepatitis C antibody; or used any drugs except for OGLAs that could affect blood glucose levels	N=581 G1: Liraglutide 1.8mg n=232 G2: Placebo n=115 G3: Insulin glargine (dose titrated to fasting blood sugar) n=234	Liraglutide vs. Placebo vs. Insulin Age: 57.6 vs. 57.5 vs. 57.5 Ethnicity: NR % Female: 43 vs. 51 vs. 40	All patients on metformin 2g and glimepiride 4mg

Evidence Table 3. Key Question 1: Studies of exenatide and liraglutide

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Intermediate Outcomes HbA1c Weight (kg)	Health and Utilization Outcomes Microvascular Disease Macrovascular Disease Lower Extremity Ulcers All-Cause Mortality Quality of Life Hospitalization Medical Visits (diabetes) Other
Russel-Jones, 2009 LEAD-5 26 weeks Multinational Novo Nordisk Good	Liraglutide vs. Placebo vs. Insulin Mean (SE) change in HbA1c: -1.33% (0.09) vs. -0.24% (0.11) vs. -1.09% (0.09) G1 vs. G2 Treatment difference −1.09%; 95% CI, −1.28 to −0.90; *P* <0.0001 G1 vs.. G3 Treatment difference −0.24%; 95% CI, −0.39 to −0.08; *P* =0.0015 G3 vs. G2 Treatment difference −0.85%; 95% CI, −1.04 to −0.66; *P* <0.0001 Mean (SE) change in weight: -1.8 kg (0.33) vs. -0.42 kg (0.39) vs. +1.6 (0.33) G1 vs. G2 −1.39 kg; 95% CI, −2.10 to −0.69; *P* =0.0001 G1 vs. G3 −3.43 kg; 95% CI, −4.00 to −2.86; *P* <0.0001	

Evidence Table 3. Key Question 1: Studies of exenatide and liraglutide

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Inclusion and Exclusion Criteria	Overall Sample Size Interventions Group Sizes	Baseline Population Characteristics Mean Age, years Race/Ethnicity % Female	Background Medications
Garber, 2009 LEAD-3 Mono 52 weeks US and Mexico Novo Nordisk Fair	Inclusion: 18–80 years, BMI of 45 kg/m² or less, with T2DM; treated with diet and exercise (36·5% of patients randomised) or up to half the highest dose of oral antidiabetic drug monotherapy (63·5%) including sulphonylureas, meglitinides, aminoacid derivatives, biguanides, α-glucosidase inhibitors, and thiazolidinediones (1500 mg metformin or 30 mg pioglitazone were allowed) for at least 2 months; a screening HbA1c value of 7–11% if treated with diet and exercise or 7–10% with oral antidiabetic monotherapy. Exclusion: insulin treatment during the previous 3 months (except short-term treatment for intercurrent illness), treatment with systemic corti costeriods, hypoglycaemia unawareness or recurrent severe hypoglycaemia, and impaired liver function (aspartate aminotransferase or alaninie aminotransferase concentrations ≥ 2.5 times normal.	N=746 G1: Liraglutide 1.2 mg n=251 G2: Liraglutide 1.8 mg n=247 G3: Glimpiride 8 mg n=248	Mean age: G1: 53.7; G2: 52.0; G3: 53.4 Race/Ethnicity: White % G1: 80; G2: 75; G3: 77 Black % G1: 14; G2: 12; G3: 12 Asian % G1: 2; G2: 6; G3: 4 Other % G1: 5; G2: 7; G3: 7 % Female: G1: 53; G2: 51; G3: 46	None

Evidence Table 3. Key Question 1: Studies of exenatide and liraglutide

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Intermediate Outcomes HbA1c Weight (kg)	Health and Utilization Outcomes Microvascular Disease Macrovascular Disease Lower Extremity Ulcers All-Cause Mortality Quality of Life Hospitalization Medical Visits (diabetes) Other
Garber, 2009 LEAD-3 Mono 52 weeks US and Mexico Novo Nordisk Fair	Liraglutide 1.2mg vs. Liraglutide 1.8mg vs. Glimiperide 8mg Mean (SD) change in HbA1c: -0.84% (1.23) vs. -1.14% (1.24) vs. -0.51% (1.20) G1 vs. G3: –0·33%; P=0·0014; 95% CI, –0·53 to –0·13 G2 vs. G3: –0·62%; P<0·0001; 95% CI, –0·83 to –0·42 G2 vs. G1: –0·29%; P=0·0046; 95% CI, –0·50 to –0·09 Mean change in weight: NR	

Evidence Table 3. Key Question 1: Studies of exenatide and liraglutide

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Inclusion and Exclusion Criteria	Overall Sample Size Interventions Group Sizes	Baseline Population Characteristics Mean Age, years Race/Ethnicity % Female	Background Medications
Madsbad, 2004 12 weeks Scandanavia and the UK Novo Nordisk Fair	Inclusion: Men and women age 30 years or more; T2DM diagnosis (according to American Diabetes Association criteria); BMI 40 kg/m2 or less, were being treated with diet or an OHA, and had an HbA1c 9.5% or less (OHA) or 7.5–10.0% (diet) Exclusion: Liver or renal disease, heart failure, unstable angina pectoris, myocardial infarction within the previous 12 months, concomitant treatment with thiazolidinediones or other investigational drugs, or other significant conditions likely to affect a patient's diabetes and/or ability to complete the trial. Women who were pregnant, breast-feeding, or not using an adequate method of contraception	N=193 (190 in ITT) G1: Liraglutide 0.045 mg n=26 G2: Liraglutide 0.225 mg n=24 G3: Liraglutide 0.45 mg n=27 G4: Liraglutide 0.60 mg n=30 G5: Liraglutide 0.75 n=28 G6: Placebo n = 29 G7: Glimepiride n=26	Liraglutide 0.045 mg vs. Liraglutide 0.225 mg vs. Liraglutide 0.45 mg vs. Liraglutide 0.60 mg vs. Liraglutide 0.75 mg vs. Placebo vs. Glimepiride Age: G1: 53 (9.0) vs. 58 (7.5) vs. 57 (11.3) vs. 57 (7.7) vs. 58 (9.7) vs. 57 (9.4) vs. 57 (9.2) Race/Ethnicity: NR % Female: 15% vs. 38% vs. 33% vs. 33% vs. 43% vs. 31% vs. 38%	None

Evidence Table 3. Key Question 1: Studies of exenatide and liraglutide

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Intermediate Outcomes HbA1c Weight (kg)	Health and Utilization Outcomes Microvascular Disease Macrovascular Disease Lower Extremity Ulcers All-Cause Mortality Quality of Life Hospitalization Medical Visits (diabetes) Other
Madsbad, 2004 12 weeks Scandanavia and the UK Novo Nordisk Fair	does not report change from baseline Compared to placebo change in HbA1c (%) after 12 weeks: G1: +0.25 (*P* =0.1905) G2: -0.34 (*P* =0.0877) G3: -0.30 (*P* =0.1131) G4: -0.70 (*P* =0.0002) G5: -0.75 (*P* <0.0001) G6: NA G7: -0.74 (*P* =0.0001) Compared to placebo change in weight (kg) after 12 weeks: G1: - 0.03 (*P* =0.9602) G2: -0.74 (*P* =0.1544) G3: -1.20 (*P* =0.0184) G4: +0.27 (*P* =0.5838) G5: -0.39 (*P* =0.4391) G6: NA G7: + 0.94 (*P* =0.0622)	

Evidence Table 3. Key Question 1: Studies of exenatide and liraglutide

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Inclusion and Exclusion Criteria	Overall Sample Size Interventions Group Sizes	Baseline Population Characteristics Mean Age, years Race/Ethnicity % Female	Background Medications
Nauck, 2009 LEAD-2 26 weeks Multinational Novo Nordisk Fair	Inclusion: 18–80 years of age, had A1C between 7 and 11% (prestudy OAD monotherapy for 3 months) or between 7 and 10% (prestudy combination OAD therapy for 3 months); BMI 40 kg/m2 or less Exclusion: Insulin during the previous 3 months (except short-term treatment)	N=1091 (1087 in ITT) G1: Liraglutide 0.6 mg n=242 G2: Liraglutide 1.2 mg n=240 G3: Liraglutide 1.8 mg n=242 G4: Glimepiride 4 mg n=242 G5: Placebo n=121	Liraglutide 0.6mg vs. Liraglutide 1.2mg vs. 1.8mg vs. 4mg vs. Placebo Age: 56 vs. 57 vs. 57 vs. 57 vs. 56 Race/Ethnicity %: Caucasian: 84 vs. 88 vs. 88 vs. 89 vs. 88 Black: 2 vs. 4 vs. 2 vs. 2 vs. 3 Asian/Pacific Islander: 13 vs. 8 vs. 7 vs. 9 vs. 7 Other: 2 vs. 1 vs. 2 vs. 1 vs. 3 % Female: 38 vs. 46 vs. 41 vs. 43 vs. 40	Metformin

Evidence Table 3. Key Question 1: Studies of exenatide and liraglutide

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Intermediate Outcomes HbA1c Weight (kg)	Health and Utilization Outcomes Microvascular Disease Macrovascular Disease Lower Extremity Ulcers All-Cause Mortality Quality of Life Hospitalization Medical Visits (diabetes) Other
Nauck, 2009 LEAD-2 26 weeks Multinational Novo Nordisk Fair	Mean change in HbA1c: G1: -0.7% (0.1) vs. G5 -0.8; 95% CI, -1.0 to -0.61 G2: -1.0% (0.1) vs. G5 -1.1; 95% CI, -1.3 to -0.9 vs. G4 0.0%; 95% CI, -0.2 to 0.2 G3: -1.0% (0.1) vs. G5 -1.1; 95% CI, -1.3 to -0.9 vs. G4 0.0%; 95% CI, -0.2 to 0.2 G4: -1.0% (0.1) vs. G5 -0.8; 95% CI, -1.0 to -0.61 G5: +0.1% (0.1) Mean change in weight: G1: -1.8 (0.2) kg vs. G4 *P* <0.0001 G2: -2.6 (0.2) kg vs. G4 *P* <0.0001 vs. G5 *P* ≤ 0.01 G3: -2.8 (0.2) kg vs. G4 *P* <0.0001 vs. G5 *P* ≤0.01 G4: +1.0 (0.2) kg G5: -1.5 (0.3) kg	NR

Evidence Table 3. Key Question 1: Studies of exenatide and liraglutide

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Inclusion and Exclusion Criteria	Overall Sample Size Interventions Group Sizes	Baseline Population Characteristics Mean Age, years Race/Ethnicity % Female	Background Medications
Feinglos, 2005 12 weeks US Novo Nordisk Poor	data not abstracted b/c of poor quality rating	N=210 (179 analyzed- per protocol)		
Placebo-controlled studies				
Gao, 2009 16 weeks Multiple, Asia Amylin Pharmaceuticals and Eli Lilly Good	Inclusion: Age 21-75, T2DM, treated with stable dose of metformin and/or sulfonylurea for at least 3 months, inadequate glycemic control (HbA1c >=7.0% and <=11.0%), BMI>21kg/m^2 and <35kg/m^2 Exclusion: Previous participation in any study using exenatide or GLP-1 analogs, participation in any study within 30 days, contraindications for metformin or sulfonylurea, treated with exogenous insulin for >1 week within 3 months, use of weight loss drugs within 1 month	N=472 randomized, 466 analyzed G1 (5ug [1st 4 weeks] to 10ug [12 weeks] exenatide twice daily + oral antidiabetic agents) n=234 G2 (placebo + oral antidiabetic agents) n=232	G1 :Age 55 (9); 100% Asian/Indian; Female 52% G2: Age 54 (9); 100% Asian/Indian; Female 59%	Metformin alone or metformin + sulfonylurea (usual dose)

Evidence Table 3. Key Question 1: Studies of exenatide and liraglutide

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Intermediate Outcomes HbA1c Weight (kg)	Health and Utilization Outcomes Microvascular Disease Macrovascular Disease Lower Extremity Ulcers All-Cause Mortality Quality of Life Hospitalization Medical Visits (diabetes) Other
Feinglos, 2005 12 weeks US Novo Nordisk Poor		
Placebo-controlled studies		
Gao, 2009 16 weeks Multiple, Asia Amylin Pharmaceuticals and Eli Lilly Good	Exenatide + oral antidiabetic vs. Placebo + oral antidiabetic HbA1c At week 16: -1.2% [-1.3, -1.1] vs. -0.4% [-0.5, -0.2] Weight at week 16: -1.2kg [-1.5, -0.9] vs. -0.1 [-0.3, 0.2] (NS)	NR

Evidence Table 3. Key Question 1: Studies of exenatide and liraglutide

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Inclusion and Exclusion Criteria	Overall Sample Size Interventions Group Sizes	Baseline Population Characteristics Mean Age, years Race/Ethnicity % Female	Background Medications
Gill, 2010 12 weeks Multinational Eli Lilly Fair	Inclusion: 18-75 y; Stable metformin dose for 30 days or TZD for 120 days; BMI >25 and < 40 kg/m2; HbA1c 6.5-9.5%; Body weight with ≤ 10% variation for 3 mo; stable antihypertensive regimens maintained ≥ 6wk Exclusion: History of clinically significant cardiac disease or cardiac disease within one year; Clinically significant arrhythmia; Resting heart rate <60 or>100 beats/minute; repeated systolic blood pressure > 1600 mm Hg or diastolic blood pressure > 100 mm Hg; current treatment with beta blockers	N = 54 G1: Exenatide (5-10mg/bid): n=28 G2: Placebo: n=26	G1: Age 57; Caucasian 86%, African 7%, East Asian 4%, Hispanic 4%, Female 32% G2: Age 54, Caucasian 96%, African 0%, East Asian 4%, Hispanic 0%; Female 58%	"Metformin (stable dose 30 days) or TZD (stable dose for 120 days)"

Evidence Table 3. Key Question 1: Studies of exenatide and liraglutide

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Intermediate Outcomes HbA1c Weight (kg)	Health and Utilization Outcomes Microvascular Disease Macrovascular Disease Lower Extremity Ulcers All-Cause Mortality Quality of Life Hospitalization Medical Visits (diabetes) Other
Gill, 2010 12 weeks Multinational Eli Lilly Fair	HbA1c -0.3 + 0.2% reduction in HbA1c for exenatide relative to placebo P=0.26 Weight: Mean change G1: -1.8 SD 0.4 kg, *P* <0.0001 G2: -0.3 SD 0.4 kg, *P* =0.52 Treatment difference: -1.5 SD 0.6 kg (*P* <0.05)	NR

Evidence Table 3. Key Question 1: Studies of exenatide and liraglutide

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Inclusion and Exclusion Criteria	Overall Sample Size Interventions Group Sizes	Baseline Population Characteristics Mean Age, years Race/Ethnicity % Female	Background Medications
Kadowaki, 2009 12 weeks Japan Amylin Pharmaceuticals and Eli Lilly Fair	Inclusion: 20-75 years, T2DM, weight >=50kg, been managing DM with sulfonylurea alone, sulfonylurea plus a biguanide, or sulfonylurea plus a TZD for at least 3 months, treatment with a-glucosidase inhibitor or meglitinide included after discontinuation; suboptimal glycemic control (HbA1c from 7%-10% for patients on sulfonylurea alone or sulfonylurea plus biguanide; 6.5-9.5% for patients treated with a-glucosidase inhibitor or meglitinide) Exclusion: Treatment with any exogenous insulin or drug directly affecting GI motility within last 3 months, clinically significant renal or hepatic disease, blood pressure >=160/100mm/Hg, hospitalization for cardiac disease within 1 year, clinically significant history of or active digestive disease within 1 year, active or untreated malignancy or remission from clinical malignancy for <5 years, hyperglycemia (self-monitored blood glucose >=250mg/dL fasting or >=350mg/dL anytime), >1 severe hypoglycemic episode requiring assistance within 3 months, pregnancy, no reliable birth control	N=153 randomized; 151 included in full analysis G1: (placebo + sulfonylurea/ sulfonyurea+biguanide/ sulfonylurea+TZD) n=40 G2: (2.5ug exenatide twice daily + sulfonylurea/ sulfonyurea+biguanide/ sulfonylurea+TZD) n=38 G3 (5ug exenatide twice daily + sulfonylurea/ sulfonyurea+biguanide/ sulfonylurea+TZD) n=37 G4 (5ug for 4 weeks then 10ug exenatide twice daily + sulfonylurea/ sulfonyurea+biguanide/ sulfonylurea+TZD) n=38	Age: G1 = 60.5 (10.2) G2 = 62.2 (7.8) G3 = 60.7 (9.8) G4 = 57.8 (10.4) 100% Japanese Female: G1 = 25.0% G2 = 29.7% G3 = 32.4% G4 = 37.8%	Sulfonylurea alone or with biguanise or TZD; patients using an a-glucosidase inhibitor or a meglitinide derivative could be included but were required to discontinue them before starting study drug

Evidence Table 3. Key Question 1: Studies of exenatide and liraglutide

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Intermediate Outcomes HbA1c Weight (kg)	Health and Utilization Outcomes Microvascular Disease Macrovascular Disease Lower Extremity Ulcers All-Cause Mortality Quality of Life Hospitalization Medical Visits (diabetes) Other
Kadowaki, 2009 12 weeks Japan Amylin Pharmaceuticals and Eli Lilly Fair	Placebo vs. Exenatide 2.5ug vs. Exenatide 5ug vs. Exenatide 10ug Mean (SE) change in HbA1c at 12 weeks: +0.02% (0.1) vs. -0.9% (0.1) vs. -1.2% (0.1) vs. -1.4% (0.1) Mean (SE) change in weight at 12 weeks: -0.7kg (0.2) vs. +0.08kg (0.2) vs. -0.2kg (0.3) vs. -1.3kg (0.3)	

Evidence Table 3. Key Question 1: Studies of exenatide and liraglutide

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Inclusion and Exclusion Criteria	Overall Sample Size Interventions Group Sizes	Baseline Population Characteristics Mean Age, years Race/Ethnicity % Female	Background Medications
Moretto, 2008 24 weeks United States, Puerto Rico, Romania, Russia, and India Amylin Pharamceuticals and Eli Lilly and Company Good	Inclusion: >18 years of age, T2DM, BMI of 25 to 45 kg/m2, manage T2DM with diet and exercise consistent with local standards of medical care, have HbA1c between 6.5% and 10.0%. (Female patients eligible if they were postmenopausal, surgically sterile, or using contraceptives for >12 weeks before screening and continuing throughout the study.) Exclusion: Ever been treated with an antidiabetic agent; blood pressure >160/>110mm Hg, history or presence of clinically significant cardiac disease within the year prior to inclusion in the study, history of renal transplant or active renal or hepatic disease, received any medication for weight loss within 12 weeks prior to screening.	N=232 G1: (Exenatide 5 ug bid) n=77 G2: (Exenatide 10 bid) n=78 G3: (Placebo) n=78 randomized, 77 analyzed	G1: 54 (10); White 65%, Asian 29%, Hispanice 6%, Black, 0%; Female 48% G2: 55 (10); White 72%, Asian 23%, Hispanic 1%, Black, 4%; Female 38% G3: 53 (9); White 66%, Asian 27%, Hispanice 3%, Black, 4%; Female 45%	None

Evidence Table 3. Key Question 1: Studies of exenatide and liraglutide

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Intermediate Outcomes HbA1c Weight (kg)	Health and Utilization Outcomes Microvascular Disease Macrovascular Disease Lower Extremity Ulcers All-Cause Mortality Quality of Life Hospitalization Medical Visits (diabetes) Other
Moretto, 2008 24 weeks United States, Puerto Rico, Romania, Russia, and India Amylin Pharamceuticals and Eli Lilly and Company Good	Exenatide 5ug vs. Exenatide 10ug vs. Placebo Mean (SE) change in HbA1c: -0.7% (0.1) vs. -0.9% (0.1) vs. -0.2% (0.1) *P* =0.003, G1 v G3; *P* <0.001, G2 v G3 Mean change in weight: -2.8 kg (0.3) vs. -3.1 kg (0.3) vs. -1.4 kg (0.2) *P* =0.004 G1 v G3; *P* <0.001 G2 v G3	

Evidence Table 3. Key Question 1: Studies of exenatide and liraglutide

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Inclusion and Exclusion Criteria	Overall Sample Size Interventions Group Sizes	Baseline Population Characteristics Mean Age, years Race/Ethnicity % Female	Background Medications
Seino, 2008 14 weeks Japan Novo Nordisk Good	Inclusion: T2DM treated with diet therapy with or without oral antidiabetic drug (OAD) monotherapy, HbA1c 7.0% and <10.0%, to be aged between 20 and 75 years and to have BMI <30 Exclusion: Insulin or insulin sensitizer within 16 weeks, or systemic corticosteroids, impaired hepatic or renal function;, congestive heart failure (New York Heart Association class III or IV), unstable angina pectoris or myocardial infarction within 12 months, uncontrolled hypertension (systolic blood pressure > 160 mmHg or diastolic blood pressure >100 mmHg), non-stabilised proliferative retinopathy or maculopathy.	N=226 G1: Liraglutide 0.1 mg n=45 G2: Liraglutide 0.3 mg n=46 G3: Liraglutide 0.6 mg n=45 G4: Liraglutide 0.9 mg n=44 G5: Placebo n=46	Age: G1: 56.5 SD 8.4 G2: 56.8 SD 8.8 G3: 60.0 SD 7.0 G4: 55.5 SD 7.6 G5: 57.5 SD 8.7 Race/Ethnicity: NR % Female G1: 31 G2: 30 G3: 38 G4: 30 G5: 37	None

Evidence Table 3. Key Question 1: Studies of exenatide and liraglutide

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Intermediate Outcomes HbA1c Weight (kg)	Health and Utilization Outcomes Microvascular Disease Macrovascular Disease Lower Extremity Ulcers All-Cause Mortality Quality of Life Hospitalization Medical Visits (diabetes) Other
Seino, 2008 14 weeks Japan Novo Nordisk Good	Liraglutide 0.1mg vs. Liraglutide 0.3mg vs. Liraglutide0.6 mg vs. Liraglutide 0.9 mg vs. Placebo Mean change from baseline, %HbA1c: -0.72 vs. -1.07 vs. -1.5 vs. -1.67 vs. +0.09 Mean change from baseline, Weight: -0.05 vs. +0.13 vs. -0.10 vs. -0.48 vs. -0.95	NR

Evidence Table 3. Key Question 1: Studies of exenatide and liraglutide

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Inclusion and Exclusion Criteria	Overall Sample Size Interventions Group Sizes	Baseline Population Characteristics Mean Age, years Race/Ethnicity % Female	Background Medications
Vilsboll, 2008 14 weeks Denmark, France, the Netherlands, Slovakia Novo Nordisk Poor	Inclusion/Exclusion: reported in a related article	N=39 G1: (placebo) n=10 randomized, 5 completed G2: (0.65mg liraglutide) n=8 randomized, 7 completed G3: (1.25mg liraglutide) n=10 randomized, 9 completed G4: (1.9mg liraglutide) n=11 randomized, 7 completed	G1: Placebo (n=5) Age = 55.4 (6.7) Race NR Female = 20% G2: Liraglutide 0.65mg (n=7) Age = 61.1 (7.6) Race NR Female = 0% G3: Liraglutide 1.25mg (n=9) Age = 56.9 (10.1) Race NR Female = 0% G4: Liraglutide 1.9mg (n=7) Age = 58.6 (10.3) Race NR Female = 14%	None

Evidence Table 3. Key Question 1: Studies of exenatide and liraglutide

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Intermediate Outcomes HbA1c Weight (kg)	Health and Utilization Outcomes Microvascular Disease Macrovascular Disease Lower Extremity Ulcers All-Cause Mortality Quality of Life Hospitalization Medical Visits (diabetes) Other
Vilsboll, 2008 14 weeks Denmark, France, the Netherlands, Slovakia Novo Nordisk Poor	Mean change at 14 weeks, HbA1c: G1 (N=5): +1.5 (1.8); G2 (N=7): -1.0 (0.8); G3 (N=9): -1.3 (0.7); G4 (N=7): -1.5 (0.7) Mean change, weight: G1: -4.0kg (4.8) G2: -1.3kg (2.0) G3: -2.4kg (2.4) G4: -2.8kg (2.7)	

Evidence Table 3. Key Question 1: Studies of exenatide and liraglutide

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Inclusion and Exclusion Criteria	Overall Sample Size Interventions Group Sizes	Baseline Population Characteristics Mean Age, years Race/Ethnicity % Female	Background Medications
Vilsboll, 2007 14 weeks Denmark, France, the Netherlands, Slovakia Novo Nordisk Fair	Inclusion: Age >=18 years; T2DM; HbA1c >=7.5% and <=10.0% (diet) or >=7.0% and <=9.5% (mono-oral antidiabetes drug); BMI<=40 (from a related article) Exclusion: NR	N=165 randomized, 163 exposed G1: (1.90mg liraglutide) n=41 G2: (1.25mg liraglutide) n=42 G3: (0.65mg liraglutide) n=40 G4: (placebo) n=40	G1: Age = 55.4 (11.4) Race NR Female = 27% G2: Age = 53.8 (10.7) Race NR Female = 45% G3: Age = 56.5 (9.3) Race NR Female = 33% G4: Age = 57.7 (8.2) Race NR Female = 53%	None

Evidence Table 3. Key Question 1: Studies of exenatide and liraglutide

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Intermediate Outcomes HbA1c Weight (kg)	Health and Utilization Outcomes Microvascular Disease Macrovascular Disease Lower Extremity Ulcers All-Cause Mortality Quality of Life Hospitalization Medical Visits (diabetes) Other
Vilsboll, 2007 14 weeks Denmark, France, the Netherlands, Slovakia Novo Nordisk Fair	Changes at 14 weeks, HbA1c: Overall: G1 = -1.45% SD NR G2 = -1.40% SD NR G3 = -0.98% SD NR G4 = +0.29% SD NR Vs. placebo: G1 = -1.74% [-2.18, -1.29]; G2 = -1.69% [-2.13, -1.24] G3 = -1.27% [-1.72, -0.82] Change in weight at 14 wks (vs placebo): G1 = -1.21 [-2.36, -0.06] G2 NS G3 NS	NR

Evidence Table 3. Key Question 1: Studies of exenatide and liraglutide

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Inclusion and Exclusion Criteria	Overall Sample Size Interventions Group Sizes	Baseline Population Characteristics Mean Age, years Race/Ethnicity % Female	Background Medications
Zinman, 2009 LEAD-4 26 weeks US and Canada Novo Nordisk Fair	Inclusion: T2DM, 18–80 years, had A1C between 7 and 11% (prestudy OAD monotherapy for 3 months) or 7–10% (prestudy combination OAD therapy for 3 months), and had BMI ≤45 kg/m2 Exclusion: Insulin treatment in previous 3 months(except shortterm treatment for intercurrent illness)	N=821 screened/enrolled N=533 randomized G1: Liraglutide 1.2 mg n= 178 G2: Liraglutide 1.8 mg n= 178 G3: Placebo n = 177	G1: Age 55, Caucasian 81, Black 15, Asian 1, Indian 1, Other 2, Female 43% G2: Age 55, Caucasian 83, Black 10, Asian 3, Indian 1, Other 3, Female 49% G3: Age 55, Caucasian84, Black 10, Asian 2, Indian 1, Other 3, Female 38%	Metformin and rosiglitazone
Apovian, 2010 24 weeks US Eli Lilly Fair	Inclusion: 8-75 years of age withn T2DM, treated for at least 6 weeks with a stable dose of metformin or a sulfonylurea, hemoglobin A1c (HbA1c) 6.6%-10.0%, body mass index 25-39.9 kg/m2, and history of stable body weight (not varying by >5% for at least 6 months Exclusion: Use of exogenous insulin, alpha-glucosidase inhibitors, a thiazolidinedione, weight loss agents within 6 months before study entry, evidence of poorly controlled hypertension within the previous 3 months, or history or presence of cardiac disease within 3 years	N = 194 G1: Exenatide n=96 G2: Placebo n=98	Age: G1: 54.5 G2: 55.1 Ethnicity: NR % Female: G1: 63 G2: 62	Yes

Evidence Table 3. Key Question 1: Studies of exenatide and liraglutide

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Intermediate Outcomes HbA1c Weight (kg)	Health and Utilization Outcomes Microvascular Disease Macrovascular Disease Lower Extremity Ulcers All-Cause Mortality Quality of Life Hospitalization Medical Visits (diabetes) Other
Zinman, 2009 LEAD-4 26 weeks US and Canada Novo Nordisk Fair	Mean (SE) change in HbA1c: G1: -1.5 (0.1%) G2: -1.5 (0.1%) G3: -0.5 (0.1%) Mean change in weight: G1: -1.0 (0.3) kg G2: -2.0 (0.3) kg G3: + 0.6 (0.3) kg G1 or G2 vs. G3 *P* <0.0001 G1 vs G2 *P* =0.011	Cardiovascular events: G1: 5 G2: 3 G3: 4
Apovian, 2010 24 weeks US Eli Lilly Fair	Mean change in HbA1c: G1: -1.2 G2: -0.7 Change in Weight: G1: -6.2 kg G2: -4.0 kg	NR

Evidence Table 4. Key Question 1: Studies of rosiglitazone and pioglitazone

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality Head-to-head studies	Inclusion and Exclusion Criteria	Overall Sample Size Interventions Group Sizes	Baseline Population Characteristics Mean Age, years Race/Ethnicity % Female	Background Medications
Brackenridge, 2009 Poor	data not abstracted because of poor quality rating			
Chogtu, 2009 12 weeks India Funding NR Poor	Inclusion: both genders; age 30-70; T2DM; perscribed glimeperide and required an add-on therapy for poor glycemic control, normotensive, not on antihypertensive or hypolipidaemic drugs Exclusion: NR	N=63 patients randomized G1: (pioglitazone, titrated dose + glimeperide 2mg/day) n=28 G2: (rosiglitazone, titrated dose + glimeperide 2mg/day) n=28	NR	Glimepiride

Evidence Table 4. Key Question 1: Studies of rosiglitazone and pioglitazone

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality Head-to-head studies	Intermediate Outcomes HbA1c	Health and Utilization Outcomes Microvascular Disease Macrovascular Disease Lower Extremity Ulcers All-Cause Mortality Quality of Life Hospitalization Medical Visits (diabetes) Other
Brackenridge, 2009 Poor		
Chogtu, 2009 12 weeks India Funding NR Poor	HbA1c: NR, states that decreases in A1c not significant between groups *P* >0.05	NR

Evidence Table 4. Key Question 1: Studies of rosiglitazone and pioglitazone

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Inclusion and Exclusion Criteria	Overall Sample Size Interventions Group Sizes	Baseline Population Characteristics Mean Age, years Race/Ethnicity % Female	Background Medications
Berneis, 2008 12 weeks Switzerland Government funding Poor	Inclusion: T2DM ≥ 6 months; HbA1c 6.5-9.0; maximum of two oral antidiabetic agents Exclusion: reated with insulin or glitazones, New York Heart Association stage class III/IV congestive heart failure, active neoplasia, unstable cardiovascular disease, severly impaired liver or kidney function	N=9 patients randomized NA; all one group. Patients randomized to either receive pioglitazone (30mg/day x 4 weeks followed by 45mg/day x 8 weeks) or rosiglitazone (4mg/day x 4 weeks followed by 8mg/day x 8 weeks). Then crossed-over to other group after washout	Identical groups (cross-over). Age: 61 Race: NR Female: 44.4%	NR

Evidence Table 4. Key Question 1: Studies of rosiglitazone and pioglitazone

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Intermediate Outcomes HbA1c	Health and Utilization Outcomes Microvascular Disease Macrovascular Disease Lower Extremity Ulcers All-Cause Mortality Quality of Life Hospitalization Medical Visits (diabetes) Other
Berneis, 2008 12 weeks Switzerland Government funding Poor	HbA1c: mean change after 12 weeks of treatment G1: -0.54 G2: -0.59 NS vs. baseline NS, G1 vs. G2	NR

Evidence Table 4. Key Question 1: Studies of rosiglitazone and pioglitazone

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Inclusion and Exclusion Criteria	Overall Sample Size Interventions Group Sizes	Baseline Population Characteristics Mean Age, years Race/Ethnicity % Female	Background Medications
Beysen, 2008 20 weeks US Funding NR Fair	Inclusion: T2D; HbA1c > 7.5 or fasting glucose > 180mg/dl; not controlled with metformin alone or metformin in combination with sulfonylurea; hypertriglyceridemia (150-400mg/dl) Exclusion: pregnancy; ALT>1.5 times normal upper limit; creatinine > 1.4mg/dl; congestive heart failure; history of coronary artery, pulmonary or neurological disesae; treatment with insulin; treatment with statin or fibric acid derivative within 2 months of study	N=12 patients randomized G1: (rosiglitazone 15-30mg/day x 4 weeks, 45mg/day x 16 weeks) n=6 G2: (pioglitazone 4mg/day x 4 weeks, 8mg/day x 16 weeks) n=6	G1: Age: 56 Race: NR Female: 66.7% G2: Age: 53 Race: NR Female: 50%	NR

Evidence Table 4. Key Question 1: Studies of rosiglitazone and pioglitazone

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Intermediate Outcomes HbA1c	Health and Utilization Outcomes Microvascular Disease Macrovascular Disease Lower Extremity Ulcers All-Cause Mortality Quality of Life Hospitalization Medical Visits (diabetes) Other
Beysen, 2008 20 weeks US Funding NR Fair	HbA1c: mean change after 20 weeks of treatment: G1: -1.3 (SD 0.8) G2: -1.1 (SD 0.6) *P* <0.05, G1/G2 vs. baseline NS, G1 vs. G2	NR

Evidence Table 4. Key Question 1: Studies of rosiglitazone and pioglitazone

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Inclusion and Exclusion Criteria	Overall Sample Size Interventions Group Sizes	Baseline Population Characteristics Mean Age, years Race/Ethnicity % Female	Background Medications
Vijay, 2009 16 weeks India UGC, India Fair	Inclusion: HbA1c > 8%; cardiovascular risk factors; age 30-70; BMI <36; stable body weight for 3 months prior to study Exclusion: Hepatic or other preexisting chronic disease; any smoking in 6 months prior to study; previous use of insulin or thiazonlidinediones; history of stroke; patients taking glucocorticoids or other drugs that affect glucose metabolism, lipid lowering drugs, alcohol, or psychoactive substances.	N=50 G1: (pioglitazone 30-45mg/day) n=20 G2: (rosiglitazone 4-8mg/day) n=20 G3: (controls (sulfonylureas/other secretagogues)) n=10	G1: Age: 48.1 Race/Ethnicity: NR Female: NR G2: Age: 47.75 Race/Ethinicity: NR Female: NR G3: Age: 49.7 Race/Ethnicity: NR Female: NR Study reports that overall the male/female ratio was 3:2	NR

Evidence Table 4. Key Question 1: Studies of rosiglitazone and pioglitazone

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Intermediate Outcomes HbA1c	Health and Utilization Outcomes Microvascular Disease Macrovascular Disease Lower Extremity Ulcers All-Cause Mortality Quality of Life Hospitalization Medical Visits (diabetes) Other
Vijay, 2009 16 weeks India UGC, India Fair	G1: -1.27 (SD NR) *P* =0.00, G1 vs. baseline G2: -1.26 (SD NR) *P* =0.00, G2 vs. baseline G3: -0.94 (SD NR) *P* =0.00, G3 vs. baseline NR, G1 vs. G2 vs. G3	NR

Evidence Table 4. Key Question 1: Studies of rosiglitazone and pioglitazone

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Inclusion and Exclusion Criteria	Overall Sample Size Interventions Group Sizes	Baseline Population Characteristics Mean Age, years Race/Ethnicity % Female	Background Medications
Oz, 2008 12 weeks Turkey Funding NR Fair	Inclusion: Newly diagnosed T2DM (<6 months) Exclusion: Impaired hepatic function or renal function; Serious cardiovascular disease including heart failure, history of myocardial infarction or stroke; Pregnant or breastfeeding women; Severe anemia	N=35 G1: (pioglitazone 30mg/day) n=14 G2: (rosiglitazone 4mg/day) n=11 G3: (placebo + medical nutrition therapy) n=10	Age: 55.2 Race/Ethnicity: NR Female: 49% NR by individual groups	NR
OZ Gul, 2010 12 weeks Turkey Funding NR Fair	Inclusion: Newly diagnosed type 2 diabetes mellitus (<6 months) naïve to prior antidiabetic therapy Exclusion: Taking statins, ACE inhibitors, ARBs; Acute complications with need for insulin therapy; Impaired hepatic function or renal function; Severe anemia; Serious cardiovascular disease including heart failure, history of myocardial infarction or stroke; Pregnant or breastfeeding women.	N=60 G1: (pioglitazone 30mg/day) n=19 G2: (rosiglitazone 4mg/day) n=20 G3: (placebo + medical nutrition therapy) n=21	Age: 56.4 Race/Ethnicity: Turkish 100% Female: 42% NR by individual groups	None

Evidence Table 4. Key Question 1: Studies of rosiglitazone and pioglitazone

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Intermediate Outcomes HbA1c	Health and Utilization Outcomes Microvascular Disease Macrovascular Disease Lower Extremity Ulcers All-Cause Mortality Quality of Life Hospitalization Medical Visits (diabetes) Other
Oz, 2008 12 weeks Turkey Funding NR Fair	G1: -1.22 (SD NR) *P* =0.003, G1 vs. baseline G2: -0.8 (SD NR) *P* =0.019, G2 vs. baseline G3: 0.06 (SD NR) NS, G3 vs. baseline NR, G1/G2 vs. G3	NR
OZ Gul, 2010 12 weeks Turkey Funding NR Fair	HbA1c: mean change at 12 weeks: G1: -1.1 (SD NR) *P* <0.001, G1 vs. baseline G2: -1.1 (SD NR) *P* =0.003, G2 vs. baseline G3: -0.1 (SD NR) NS, G3 vs. baseline NR, G1/G2 vs. G3	NR

Evidence Table 4. Key Question 1: Studies of rosiglitazone and pioglitazone

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Inclusion and Exclusion Criteria	Overall Sample Size Interventions Group Sizes	Baseline Population Characteristics Mean Age, years Race/Ethnicity % Female	Background Medications
Active-control studies				
Erdem, 2008 12 weeks Turkey Gulthane School of Medicine Poor	Inclusion: age between 30 and 70 years, body mass index (BMI) less than 35 kg/m2, no other illnesses including liver failure, renal failure, heart failure or other chronic disease as determined by history, physical examination, and screening tests Exclusion: NR	N=53 patients randomized G1: (pioglitazone 15mg/day, titrated up to 45 mg in 15mg increments if mean serum glc >110 mg/dL) n=21 G2: (Metformin, 1000mg/day; up to 2000mg if mean serum glc >110mg/dL) n=23	G1: Age: 54.9 Race: NR Female: 62% G2: Age: 55.1 Race: NR Female: 52%	NR

Evidence Table 4. Key Question 1: Studies of rosiglitazone and pioglitazone

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Intermediate Outcomes HbA1c	Health and Utilization Outcomes Microvascular Disease Macrovascular Disease Lower Extremity Ulcers All-Cause Mortality Quality of Life Hospitalization Medical Visits (diabetes) Other
Active-control studies		
Erdem, 2008 12 weeks Turkey Gulthane School of Medicine Poor	Change in HbA1c at 12 weeks: G1: -.74, calculated G2: -0.59, calculated. G1 vs baseline: *P* =0.01 G2 vs baseline: *P* =0.02	NR

Evidence Table 4. Key Question 1: Studies of rosiglitazone and pioglitazone

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Inclusion and Exclusion Criteria	Overall Sample Size Interventions Group Sizes	Baseline Population Characteristics Mean Age, years Race/Ethnicity % Female	Background Medications
DeFronzo, 2010 20 weeks USA Eli Lilly Fair	Inclusion: age 18 –75 years, BMI 25–40 kg/m2, stable body weight for at least 6 months prior to screening, A1C 6.8–10.0%, stable dose of metformin for at least 6 weeks prior to screening and no treatment with any other antidiabetic medication, and absence of islet cell autoantibodies. Exclusion: NR	N = 137 G1: Exenatide 10mcg N = 45 G2: Exenatide 10mcg + Rosiglitazone 4mcg N = 47 G3: Rosglitazone 4mg N = 45	Baseline characteristics not reported for each arm. For entire study population: Mean age 56 yrs 61% white 49% female	Metformin

Evidence Table 4. Key Question 1: Studies of rosiglitazone and pioglitazone

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Intermediate Outcomes HbA1c	Health and Utilization Outcomes Microvascular Disease Macrovascular Disease Lower Extremity Ulcers All-Cause Mortality Quality of Life Hospitalization Medical Visits (diabetes) Other
DeFronzo, 2010 20 weeks USA Eli Lilly Fair	Change in HbA1c G1: -0.9 (0.1) G2: -1.3 (0.1) G3: -1.0 (0.1) G1 vs. G2 *P* = 0.016 G1 vs. G3 *P* = 0.720 G3 vs. G2 *P* = 0.039 Change in weight G1: -2.8 (0.5) G2: -1.2 (0.5) G3: +1.5 (0.5) G1 vs. G2 *P* = 0.038 G1 vs. G3 *P* < 0.001 G3 vs. G2 *P* < 0.001	NR

Evidence Table 4. Key Question 1: Studies of rosiglitazone and pioglitazone

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Inclusion and Exclusion Criteria	Overall Sample Size Interventions Group Sizes	Baseline Population Characteristics Mean Age, years Race/Ethnicity % Female	Background Medications
Gerstein, 2010 APPROACH 18 months Multinational GlaxoSmithKline Fair	Inclusion: 30-80y; established T2DM; clinically indicated coronary angiography or percutaneous coronary intervention; ≥ atherosclerotic plaque with 10%-50% luminal narrowing in a coronary artery that had not undergone intervention and if their DM was treated with either lifestyle approaches alone or with oral agents. Exclusion: ST-segment elevation myocardial infarction in past 30 days; coronary artery bypass graft surgery; severe valvular heart disease; left ventricular efection fraction <40%; any heart failure NY Heart Association class I-IV; systolic blood pressure >170 mmHG or diastolic blood pressure > 100 mm Hg; serum creatinine ≥ 1.5 mg/dL for men; serum creatinine ≥ 1.4 mg/dL for women; active liver disease	N = 672 G1: Glipizide (10-15mg/d) N = 339 G2: Rosiglitazone (4-8mg/d) N = 333	G1: Age 60.2, Race NR, Female 34.2% G2: Age 61.8, Race NR, Female 30.0% Age, G1 vs. G2, p = 0.03	Metformin max 2550 mg/d and once-daily basal insulin or both if needed to maintain a HbA1c of ≤ 7%

Evidence Table 4. Key Question 1: Studies of rosiglitazone and pioglitazone

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Intermediate Outcomes HbA1c	Health and Utilization Outcomes Microvascular Disease Macrovascular Disease Lower Extremity Ulcers All-Cause Mortality Quality of Life Hospitalization Medical Visits (diabetes) Other
Gerstein, 2010 APPROACH 18 months Multinational GlaxoSmithKline Fair	Change in HbA1c G1: -0.2 SD NR G2: -0.3 SD NR G1 vs. G2, *P* = 0.44	Composite of all-cause death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, or hospitalization for myocardial ischemia, No. of patients (%): G1: 38 (11.2) G2: 39 (11.7) G1 vs. G2, *P* = 0.58 Composite of cardiovascualr death, nonfatal myocardial infarction, or nonfatal stroke, No. of patients (%) G1: 10 (2.9) G2: 14 (4.2) G1 vs. G2, *P* = 0.31 Cardiovascular Death, No. of patients (%) G1: 3 (0.9) G2: 4 (1.2) G1 vs. G2, *P* =0.50

Evidence Table 4. Key Question 1: Studies of rosiglitazone and pioglitazone

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Intermediate Outcomes HbA1c	Health and Utilization Outcomes Microvascular Disease Macrovascular Disease Lower Extremity Ulcers All-Cause Mortality Quality of Life Hospitalization Medical Visits (diabetes) Other
Gerstein, 2010 cont'd		Myocardial Infarction, No. of patients (%) - Nonfatal G1: 6 (1.8) G2: 7 (2.1) G1 vs. G2, *P* =0.71 Myocardial Infarction, No. of patients (%) - Fatal G1: 1 (0.3) G2: 1 (0.3) G1 vs. G2, *P* =0.89 Stroke, No. of patients (%) - Nonfatal G1: 1 (0.3) G2: 5 (1.5) G1 vs. G2,*P* = 0.13

Evidence Table 4. Key Question 1: Studies of rosiglitazone and pioglitazone

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Intermediate Outcomes HbA1c	Health and Utilization Outcomes Microvascular Disease Macrovascular Disease Lower Extremity Ulcers All-Cause Mortality Quality of Life Hospitalization Medical Visits (diabetes) Other
Gerstein, 2010 cont'd		Stroke, No. of patients (%) - Fatal G1: 0 (0) G2: 0 (0) G1 vs. G2, *P* = NR Coronary Revascularization No. of patients (%) - G1: 27 (8.0) G2: 26 (7.8) G1 vs. G2, *P* = 0.82 All cause mortality: No. of patients (%) G1: 7 (2.1) G2: 8 (2.4) G1 vs. G2, *P* =0.72
Gerstein, 2010 cont'd		Hospitalization for myocardial ischemia, No. of patients (%) G1: 7 (2.1) G2: 11 (3.3) G1 vs. G2, p = 0.25 Congestive heart failure, No. of patients (%) G1: 3 (0.9) G2: 8 (2.4) G1 vs G2 P = 0.14

Evidence Table 4. Key Question 1: Studies of rosiglitazone and pioglitazone

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Inclusion and Exclusion Criteria	Overall Sample Size Interventions Group Sizes	Baseline Population Characteristics Mean Age, years Race/Ethnicity % Female	Background Medications
Kadoglou, 2010 14 weeks Greece European Social Fund and National Resources - PYTHAGORAS II & Alexander S Onassis Public Benefit Foundation Fair	Inclusion: 50-70 y; T2DM; treated with metformin (850 mg/d) alone for ≥ 4 mo; HbA1c > 6.5%; BMI > 25 kg/m2 Exclusion: Creatinine > 2mg/dL; Alanine amino transferase > 3 times higher than the upper normal limit; congestive heart failure (NY Heart Association II-IV); Prior TZD treamtent; >5% change in body weight for up to 4 mo prior study initiation.	N = 100 G1: Rosiglitazone(8 mg/d) + Metformin (850 mg/d) N= 50 analyzed = 49 G2: Metformin (titration from 850 mg/d - 2550 mg/d) N = 50 analyzed = 48	G1: Age 62, Race NR, Female 74% G2: Age 62.7, Race NR, Female 67%	Metformin 850 mg/d

Evidence Table 4. Key Question 1: Studies of rosiglitazone and pioglitazone

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Intermediate Outcomes HbA1c	Health and Utilization Outcomes Microvascular Disease Macrovascular Disease Lower Extremity Ulcers All-Cause Mortality Quality of Life Hospitalization Medical Visits (diabetes) Other
Kadoglou, 2010 14 weeks Greece European Social Fund and National Resources - PYTHAGORAS II & Alexander S Onassis Public Benefit Foundation Fair	Change in HbA1c (calculated change from baseline) G1: -0.87 SD NR, *P* <0.001 G2: -0.54 SD NR, *P* = 0.014 G1 vs. G2, *P* =0.291	NR

Evidence Table 4. Key Question 1: Studies of rosiglitazone and pioglitazone

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Inclusion and Exclusion Criteria	Overall Sample Size Interventions Group Sizes	Baseline Population Characteristics Mean Age, years Race/Ethnicity % Female	Background Medications
Kato, 2009 12 weeks Japan NR Fair	Inclusion: Recent diagnosis of T2DM associated with metabolic syndrome; Abdominal ultrasound determining fatty liver; no history of treamtne with oral antihyperglycemic drugs, antihyperlipidemic drugs, or antihypertensive drugs. Exclusion: Diabetic retinopathy, nephropathy, or neuropathy whose condition was unstable or underwent sudden progression; Aspartate aminotransferase or alanin aminotransferase > 1.5 times the upper limit of normal level; serum creatinine > 133 µmol/L; anemia; myocardial infar4ction; angina pectoris; congestive heart failure; history of cerebrovascular disease.	N = 50 G1:Pioglitazone (15mg/d) N = 25 G2: Metformin (500 mg/d) N = 25	G1: Age 51.4, Race NR, Female 52% G2: Age 58.6, Race NR, Female 44%	All patients received diet therapy and exercise therapy. Parameters: total energy intake within 1200-1800kcal, fat ration of caloric intake to < 25-30% and to do ≥ 150 min of exercise per wk.

Evidence Table 4. Key Question 1: Studies of rosiglitazone and pioglitazone

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Intermediate Outcomes HbA1c	Health and Utilization Outcomes Microvascular Disease Macrovascular Disease Lower Extremity Ulcers All-Cause Mortality Quality of Life Hospitalization Medical Visits (diabetes) Other
Kato, 2009 12 weeks Japan NR Fair	Change in HbA1c Change from baseline [%] G1: -1.05 (*P* <0.01 within group) G2: -0.83 (*P* <0.01 within group) *P* = NS between groups	NR

Evidence Table 4. Key Question 1: Studies of rosiglitazone and pioglitazone

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Inclusion and Exclusion Criteria	Overall Sample Size Interventions Group Sizes	Baseline Population Characteristics Mean Age, years Race/Ethnicity % Female	Background Medications
Papathanassiou, 2009 6 months Greece Funding NR Fair	Inclusion: T2DM treated only with metformin for 6 months prior to study; HbA1c > 6.5%; normal liver enzymes and renal function Exclusion: History of coronary artery, cerebrovascular, or peripheral vascular disease; chronic heart failure; liver or renal disease; anemia; thyroid dysfunction; and the new onset of any medications within the previous 8 weeks.	N=28 G1: (glimepiride 4mg/day) n=14 G2: (pioglitazone 30mg/day) n=14	G1: Age: 63.6 Race/Ethnicity: NR Female: 78.6% G2: Age: 62.8 Race/Ethnicity: NR Female: 78.6%	Metformin

Evidence Table 4. Key Question 1: Studies of rosiglitazone and pioglitazone

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Intermediate Outcomes HbA1c	Health and Utilization Outcomes Microvascular Disease Macrovascular Disease Lower Extremity Ulcers All-Cause Mortality Quality of Life Hospitalization Medical Visits (diabetes) Other
Papathanassiou, 2009 6 months Greece Funding NR Fair	G1: -0.56 (SD 0.57) G2: -0.60 (SD 0.85) *P* =0.398, G1 vs. G2	NR

Evidence Table 4. Key Question 1: Studies of rosiglitazone and pioglitazone

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Inclusion and Exclusion Criteria	Overall Sample Size Interventions Group Sizes	Baseline Population Characteristics Mean Age, years Race/Ethnicity % Female	Background Medications
Perez, 2009 24 weeks Multinational Takeda Fair	Inclusion: 18 y; TWDM; baseline HbA1c ≥ 7.5% but ≤ 10.0%; treatment -naïve; BMI ≤ 45 kg/m2; received counseling on lifestyle modification for T2DM including diet and exercise Exclusion:Type 1 diabetes; NY Heart Association Class II or IV heart failure; history of myocardial infarction, cerebrovascular accident, percutaneous coronary intervention, coronary arter bypass graft, transient ischemic attach within 6 mo; serum creatinine level males ≥ 1.5 mg/dL; serum creatinine level females ≥ 1.4 mg/dL; triglyceride level >500mg/dL; ALT level > 2.5 times upper limit of normal; active liver disease; jaundice; discontinuation from TZD or metformin therapy due to lack of efficacy; clinical or laboratory signs of intolerance of TZD or metformin; pregnant; intent to become pregnant; lactating during the study period.	N = 600 G1: Pioglitazone (15mg) + Metformin (850mg) bid: N = 201 G2: Pioglitazone (15mg) bid M = 189 G3: Metformin (850mg) bid N = 210	Overall: Age 54.1, American Indian 32%, Asian 2.2%, Black 6.5%, White 89.0%, Multiracial 29.7%, Hispanic/Latino 25.5%, Non-hispanic/non-Latino 20.7% Female 57.7% G1: Age 54.7, American Indian 31.3%, Asian 1.5%, Black 6.0%, White 91.5%, Multiracial 30.3%, Hispanic/Latino 24.4%, Non-hispanic/non-Latino 20.9% Female 55.2% G2: Age 54.0, American Indian 32.8%, Asian 2.6%, Black 6.9%, White 87.3%, Multiracial 29.6%, Hispanic/Latino 25.9%, Non-hispanic/non-Latino 19.0% Female 65.1% G3: Age 53.7, American Indian 31.9%, Asian 2.4%, Black 6.7%, White 88.1%, Multiracial 29.0%, Hispanic/Latino 26.2%, Non-hispanic/non-Latino 21.9% Female 53.3%	None

Evidence Table 4. Key Question 1: Studies of rosiglitazone and pioglitazone

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Intermediate Outcomes HbA1c	Health and Utilization Outcomes Microvascular Disease Macrovascular Disease Lower Extremity Ulcers All-Cause Mortality Quality of Life Hospitalization Medical Visits (diabetes) Other
Perez, 2009 24 weeks Multinational Takeda Fair	% Change in HbA1c G1: -1.83% SD NR G2: -0.96% SD NR G3: -0.99% SD NR G1 vs. G2, *P* < 0.0001 G1 vs. G3, *P* < 0.0001	Coronary Artery Disease (No. of patients) G1: 0 G2: 2 G3: 0 Myocardial Infarction(No. of patients) G1: 0 G2: 1 G3: 0 Anterior bundle Branch Block (No. of patients) G1: 0 G2: 1 G3: 0 Myocardial Ischemia (No. of patients) G1: 0 G2: 0 G3: 1

Evidence Table 4. Key Question 1: Studies of rosiglitazone and pioglitazone

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Inclusion and Exclusion Criteria	Overall Sample Size Interventions Group Sizes	Baseline Population Characteristics Mean Age, years Race/Ethnicity % Female	Background Medications
Petrica, 2009 Poor	data not abstracted because of poor quality rating			
Rigby, 2010 16 weeks Multinational Daiichi Sankyo Fair	Inclusion: Male and female; 18-80; T2DM diagnosis; HbA1c 7.0% - 10.0%; Taking a dose of metformin 1500-2550 mg/d; LDl cholesterol ≥ 60 mg/dL; Triglycerides < 500 mg/dL Exclusion: LDL Cholesterol < 60 mg/dL; Triglycerides ≥ 500 mg/dL; BMI > 40kg/m2; History of type 1 DM; Ketoacidosis; Insulin therapy > 2mo; dysphagia; swallowing disorders; intestinal motility disorders; pancreatitis; AIDS/HIV; drug or alcohol abuse w/in 2 yrs; Allergic/toxic response to colesevelam; Current treatment with TZD, colesevelam, or FDCP including metformin; Pulmonary, hepatic, gastrointestinal, uncontrolled endocrine/metabolic, hematologic/oncologic, neruologic, or psychiatric disease; Acute coronary syndrome, coronary intervention, congestive heart failure, transient ischemic attack within 3 mo; hospitalization within 14 days; participation in a weight-loss program or intensive exercise program	N = 169 G1: Rosiglitazone (4mg/d) N = 56 G2: Sitagliptin (100 mg/d) N = 56 G3: Colesevelam (3.75 g/d) N = 57	G1: Age 54.7; White 28.6%, Black 3.6%, Asian 0%, Hispanic 67.9%, Multiple 0%, Other 0%; Female 58.9% G2: Age 54.8; White 23.2%, Black 1.8%, Asian 0%, Hispanic 73.2%, Multiple 0%, Other 1.8%; Female 64.3%	Metformin (1500-2550 mg/d)

Evidence Table 4. Key Question 1: Studies of rosiglitazone and pioglitazone

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Intermediate Outcomes HbA1c	Health and Utilization Outcomes Microvascular Disease Macrovascular Disease Lower Extremity Ulcers All-Cause Mortality Quality of Life Hospitalization Medical Visits (diabetes) Other
Petrica, 2009 Poor		
Rigby, 2010 16 weeks Multinational Daiichi Sankyo Fair	Change in HbA1c Least-squares mean change from baseline (95% CI): G1: -0.6% (-0.83 to -0.32), *P* < 0.001 G2: -0.4% (-0.64 to -0.13), *P* = 0.009	NR

Evidence Table 4. Key Question 1: Studies of rosiglitazone and pioglitazone

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Inclusion and Exclusion Criteria	Overall Sample Size Interventions Group Sizes	Baseline Population Characteristics Mean Age, years Race/Ethnicity % Female	Background Medications
Tolman, 4039 Poor	data not abstracted because of poor quality rating			
Tsuchiya, 2009 Poor	data not abstracted because of poor quality rating			
Van der Meer, 2009 PIRAMID 24 weeks The Netherlands Eli Lilly, Takeda Good	Inclusion: Men with uncomplicated T2DM; ages 45-65; HbA1c 6.5-8.5; BMI 25 to 32; Blood pressure lower than 150/85 Exclusion: Any clinically significant disorder; particularly any history of cardiovascular or liver disease or diabetes-related complications; any prior use of thiazolidinediones or insulin.	N=78 G1: (pioglitazone 30mg/day) n=39 G2: (metformin 2000mg/day) n=39	G1: Age: 56.8 Race/Ethnicity: NR Female: 0% G2: Age: 56.4 Race/Ethinicity: NR Female: 0%	Glimepiride monotherapy, titrated during the 10-week run-in period
Schernthaner, 2004 Quarter Study 12 months Multinational Funding NR Good	Inclusion: age 35–75 ; T2DM; inadequately treated with diet alone, HbA1c between 7.5% and 11% with stable or worsening glycemic control for at least 3 months Exclusion: prior use of glucose-lowering pharmacotherapy; specific contraindications to either drug	N=1199 randomized G1: (pioglitazone 30-45mg/day + placebo) n=597 G2: (metformin up to 850mg-2550mg/day + placebo) n=597	G1: Age: 57 Race: NR Female: 47.4% G2: Age: 56 Race: NR Female: 42.2%	None

Evidence Table 4. Key Question 1: Studies of rosiglitazone and pioglitazone

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Intermediate Outcomes HbA1c	Health and Utilization Outcomes Microvascular Disease Macrovascular Disease Lower Extremity Ulcers All-Cause Mortality Quality of Life Hospitalization Medical Visits (diabetes) Other
Tolman, 4039 Poor		
Tsuchiya, 2009 Poor		
Van der Meer, 2009 PIRAMID 24 weeks The Netherlands Eli Lilly, Takeda Good	G1: -0.6 (SD NR) *P* <0.001, G1 vs. baseline G2: -0.7 (SD NR) *P* <0.001, G2 vs. baseline *P* =0.146, G1 vs. G2	NR
Schernthaner, 2004 Quarter Study 12 months Multinational Funding NR Good	G1: -1.41 (SD 0.04) G2: -1.50 (SD 0.04) 90% CI (-0.01, 0.19), difference between G1 vs. G2	Microvascular disease: Albumin:Cr ratio G1: -19% G2: -1% *P* =0.002, G1 vs. G2 All-cause Mortality G1: n=3 G2: n=2

Evidence Table 4. Key Question 1: Studies of rosiglitazone and pioglitazone

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Inclusion and Exclusion Criteria	Overall Sample Size Interventions Group Sizes	Baseline Population Characteristics Mean Age, years Race/Ethnicity % Female	Background Medications
Kusaka, 2008 4 months Japan Funding NR Fair	Inclusion: T2DM; inadequate glucose control Exclusion: cardiovascular disease; apparent liver or kidney disease; severe diabetic complications	N=35 patients randomized G1: (metformin 750mg/day) n=17 G2: (pioglitazone 15-30mg/day) n=16	G1: Age: 60 Race: NR Female: 41.2% G2: Age: 64 Race: NR Female: 43.8%	Patients stayed on sulfonylurea if on them (82% and 75%, respectively)
Nissen, 2008 PERISCOPE 18 months Multinational Takeda Pharmaceuticals Fair	Inclusion: age 35-85; HbA1c 6.0-9.0 (if taking glucose-lowering meds) and 6.5-10.0 (if not); one angiographic stenosis at least 20% narrowing; a "target vessel" for ultrasound was required to have less than 50% obstruction throughout a 40mm or longer segment Exclusion: T1DM; 3 or more antidiabetic meds; received any TZD within 12 weeks; serum creatinine > 2.0mg/dL; triglycerides > 500mg/dl; blood pressure >160/100 despite therapy; active liver disease; left main coronary artery stenosis more than 50%;	N=547 patients randomized G1 (glimepiride titrated): 273 randomized, 181 included in primary analysis G2 (pioglitazone titrated): 274 randomized, 179 included in primary analysis	G1: Age: 59.7 Race: White 80.6%, Black 9.9%, Asian 5.9%, Native American 3.7%; Female: 34.1% G2: Age: 60.0 Race: White 83.3%, Black 11.1%, Asian 4.4%, Native American 1.1% Female: 31.1%	Patients stayed on baseline therapy (unless a TZD or sulfonylurea)

Evidence Table 4. Key Question 1: Studies of rosiglitazone and pioglitazone

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Intermediate Outcomes HbA1c	Health and Utilization Outcomes Microvascular Disease Macrovascular Disease Lower Extremity Ulcers All-Cause Mortality Quality of Life Hospitalization Medical Visits (diabetes) Other
Kusaka, 2008 4 months Japan Funding NR Fair	HbA1cmean change at 4 months: G1: -1.0 (SD NR) G2: -1.1 (SD NR) *P* <0.0005, G1&G2 vs. baseline significance NR for G1 vs. G2	NR
Nissen, 2008 PERISCOPE 18 months Multinational Takeda Pharmaceuticals Fair	HbA1c mean change (95% CI at 18 months): G1: -0.36 (-0.48, -0.24) G2: -0.55 (-0.68, -0.42) *P* =0.03, G1 vs. G2	All-cause Mortality G1: n=2 G2: n=3

Evidence Table 4. Key Question 1: Studies of rosiglitazone and pioglitazone

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Inclusion and Exclusion Criteria	Overall Sample Size Interventions Group Sizes	Baseline Population Characteristics Mean Age, years Race/Ethnicity % Female	Background Medications
Marre, 2009 LEAD-1SU 26 weeks Multinational Novo Nordisk Fair	Inclusion: T2DM treated with oral glucose-lowering agents (OGLAs) for ≥ 3 months; 18–80 years of age; HbA1c 7.0–11.0% (previous OGLA monotherapy) or 7.0–10.0% (previous OGLA combination therapy); body mass index (BMI) ≤ 45.0 kg/m 2. Exclusion: Insulin within 3 months, impaired liver or renal function, uncontrolled hypertension (≥ 180/100 mmHg), cancer or used any drugs apart from OGLAs likely to affect glucose concentrations	N=1041 G1: (liraglutide 0.6 mg) n=233 G2: (liraglutide 1.2 mg) n=228 G3: (liraglutide 1.8 mg) n=234 G4: (placebo) n=114 G5: (rosiglitizone) n=232	Age: 56 Race/Ethnicity: NR % Female: G1: 46 G2: 55 G3: 47 G4: 53 G5: 53	glimepiride (2-4 mg)
Bao, 2009 48 weeks China Government funding Poor	Inclusion: newly diagnosed T2D; no previous treatment with hypoglycemic agents or lipid drugs, HbA1c > 6.5 during wash out period Exclusion: NR	N=82 patients randomized G1 (repaglinide 1.5-6mg/day): n=35 G2 (metformin 0.75-1.5mg/day): n=22 G3: (rosiglitazone 4-8mg/day): n=25	NR	NR

Evidence Table 4. Key Question 1: Studies of rosiglitazone and pioglitazone

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Intermediate Outcomes HbA1c	Health and Utilization Outcomes Microvascular Disease Macrovascular Disease Lower Extremity Ulcers All-Cause Mortality Quality of Life Hospitalization Medical Visits (diabetes) Other
Marre, 2009 LEAD-1SU 26 weeks Multinational Novo Nordisk Fair	HbA1c G1: -0.6% vs. placebo -0.8% (-1.1, -0.6) *P* <0.0001 G2: -1.1% vs. placebo -1.3% (1.5, -1.1) *P* <0.0001 G3: -1.1% vs. placebo -1.4% (1.6, -1.1) *P* <0.0001 G4: +0.2% G5: -0.4% vs. placebo -0.7% (-0.9, -0.4) *P* <0.0001	NR
Bao, 2009 48 weeks China Government funding Poor	HbA1c: mean change at 48 weeks: G1: -2.15 (SD NR) G2: -1.92 (SD NR) G3: -2.47 (SD NR) *P* <0.01, G1/G2/G3 vs. baseline NS, G1 vs. G2 vs. G3	NR

Evidence Table 4. Key Question 1: Studies of rosiglitazone and pioglitazone

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Inclusion and Exclusion Criteria	Overall Sample Size Interventions Group Sizes	Baseline Population Characteristics Mean Age, years Race/Ethnicity % Female	Background Medications
Pop-Busui, 2009 6 months US GlaxoSmithKline, Eli Lilly, Research Foundations Fair	Inclusion: Subjects with T2DM without known coronary artery disease; HbA1c between 6% and 9%; treatment with diet/exercise or sulfonylurea therapy or insulin < 20 U/d; If previously on metformin, 4-wk washout period prior to study. Exclusion: NR	N = 27 G1: (rosiglitazone 8mg/day) n=14 G2: (glyburide 10mg/day) n=13	Age: 49.5 Race/Ethnicity: NR Female: 48% NR by individual groups	NR
Turkmen Kemal, 2007 Poor	data not abstracted because of poor quality rating			

Evidence Table 4. Key Question 1: Studies of rosiglitazone and pioglitazone

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Intermediate Outcomes HbA1c	Health and Utilization Outcomes Microvascular Disease Macrovascular Disease Lower Extremity Ulcers All-Cause Mortality Quality of Life Hospitalization Medical Visits (diabetes) Other
Pop-Busui, 2009 6 months US GlaxoSmithKline, Eli Lilly, Research Foundations Fair	G1: - 0.5 (SD NR) G2: -0.9 (SD NR) NS, G1 vs. G2	NR
Turkmen Kemal, 2007 Poor		

Evidence Table 4. Key Question 1: Studies of rosiglitazone and pioglitazone

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Inclusion and Exclusion Criteria	Overall Sample Size Interventions Group Sizes	Baseline Population Characteristics Mean Age, years Race/Ethnicity % Female	Background Medications
von Bibra, 2008 16 weeks (32-week cross-over) Germany Funding NR Fair	Inclusion: T2DM of relative short duration; taking metformin monotherapy; age 35-75; BMI 25-35; HbA1c 6.5-9%; no major complications of macrovascular disease; normal left ventricular function by 2-dimensional echocardiography; blood pressure normal or <140/90 if treated; cholesterol <250 mg/dL; triglyceride <250mg/dL; no microvascular complications and no albuminuria Exclusion: Atrial fibrillation; ischemic heart disease; severe left ventricular hypertrophy; history or signs of heart failure; hepatic, or renal insufficiency	N=12 G1: (rosiglitazone 8mg/day) n=12 G2: (glimpiride 3mg/day) n=12	Age: 59 y Race/Ethnicity: NR Female: 33.3%	Metformin and other previous medications continued

Evidence Table 4. Key Question 1: Studies of rosiglitazone and pioglitazone

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Intermediate Outcomes HbA1c	Health and Utilization Outcomes Microvascular Disease Macrovascular Disease Lower Extremity Ulcers All-Cause Mortality Quality of Life Hospitalization Medical Visits (diabetes) Other
von Bibra, 2008 16 weeks (32-week cross-over) Germany Funding NR Fair	HbA1c: G1: -0.4 (SD NR) *P* =0.208, G1 vs. baseline G2: -0.2 (SD NR) *P* =0.196, G2 vs. baseline NR, G1 vs. G2	

Evidence Table 4. Key Question 1: Studies of rosiglitazone and pioglitazone

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Inclusion and Exclusion Criteria	Overall Sample Size Interventions Group Sizes	Baseline Population Characteristics Mean Age, years Race/Ethnicity % Female	Background Medications
Iliadis, 2007 18 weeks Greece Funding NR Poor	Inclusion: recently diagnosed T2DM (<3years); not on any anti-diabetic medication; fasting hyperglycemia after 1 month of intensive dietary intervention Exclusion: renal and liver impairment	48 patients randomized, 41 patients included in analysis G1 (diet alone): n=12 G2 (diet + rosiglitazone 8mg/day): n=14 G3 (diet + metformin 1700mg/day): n=15	G1: Age: 58.0 Race: NR Female: NR G2: Age: 56.3 Race: NR Female: NR G3: Age: 57.8 Race: NR Female: NR	none

Evidence Table 4. Key Question 1: Studies of rosiglitazone and pioglitazone

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Intermediate Outcomes HbA1c	Health and Utilization Outcomes Microvascular Disease Macrovascular Disease Lower Extremity Ulcers All-Cause Mortality Quality of Life Hospitalization Medical Visits (diabetes) Other
Iliadis, 2007 18 weeks Greece Funding NR Poor	HbA1C mean change at 18 weeks: G1: -0.6 (SD 1.8) G2: -1.0 (SD 0.7) G3: -1.7 (SD 1.1) NS, G1 vs. baseline *P* <0.01, G2 vs. baseline *P* <0.001, G3 vs. baseline NR, G1 vs. G2 vs. G3	

Evidence Table 4. Key Question 1: Studies of rosiglitazone and pioglitazone

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Inclusion and Exclusion Criteria	Overall Sample Size Interventions Group Sizes	Baseline Population Characteristics Mean Age, years Race/Ethnicity % Female	Background Medications
Home, 2009 RECORD 7 year study, mean follow up time 5.5 years Multinational GlaxoSmithKline Fair	Inclusion: age between 40-75; BMI > 25; being on maximum tolerated doses of metformin or a sulfonylurea monotherapy Exclusion: hospitalizations for a major cardiovascular event in prior 3 months; planned cardiovascular intervention; presence, history or treatment for heart failure	N=4458 randomized G1 (addition of rosiglitazone) n=2,220 G1a (rosiglitazone + metformin) n=1,117 G1b (rosiglitazone + sulfornylurea) n=1,103 G2 (metformin + sulfonylurea) n=2,227 G2a (background metformin) n=1,105 G2b (background sulfonylurea) n=1,122	G1a: Age: 57.0; White 98.9%, Other 1.1%; Female 46.2% G1b: Age: 59.8; White 99.3%, Other 0.7%; Female 51.0% G2a: Age: 57.2; White 98.4%; Other 1.6%; Female 47.1% G2b: Age: 59.7; White 99.1%; Other 0.9%; Female 49.4%	all patients stayed on their metformin or sulfonylurea that they used as monotherapy

Evidence Table 4. Key Question 1: Studies of rosiglitazone and pioglitazone

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Intermediate Outcomes HbA1c	Health and Utilization Outcomes Microvascular Disease Macrovascular Disease Lower Extremity Ulcers All-Cause Mortality Quality of Life Hospitalization Medical Visits (diabetes) Other
Home, 2009 RECORD 7 year study, mean follow up time 5.5 years Multinational GlaxoSmithKline Fair	HbA1c mean change at 5 years: G1a: -0.28 (SD 0.03) G2a: 0.01 (SD 0.04) *P* <0.0001, G1a vs. G2a G1b: -0.44 (SD 0.03) G2b: -0.18 (0.04) *P* <0.0001, G1b vs. G2b	Cardiovascular death or hospitalization: G1: n=321 G2: n=323 HR = 0.99 (0.85-1.16) CV death: G1: n=60 G2: n=71 HR 0.84 (0.59-1.18) Myocardial infarction: G1: n=64 G2: n=56 HR 1.14 (0.80-1.63) Stroke: G1: n=46 G2: n=63 HR: 0.72 (0.49-1.06) All-cause Mortality G1: n=136 G2: n=157 HR 0.86 (0.68-1.08)

Evidence Table 4. Key Question 1: Studies of rosiglitazone and pioglitazone

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Inclusion and Exclusion Criteria	Overall Sample Size Interventions Group Sizes	Baseline Population Characteristics Mean Age, years Race/Ethnicity % Female	Background Medications
Kiyici, 2009 12 months Turkey Funding NR Fair	Inclusion: age 30-65; baseline HbA1c<8; BMI < 40 Exclusion: usage of any medications for T2DM before study; presence of cardiovascular, gastrointestinal, hepatic, renal, rhematologic, neoplastic, infectious or other endocrine diseases (except hyperlipidemia), micro or macrovascular complications of diabetes, previous history of substance abuse	N=50 randomized G1 (medical nutrition therapy): n=15 G2 (metformin + medical nutrition therapy): n=16 G3 (rosiglitazone + medical nutrition therapy): n=19	G1: Age: 52.1; Race NR; Female NR G2: Age: 52.4; Race NR; Female NR G3: Age 50.7; Race NR; Female NR	none
Scott, 2008 18 weeks Multinational Merck Fair	Inclusion: age 18-75; taking metformin monotherapy >1500mg/day for a t least 10 weeks prior to screening; HbA1c 7-11% Exclusion: T1DM; insulin use within 8 weeks of the screening visit; contraindications for use of TZDs or metformin; impaired renal function, ALT or AST levels more than 2-fold the upper limit of normal, fasting glucose values >270mg/dl	N=273 randomized G1 (placebo): n=92 G2 (sitagliptin 100mg/day): n=94 G3 (rosiglitazone 8mg/day): n=87	G1: Age: 55.3; White 61%, Asian 39%, Other 0%; Female 41% G2: Age: 55.2; White 61%, Asian 38%, Other 1%; Female 45% G3: Age: 54.8; White 59%, Asian 38%, Other 3%; Female 37%	metformin

Evidence Table 4. Key Question 1: Studies of rosiglitazone and pioglitazone

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Intermediate Outcomes HbA1c	Health and Utilization Outcomes Microvascular Disease Macrovascular Disease Lower Extremity Ulcers All-Cause Mortality Quality of Life Hospitalization Medical Visits (diabetes) Other
Kiyici, 2009 12 months Turkey Funding NR Fair	HbA1c mean change at 12 months: G1: +0.1 (SD NR) G2: -0.3 (SD NR) G3: -0.7 (SD NR) *P* =0.014, G2/G3 vs. G1	NR
Scott, 2008 18 weeks Multinational Merck Fair	HbA1c mean change from baseline (95% CI): G1: -0.22 (-0.36, -0.08) G2: -0.73 (-0.87, -0.60) G2 vs. G1: -0.51 (-0.70, -0.32) G3: -0.79 (-0.92, -0.65) G3 vs. G1: -0.57 (-0.76, -0.37) G3 vs. G2: -0.06 (-0.25, 0.14)	NR

Evidence Table 4. Key Question 1: Studies of rosiglitazone and pioglitazone

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Inclusion and Exclusion Criteria	Overall Sample Size Interventions Group Sizes	Baseline Population Characteristics Mean Age, years Race/Ethnicity % Female	Background Medications
Hamann, 2008 52 weeks Multinational Funding NR Fair	Inclusion: BMI ≥ 25 T2DM; HbA1c 7-10; received metfromin for at least 8 weeks prior to screening Exclusion: used any oral diabetic drug other than metformin in last 12 weeks; insulin at any time other than pregnancy or emergency; history of metabolic acidosis; edema requiring treatment; anemia; renal or hepatic disease; known congestive heart failure; unstable or severe angina; history of myocardial infarction; angioplasty; coronary artery bypass graft; stroke within 3 months; left ventricular dysfunction within 6 monhts; fasting C-peptide ≤ 0.5nmol/L; systolic blood pressure > 170; diastolic > 100	818 entered run-in, 596 randomized G1: (rosiglitazone 4mg/day + metformin 2g/day) n=294 G2: (sulfonylurea (glibenclamide 5mg/day or glicazide 80mg/day + metformin 2g/day) n=288 All medications uptitrated	G1: Age 58.5; 94% white, 6% other; Female 47% G2: Age 59.3; 95% white, 5% other; Female 48%	Metformin

Evidence Table 4. Key Question 1: Studies of rosiglitazone and pioglitazone

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Intermediate Outcomes HbA1c	Health and Utilization Outcomes Microvascular Disease Macrovascular Disease Lower Extremity Ulcers All-Cause Mortality Quality of Life Hospitalization Medical Visits (diabetes) Other
Hamann, 2008 52 weeks Multinational Funding NR Fair	HbA1c mean change at 52 weeks: G1: -0.78 (SD 0.06) G2: -0.86 (SD 0.06) treatment difference: 0.09 (-0.08, 0.25), NS	All-cause Mortality G1: n=2 G2: n=2

Evidence Table 4. Key Question 1: Studies of rosiglitazone and pioglitazone

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Inclusion and Exclusion Criteria	Overall Sample Size Interventions Group Sizes	Baseline Population Characteristics Mean Age, years Race/Ethnicity % Female	Background Medications
Nauck, 2009 LEAD-1 / LEAD-2 26 weeks Multinational Funding NR Fair (subset of LEAD1 and LEAD2 studies)	Inclusion: age 18-80; T2DM treated with monotherapy and had HbA1c between 7-11% on oral antidiabetic monotherapy for 3 months or between 7 - 10% on combination oral antidiabetic therapy for 3 months. Exclusion: patients on combination therapy (although these were in original trial); insulin use within 3 months; impaired liver or renal function; blood pressure ≥ 180/100; cancer; use of drugs besides antidiabetic drugs likely to affect glucose	N=386 patients from 2 other RCTs G1 (liglutinide 1.8mg + glimepiride): n=63 G2 (placebo + glimepiride): n=37 G3 (rosiglitazone + glimepiride): n=73 G4 (liraglutide 1.8mg + metformin): n=83 G5 (placebo + metformin): n=41 G6 (glimepiride + metformin): n=89	G1: Age 55.6; White 68.3%, Black 3.2%, Asian 28.6%, Other 0%; Female 47.6% G2: Age 55.8; White 75.7%, Black 0%, Asian 24.3%, Other 0%; Female 45.9% G3: Age: 57.1; White 68.5%, Black 2.7%, Asian 27.7%, Other 1.4%; Female 53.4% G4: Age 55.3; White 86.7, Black 4.8%, Asian 8.4%, Other 0%; Female 44.6% G5: Age 54.2; White 82.9%, Black 4.9%, Asian 12.2%, Other 0%; Female 41.5% G6: Age 56.4; White 87.6%, Black 2.2%, Asian 10.1%, Other 0%; Female 39.3%	In LEAD-1 (Arms 1-3), background glimepiride In LEAD-2 (Arms 4-6), background metformin

Evidence Table 4. Key Question 1: Studies of rosiglitazone and pioglitazone

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Intermediate Outcomes HbA1c	Health and Utilization Outcomes Microvascular Disease Macrovascular Disease Lower Extremity Ulcers All-Cause Mortality Quality of Life Hospitalization Medical Visits (diabetes) Other
Nauck, 2009 LEAD-1 / LEAD-2 26 weeks Multinational Funding NR Fair (subset of LEAD1 and LEAD2 studies)	mean change at 26 weeks: G1: -1.4 (SD NR) G2: -0.3 (SD NR) G3: -0.8 (SD NR) *P* <0.0001, G1 vs. G2 *P* <0.0001, G1 vs. G3 G4: -1.3 (SD NR) G5: -0.4 (SD NR) G6: -1.2 (SD NR) *P* <0.0001, G4 vs. G5 Non-inferior, G4 vs. G6	NR

Evidence Table 5. Key Question 1: Studies of fixed-dose combination products and dual therapy

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Inclusion and Exclusion Criteria	Overall Sample Size Interventions Group Sizes	Baseline Population Characteristics Mean Age, years Race/Ethnicity % Female	Background Medications
Active-control studies				
Derosa, 2009 The 60's study 12 months Italy Funding NR Fair	Inclusion: >18yrs, T2DM, treatment naïve, HbA1c> 6.5, BMI 25-30 Exclusion: ketoacidosis; unstable or rapidly progressive retinopathy, nephropathy or neuropathy; impared liver function; impaired kidney function; anemia; New York Heart Association class I-IV congestive heart failure, history of myocardial infarction or stroke; cerebrovascular conditions within 6 months; women who were pregnant or childbearing potential not taking adequate contraceptive precautions	N=271 randomized G1 (pioglitazone 15mg/day): n=69 G2 (metformin 1000mg/day): n=67 G3 (pioglitazone 15mg/day + metformin 850mg/day): n=69 G4 (glimepiride 2mg/day + metformin 850mg/day): n=66	G1: Age: 54; White 100%; Female 53.6% G2: Age: 55; White 100%; Female 49.3% G3: Age: 57; White 100%; Female 50.7% G4: Age: 57.7; White 100%; Female 51.5%	NR
McCluskey, 2004 20 weeks US Funding NR Fair	Inclusion: T2DM ≥ 1 year; age 18-80; managed on rosiglitazone 4 or 8mg for at least 2 months; HbA1c 7.5-9.5; BMI 26-42; fasting C-peptide ≥ 0.27 nmol/L; fasing plasma glucose 126-235 mg/dl Exclusion: require insulin therapy; receiving other sulfonylureas; history of sulfonylurea hypersensitivity; rosiglitazone dose increased within 2 months; body weight increases >2% (for patients weighing ≤ 250 lbs. or >3% (for patients weighing > 250 lbs.) during the stabilization period; clinically abnormal baseline values	N=40 patients randomized G1 (Glimeperide 8mg/day + rosiglitazone 4 or 8mg/day): n=25 G2 (placebo + rosiglitazone 4 or 8mg/day): n=15	G1: Age: 60.2; White 96%, Other 4%; Female 56% G2: Age: 50.8; White 80%, Other 20%; Female 60%	NR

Evidence Table 5. Key Question 1: Studies of fixed-dose combination products and dual therapy

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Intermediate Outcomes HbA1c	Health and Utilization Outcomes Microvascular Disease Macrovascular Disease Lower Extremity Ulcers All-Cause Mortality Quality of Life Hospitalization Medical Visits (diabetes) Other
Active-control studies		
Derosa, 2009 The 60's study 12 months Italy Funding NR Fair	HbA1c mean change at 15 months: G1: -1.0 (SD NR) G2: -1.2 (SD NR) G3: -2.1 (SD NR) G4: -1.2 (SD NR) *P* <0.01, all groups vs. baseline (*P* <0.001 for G3) *P* <0.05, G3 vs. G2 *P* <0.01, G3 vs. G1	NR
McCluskey, 2004 20 weeks US Funding NR Fair	mean change at 20 weeks: G1: -1.2 (SD 0.1) G2: -0.3 (SD 0.2) *P* <0.001, G1 vs. G2	

Evidence Table 5. Key Question 1: Studies of fixed-dose combination products and dual therapy

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Inclusion and Exclusion Criteria	Overall Sample Size Interventions Group Sizes	Baseline Population Characteristics Mean Age, years Race/Ethnicity % Female	Background Medications
Stewart, 2006 32 weeks Multinational GlaxoSmithKline Fair	Inclusion: 18-70 years old; T2DM; drug naïve subjects with fasting plasma glucose 7-9 mmol/l and HbA1c 7.0-9.0 mmol/l or treated with monotherapy with fasting plasma glucose 6-8mmol/l and HbA1c 6.5-8.0. Prior to visit 2 all subjects must have had fasting plasma glucose 7.0-9.0 mmol/l Exclusion: prior exposure to TZDs within 6 months; use of insulin; unstable or severe angina; coronary insufficiency; New York Heart Association class I-IV congestive heart failure; blood pressure > 170/100 while on anti-hypertensive treatment	N=526 patients randomized, 509 in ITT population G1 (rosiglitazone titrated up to 8mg day/ metformin titrated to 2000mg day): n=254 G2 (Metformin titrated up to 3000mg): n=272	G1: Age 58.9; White 98%, Asian 1%, Hispanic <1%, African American 0%, Native Hawaiian/other Pacific Islander 0%; Female 45% G2: Age: 59.0; White 99%, Asian <1%, Hispanic <1%, African American <1%, Native Hawaiian/other Pacific Islander <1%; Female 44%	None

Evidence Table 5. Key Question 1: Studies of fixed-dose combination products and dual therapy

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Intermediate Outcomes HbA1c	Health and Utilization Outcomes Microvascular Disease Macrovascular Disease Lower Extremity Ulcers All-Cause Mortality Quality of Life Hospitalization Medical Visits (diabetes) Other
Stewart, 2006 32 weeks Multinational GlaxoSmithKline Fair	change at 32 weeks: G1: -0.51% (SD NR) G2: -0.38% (SD NR) *P* =0.0357, G1 vs. G2	Macrovascular disease Myocardial Infarction: G1: 1 G2: 0 *P* =NR Angina Pectoris G1: 2 G2: 0 *P* =NR Myocardial ischaemia: G1: 1 G2: 0 *P* =NR

Evidence Table 5. Key Question 1: Studies of fixed-dose combination products and dual therapy

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Inclusion and Exclusion Criteria	Overall Sample Size Interventions Group Sizes	Baseline Population Characteristics Mean Age, years Race/Ethnicity % Female	Background Medications
Weissman, 2005 EMPIRE 24 weeks US GlaxoSmithKline Fair	Inclusion: age 18-75; T2DM; HbA1c 6.5-8.5 for subjects with prior treatment, 7-10 for drug naïve subjects; fasting plasma glucose 7.0-15.0mmol/l; BMI ≥ 27; previous therapy could include diet, exercise or oral therapy (acarbose, sulfonylurea, metformin or metformin + sulfonylurea); metformin dose must have been ≤ 1000mg/day for at least 3 months prior to study; subjects must have stopped TZD at least 3 months prior to screening Exclusion: uncontrolled hypertension; congestive heart failure requiring treatment; severe angina; anemia or severe edema associated with TZDs; active or chronic metabolic acidosis; clinically significant renal or hepatic disease; prior insulin use within 3 months; subjects non-compliant with metformin up-titration	N=766 randomized, 709 in ITT population G1 (rosiglitazone titrated to 8mg/day + metformin 1000mg/day): n=358 ITT G2 (metformin titrated to 2000mg/day): n=351 ITT	G1: Age: 55.5 Race/Female: NR G2: Age: 55.7 Race/Female: NR	NR

Evidence Table 5. Key Question 1: Studies of fixed-dose combination products and dual therapy

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Intermediate Outcomes HbA1c	Health and Utilization Outcomes Microvascular Disease Macrovascular Disease Lower Extremity Ulcers All-Cause Mortality Quality of Life Hospitalization Medical Visits (diabetes) Other
Weissman, 2005 EMPIRE 24 weeks US GlaxoSmithKline Fair	mean change from baseline (95% CI): G1: -0.93 (-1.06, -0.80) G2: -0.71 (-0.83, -0.60) non-inferior, G1 vs. G2	Macrovascular disease Myocardial Infarction (withdrew): G1: 2 G2: 0 Coronary artery disease (withdrew): G1: 0 G2: 1 Cardiac Ischemia: G1: 5 (1.3%) G2: 3(0.8%)

Evidence Table 5. Key Question 1: Studies of fixed-dose combination products and dual therapy

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Inclusion and Exclusion Criteria	Overall Sample Size Interventions Group Sizes	Baseline Population Characteristics Mean Age, years Race/Ethnicity % Female	Background Medications
Goldstein, 2006 EMPIRE 24 weeks US GlaxoSmithKline Fair	Inclusion: Age 18-75; HbA1c of 6.5-8.5% for subjects having received prior combination treatment and 7-10% for drug-naive or monotherapy subjects; fasting plasma glucose 126-270mg/dL; BMI >=27kg/m2; previous treatment with either diet & exercise or with oral therapy with metformin (<=1,000mg/day for at least 3 months prior to study), either as monotherapy or in combination with a sulfonylurea. Exclusion: Uncontrolled hypertension; congestive heart failure requiring treatment, severe angina, clinically significant renal or hepatic disease; active or chronic metabolic acidosis; receipt of insulin or TZD in 3 months prior to study; history of anemia or severe edema associatyed with TZD therapy; non-compliance with metformin during run-in period.	N=122 G1: (rosiglitazone 4mg/day up-titrated to 8mg/day at week 8 + metformin 1,000mg day) n=71 G2: (metformin 1,500mg/day up-titrated to 2,000mg/day at week 8) n=51	Age: G1 = 54.6 G2 = 56.0 Race (%): Caucasian: G1 = 71.8 G2 = 66.7 Black: G1 = 7.0 G2 = 5.9 Hispanic: G1 = 16.9 G2 = 25.5 Other: G1 = 4.2 G2 = 2.0 % Female: G1 = 49.3 G2 = 35.3	NR

Evidence Table 5. Key Question 1: Studies of fixed-dose combination products and dual therapy

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Intermediate Outcomes HbA1c	Health and Utilization Outcomes Microvascular Disease Macrovascular Disease Lower Extremity Ulcers All-Cause Mortality Quality of Life Hospitalization Medical Visits (diabetes) Other
Goldstein, 2006 EMPIRE 24 weeks US GlaxoSmithKline Fair	At 24 weeks: G1 = -0.61% (1.16) G2 = -0.65% (1.18)	

Evidence Table 6. Key Question 1: Quality assessment of trials for Key Question 1

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Randomization adequate? Yes, No, NR	Allocation concealment adequate? Yes, No, NR	Groups similar at baseline? Yes, No, NR	Outcome assessors masked? Yes, No, NR	Care provider masked? Yes, No, NR	Patient masked? Yes, No, NR	Run-in/Washout? Yes, No, NR
Bergenstal, 2009 Novo-Log Mix vs Exenatide Study Group 24 weeks United States Novo Nordisk Poor	Yes	Yes	Yes	No	No	No	No
Brodows, 2008 Duration NR Eli Lilly and Amylin Pharmaceuticals Poor	NR	No	Yes	No	No	No	NR
Buse, 2009 LEAD-6 26 weeks Mulitnational Novo Nordisk Fair	Yes	Yes	Yes	No	No	No	Yes
Feinglos, 2005 12 weeks US Novo Nordisk Poor	NR	NR	Yes	NR	NR	Yes	Yes

Evidence Table 6. Key Question 1: Quality assessment of trials for Key Question 1

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Overall attrition high (>20%)? Yes, No, NR	Loss to follow-up differential high (>15%)? Yes, No, NR	Outcome measures (ascertainment) equal, valid, and reliable? Yes, No, Mixed	Intention-to-treat (ITT) analysis? Yes, No, NR, Modified ITT	Post-randomization exclusions? Yes, No, NR
Bergenstal, 2009 Novo-Log Mix vs Exenatide Study Group 24 weeks United States Novo Nordisk Poor	Yes	No	Yes	NR	Yes
Brodows, 2008 Duration NR Eli Lilly and Amylin Pharmaceuticals Poor	Yes	No	Yes	No	Yes
Buse, 2009 LEAD-6 26 weeks Mulitnational Novo Nordisk Fair	No	No	Yes	Yes	No
Feinglos, 2005 12 weeks US Novo Nordisk Poor	No	Yes	Yes	No	Yes

Evidence Table 6. Key Question 1: Quality assessment of trials for Key Question 1

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Randomization adequate? Yes, No, NR	Allocation concealment adequate? Yes, No, NR	Groups similar at baseline? Yes, No, NR	Outcome assessors masked? Yes, No, NR	Care provider masked? Yes, No, NR	Patient masked? Yes, No, NR	Run-in/Washout? Yes, No, NR
Gao, 2009 16 weeks Multiple, Asia Amylin Pharmaceuticals and Eli Lilly Good	Yes	NR	Yes	NR	Yes	Yes	Yes
Garber, 2009 LEAD-3 MoNo 52 weeks US and Mexico Novo Nordisk Fair	Yes	NR	Yes	NR	NR	Yes	Yes
Kadowaki, 2009 12 weeks Japan Amylin Pharmaceuticals and Eli Lilly Fair	Yes	Yes	Yes	NR	Yes	Yes	Yes
Madsbad, 2004 12 weeks Scandanavia and the UK Novo Nordisk Fair	NR	NR	Yes	NR	NR	Yes	Yes

Evidence Table 6. Key Question 1: Quality assessment of trials for Key Question 1

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Overall attrition high (>20%)? Yes, No, NR	Loss to follow-up differential high (>15%)? Yes, No, NR	Outcome measures (ascertainment) equal, valid, and reliable? Yes, No, Mixed	Intention-to-treat (ITT) analysis? Yes, No, NR, Modified ITT	Post-randomization exclusions? Yes, No, NR
Gao, 2009 16 weeks Multiple, Asia Amylin Pharmaceuticals and Eli Lilly Good	No	No	Yes	Modified ITT	Yes
Garber, 2009 LEAD-3 MoNo 52 weeks US and Mexico Novo Nordisk Fair	Yes	No	Yes	Yes	NR
Kadowaki, 2009 12 weeks Japan Amylin Pharmaceuticals and Eli Lilly Fair	No	No	Yes	No	Yes
Madsbad, 2004 12 weeks Scandanavia and the UK Novo Nordisk Fair	No	Yes	Yes	Modified ITT	No

Evidence Table 6. Key Question 1: Quality assessment of trials for Key Question 1

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Randomization adequate? Yes, No, NR	Allocation concealment adequate? Yes, No, NR	Groups similar at baseline? Yes, No, NR	Outcome assessors masked? Yes, No, NR	Care provider masked? Yes, No, NR	Patient masked? Yes, No, NR	Run-in/Washout? Yes, No, NR
Moretto, 2008 24 weeks United States, Puerto Rico, Romania, Russia, and India Amylin Pharamceuticals and Eli Lilly and Company Good	Yes	Yes	Yes	NR	Yes	Yes	Yes
Nauck, 2009 LEAD-2 26 weeks Multinational Novo Nordisk Fair	Yes	NR	Yes	NR	NR	Yes	Yes
Russel-Jones, 2009 LEAD-5 26 weeks Multinational Novo Nordisk Good	Yes	Yes	Yes	Yes	Yes	Yes	Yes
SeiNo, 2008 14 weeks Japan Novo Nordisk Good	Yes	Yes	Yes	Yes	NR	Yes	Yes

Evidence Table 6. Key Question 1: Quality assessment of trials for Key Question 1

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Overall attrition high (>20%)? Yes, No, NR	Loss to follow-up differential high (>15%)? Yes, No, NR	Outcome measures (ascertainment) equal, valid, and reliable? Yes, No, Mixed	Intention-to-treat (ITT) analysis? Yes, No, NR, Modified ITT	Post-randomization exclusions? Yes, No, NR
Moretto, 2008 24 weeks United States, Puerto Rico, Romania, Russia, and India Amylin Pharamceuticals and Eli Lilly and Company Good	No	No	Yes	Modified ITT	Yes
Nauck, 2009 LEAD-2 26 weeks Multinational Novo Nordisk Fair	No	Yes	Yes	Modified ITT	No
Russel-Jones, 2009 LEAD-5 26 weeks Multinational Novo Nordisk Good	No	No	Yes	Yes	NR
SeiNo, 2008 14 weeks Japan Novo Nordisk Good	No	No	Yes	Modified ITT	No

Evidence Table 6. Key Question 1: Quality assessment of trials for Key Question 1

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Randomization adequate? Yes, No, NR	Allocation concealment adequate? Yes, No, NR	Groups similar at baseline? Yes, No, NR	Outcome assessors masked? Yes, No, NR	Care provider masked? Yes, No, NR	Patient masked? Yes, No, NR	Run-in/Washout? Yes, No, NR
Vilsboll, 2007 14 weeks Denmark, France, the Netherlands, Slovakia Novo Nordisk Fair	NR	NR	Yes	NR	Yes	Yes	Yes
Vilsboll, 2008 14 weeks Denmark, France, the Netherlands, Slovakia Novo Nordisk Poor	NR	NR	No	NR	Yes	Yes	Yes
Zinman, 2009 LEAD-4 26 weeks US and Canada Novo Nordisk Fair	Yes	NR	Yes	Yes	NR	Yes	Yes
Riddle, 2009 24 weeks US Amylin Pharmaceuticals Fair	Yes	Yes	Yes	No	No	No	No

Evidence Table 6. Key Question 1: Quality assessment of trials for Key Question 1

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Overall attrition high (>20%)? Yes, No, NR	Loss to follow-up differential high (>15%)? Yes, No, NR	Outcome measures (ascertainment) equal, valid, and reliable? Yes, No, Mixed	Intention-to-treat (ITT) analysis? Yes, No, NR, Modified ITT	Post-randomization exclusions? Yes, No, NR
Vilsboll, 2007 14 weeks Denmark, France, the Netherlands, Slovakia Novo Nordisk Fair	No	No	Yes	Modified ITT	Yes
Vilsboll, 2008 14 weeks Denmark, France, the Netherlands, Slovakia Novo Nordisk Poor	Yes	No	Yes	No	Yes
Zinman, 2009 LEAD-4 26 weeks US and Canada Novo Nordisk Fair	Yes	Yes	Yes	Modified ITT	Yes
Riddle, 2009 24 weeks US Amylin Pharmaceuticals Fair	No	No	Yes	Modified ITT	Yes

Evidence Table 6. Key Question 1: Quality assessment of trials for Key Question 1

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Randomization adequate? Yes, No, NR	Allocation concealment adequate? Yes, No, NR	Groups similar at baseline? Yes, No, NR	Outcome assessors masked? Yes, No, NR	Care provider masked? Yes, No, NR	Patient masked? Yes, No, NR	Run-in/Washout? Yes, No, NR
Chacra, 2009 CV181-040 24 weeks Multinational Bristol-Myers Squibb and AstraZeneca Fair	Yes	Yes	Yes	NR	Yes	Yes	Yes
Rosenstock, 2009 CV181-011 Study 24 weeks US Bristol-Myers Squibb and Astra Zeneca Fair	NR	NR	Yes	Yes	Yes	Yes	Yes
Rosenstock, 2008 12 weeks Multinational Bristol-Myers Squibb Fair	NR	NR	Yes	NR	Yes	Yes	Yes
DeFronzo, 2009 Saxagliptin CV181-014 Study 24 weeks Multinational Bristol-Myers Squibb & AstraZeneca Fair	Yes	NR	Yes	NR	Yes	Yes	Yes

Evidence Table 6. Key Question 1: Quality assessment of trials for Key Question 1

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Overall attrition high (>20%)? Yes, No, NR	Loss to follow-up differential high (>15%)? Yes, No, NR	Outcome measures (ascertainment) equal, valid, and reliable? Yes, No, Mixed	Intention-to-treat (ITT) analysis? Yes, No, NR, Modified ITT	Post-randomization exclusions? Yes, No, NR
Chacra, 2009 CV181-040 24 weeks Multinational Bristol-Myers Squibb and AstraZeneca Fair	Yes	No	Yes	No	Yes
Rosenstock, 2009 CV181-011 Study 24 weeks US Bristol-Myers Squibb and Astra Zeneca Fair	Yes	No	Yes	Modified ITT	Yes
Rosenstock, 2008 12 weeks Multinational Bristol-Myers Squibb Fair	No	No	Yes	Modified ITT	Yes
DeFronzo, 2009 Saxagliptin CV181-014 Study 24 weeks Multinational Bristol-Myers Squibb & AstraZeneca Fair	Yes	Yes	Yes	Modified ITT	Yes

Evidence Table 6. Key Question 1: Quality assessment of trials for Key Question 1

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Randomization adequate? Yes, No, NR	Allocation concealment adequate? Yes, No, NR	Groups similar at baseline? Yes, No, NR	Outcome assessors masked? Yes, No, NR	Care provider masked? Yes, No, NR	Patient masked? Yes, No, NR	Run-in/Washout? Yes, No, NR
Hollander, 2009 CV181-013 24 weeks US Bristol-Meyers Squibb and AstraZeneca Fair	Yes	Yes	Yes	NR	Yes	Yes	Yes
Williams-Herman, 2009 54 weeks Williams-Herman, 2010 104 weeks Multinational Merck Fair	NR	Yes	Yes	Yes	Yes	Yes	Yes
Chan, 2008 54 weeks Multinational Merck Fair	Yes	NR	Yes	Yes	Yes	Yes	Yes
Hanefeld, 2007 Sitagliptin Study 014 12 weeks Multinational Fair	Yes	NR	Yes	Yes	Yes	Yes	Yes

Evidence Table 6. Key Question 1: Quality assessment of trials for Key Question 1

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Overall attrition high (>20%)? Yes, No, NR	Loss to follow-up differential high (>15%)? Yes, No, NR	Outcome measures (ascertainment) equal, valid, and reliable? Yes, No, Mixed	Intention-to-treat (ITT) analysis? Yes, No, NR, Modified ITT	Post-randomization exclusions? Yes, No, NR
Hollander, 2009 CV181-013 24 weeks US Bristol-Meyers Squibb and AstraZeneca Fair	Yes	No	Yes	Modified ITT	Yes
Williams-Herman, 2009 54 weeks Williams-Herman, 2010 104 weeks Multinational Merck Fair	Yes	Yes	Yes	Modified ITT	No
Chan, 2008 54 weeks Multinational Merck Fair	Yes	No	Yes	Modified ITT	Yes
Hanefeld, 2007 Sitagliptin Study 014 12 weeks Multinational Fair	No	Yes	Yes	Modified ITT	Yes

Evidence Table 6. Key Question 1: Quality assessment of trials for Key Question 1

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Randomization adequate? Yes, No, NR	Allocation concealment adequate? Yes, No, NR	Groups similar at baseline? Yes, No, NR	Outcome assessors masked? Yes, No, NR	Care provider masked? Yes, No, NR	Patient masked? Yes, No, NR	Run-in/Washout? Yes, No, NR
Nonaka, 2008 12 weeks Japan Banyu Pharmaceuticals (Merck) Good	NR	Yes	NR	Yes	Yes	Yes	No
Mohan, 2009 18 weeks China, India, Korea Merck Good	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Raz, 2008 30 weeks Multinational Merck Fair	Yes	No	Yes	Yes	Yes	Yes	No
Chogtu, 2009 12 weeks India Funding NR Poor	Yes	Yes	NR	NR	No	No	No
Berneis, 2008 12 weeks Switzerland Government funding Poor	NR	NR	Yes	NR	NR	NR	Yes

Evidence Table 6. Key Question 1: Quality assessment of trials for Key Question 1

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Overall attrition high (>20%)? Yes, No, NR	Loss to follow-up differential high (>15%)? Yes, No, NR	Outcome measures (ascertainment) equal, valid, and reliable? Yes, No, Mixed	Intention-to-treat (ITT) analysis? Yes, No, NR, Modified ITT	Post-randomization exclusions? Yes, No, NR
Nonaka, 2008 12 weeks Japan Banyu Pharmaceuticals (Merck) Good	No	Yes	Modified ITT	Yes	
Mohan, 2009 18 weeks China, India, Korea Merck Good	No	Yes	Modified ITT	No	
Raz, 2008 30 weeks Multinational Merck Fair	No	Yes	No	Yes	
Chogtu, 2009 12 weeks India Funding NR Poor	No	NR	Yes	No	Yes
Berneis, 2008 12 weeks Switzerland Government funding Poor	No	No	Yes	NR	No

Evidence Table 6. Key Question 1: Quality assessment of trials for Key Question 1

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Randomization adequate? Yes, No, NR	Allocation concealment adequate? Yes, No, NR	Groups similar at baseline? Yes, No, NR	Outcome assessors masked? Yes, No, NR	Care provider masked? Yes, No, NR	Patient masked? Yes, No, NR	Run-in/Washout? Yes, No, NR
Beysen, 2008 20 weeks US Funding NR Fair	NR	NR	Yes	No	No	No	No
Vijay, 2009 16 weeks India UGC, India Fair	Yes	NR	Yes	NR	NR	NR	No
Oz, 2008 12 weeks Turkey Funding NR Fair	NR	NR	Yes	NR	NR	NR	No
OZ Gul, 2010 12 weeks Turkey Funding NR Fair	NR	NR	Yes	NR	NR	NR	No
Erdem, 2008 12 weeks Turkey Gulthane School of Medicine Poor	NR	NR	Yes	NR	NR	NR	No

Evidence Table 6. Key Question 1: Quality assessment of trials for Key Question 1

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Overall attrition high (>20%)? Yes, No, NR	Loss to follow-up differential high (>15%)? Yes, No, NR	Outcome measures (ascertainment) equal, valid, and reliable? Yes, No, Mixed	Intention-to-treat (ITT) analysis? Yes, No, NR, Modified ITT	Post-randomization exclusions? Yes, No, NR
Beysen, 2008 20 weeks US Funding NR Fair	No	No	Yes	NR	Yes
Vijay, 2009 16 weeks India UGC, India Fair	NR	NR	Yes	NR	NR
Oz, 2008 12 weeks Turkey Funding NR Fair	Yes	No	Yes	NR	No
OZ Gul, 2010 12 weeks Turkey Funding NR Fair	Yes	No	Yes	NR	No
Erdem, 2008 12 weeks Turkey Gulthane School of Medicine Poor	No	No	Yes	NR	Yes

Evidence Table 6. Key Question 1: Quality assessment of trials for Key Question 1

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Randomization adequate? Yes, No, NR	Allocation concealment adequate? Yes, No, NR	Groups similar at baseline? Yes, No, NR	Outcome assessors masked? Yes, No, NR	Care provider masked? Yes, No, NR	Patient masked? Yes, No, NR	Run-in/Washout? Yes, No, NR
Papathanassiou, 2009 6 months Greece Funding NR Fair	Yes	No	Yes	NR	No	No	No
Tolman, 4039 Poor	Yes	Yes	Yes	Yes	Yes	Yes	No
Tsuchiya, 2009 Poor	NR	No	Yes	NR	NR	NR	No
Van der Meer, 2009 PIRAMID 24 weeks The Netherlands Eli Lilly, Takeda Good	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Schernthaner, 2004 Quarter Study 12 months Multinational Funding NR Good	Yes	Yes	Yes	Yes	NR	Yes	No
Kusaka, 2008 4 months Japan Funding NR Fair	NR	NR	Yes	No	No	No	No

Evidence Table 6. Key Question 1: Quality assessment of trials for Key Question 1

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Overall attrition high (>20%)? Yes, No, NR	Loss to follow-up differential high (>15%)? Yes, No, NR	Outcome measures (ascertainment) equal, valid, and reliable? Yes, No, Mixed	Intention-to-treat (ITT) analysis? Yes, No, NR, Modified ITT	Post-randomization exclusions? Yes, No, NR
Papathanassiou, 2009 6 months Greece Funding NR Fair	No	No	Yes	NR	NR
Tolman, 4039 Poor	Yes	No	Yes	Modified ITT	No
Tsuchiya, 2009 Poor	No	No	Yes	NR	No
Van der Meer, 2009 PIRAMID 24 weeks The Netherlands Eli Lilly, Takeda Good	No	No	Yes	NR	No
Schernthaner, 2004 Quarter Study 12 months Multinational Funding NR Good	No	No	Yes	Modified ITT	Yes
Kusaka, 2008 4 months Japan Funding NR Fair	No	No	Yes	No	Yes

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Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Randomization adequate? Yes, No, NR	Allocation concealment adequate? Yes, No, NR	Groups similar at baseline? Yes, No, NR	Outcome assessors masked? Yes, No, NR	Care provider masked? Yes, No, NR	Patient masked? Yes, No, NR	Run-in/Washout? Yes, No, NR
Nissen, 2008 PERISCOPE 18 months Multinational Takeda Pharmaceuticals Fair	Yes	Yes	Yes	Yes	Yes	Yes	No
Marre, 2003 LEAD-1SU 26 weeks Multinational Novo Nordisk Fair	NR	NR	Yes	NR	NR	Yes	Yes
Bao, 2009 48 weeks China Government funding Poor	NR	NR	NR	NR	NR	NR	Yes
Pop-Busui, 2009 6 months US GlaxoSmithKline, Eli Lilly, Research Foundations Fair	NR	NR	No	NR	NR	NR	Yes
Turkmen Kemal, 2007 Poor	NR	NR	Yes	NR	NR	NR	No

Evidence Table 6. Key Question 1: Quality assessment of trials for Key Question 1

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Overall attrition high (>20%)? Yes, No, NR	Loss to follow-up differential high (>15%)? Yes, No, NR	Outcome measures (ascertainment) equal, valid, and reliable? Yes, No, Mixed	Intention-to-treat (ITT) analysis? Yes, No, NR, Modified ITT	Post-randomization exclusions? Yes, No, NR
Nissen, 2008 PERISCOPE 18 months Multinational Takeda Pharmaceuticals Fair	Yes	No	Yes	No	Yes
Marre, 2003 LEAD-1SU 26 weeks Multinational Novo Nordisk Fair	No	No	Yes	Yes	Yes
Bao, 2009 48 weeks China Government funding Poor	No	No	Yes	NR	NR
Pop-Busui, 2009 6 months US GlaxoSmithKline, Eli Lilly, Research Foundations Fair	No	No	Yes	NR	NR
Turkmen Kemal, 2007 Poor	No	No	Yes	NR	No

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Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Randomization adequate? Yes, No, NR	Allocation concealment adequate? Yes, No, NR	Groups similar at baseline? Yes, No, NR	Outcome assessors masked? Yes, No, NR	Care provider masked? Yes, No, NR	Patient masked? Yes, No, NR	Run-in/Washout? Yes, No, NR
von Bibra, 2008 16 weeks (32-week cross-over) Germany Funding NR Fair	NR	No	Yes	Yes	NR	NR	Yes
Iliadis, 2007 18 weeks Greece Funding NR Poor	NR	NR	No	NR	NR	NR	Yes
Home, 2009 RECORD 7 year study, mean follow up time 5.5 years Multinational GlaxoSmithKline Fair	Yes	Yes	Yes	No	No	No	No
Kiyici, 2009 12 months Turkey Funding NR Fair	NR	NR	Yes	No	No	No	No

Evidence Table 6. Key Question 1: Quality assessment of trials for Key Question 1

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Overall attrition high (>20%)? Yes, No, NR	Loss to follow-up differential high (>15%)? Yes, No, NR	Outcome measures (ascertainment) equal, valid, and reliable? Yes, No, Mixed	Intention-to-treat (ITT) analysis? Yes, No, NR, Modified ITT	Post-randomization exclusions? Yes, No, NR
von Bibra, 2008 16 weeks (32-week cross-over) Germany Funding NR Fair	No	No	Yes	No	Yes
Iliadis, 2007 18 weeks Greece Funding NR Poor	No	No	Yes	No	Yes
Home, 2009 RECORD 7 year study, mean follow up time 5.5 years Multinational GlaxoSmithKline Fair	No	No	Yes	Modified ITT	Yes
Kiyici, 2009 12 months Turkey Funding NR Fair	No	No	Yes	NR	No

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Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Randomization adequate? Yes, No, NR	Allocation concealment adequate? Yes, No, NR	Groups similar at baseline? Yes, No, NR	Outcome assessors masked? Yes, No, NR	Care provider masked? Yes, No, NR	Patient masked? Yes, No, NR	Run-in/Washout? Yes, No, NR
Scott, 2008 18 weeks Multinational Merck Fair	NR	NR	Yes	NR	Yes	Yes	Yes
Hamann, 2008 52 weeks Multinational Funding NR Fair	Yes	Yes	Yes	NR	Yes	Yes	Yes
Nauck, 2009 LEAD-1 / LEAD-2 26 weeks Multinational Funding NR	NR	NR	Yes	Yes	Yes	Yes	Yes
Derosa, 2009 The 60's study 15 months Italy Funding NR Fair	Yes	NR	Yes	Yes	Yes	Yes	No
McCluskey, 2004 20 weeks US Funding NR Fair	No	NR	No	NR	NR	Yes	Yes

Evidence Table 6. Key Question 1: Quality assessment of trials for Key Question 1

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Overall attrition high (>20%)? Yes, No, NR	Loss to follow-up differential high (>15%)? Yes, No, NR	Outcome measures (ascertainment) equal, valid, and reliable? Yes, No, Mixed	Intention-to-treat (ITT) analysis? Yes, No, NR, Modified ITT	Post-randomization exclusions? Yes, No, NR
Scott, 2008 18 weeks Multinational Merck Fair	No	No	Yes	Modified ITT	Yes
Hamann, 2008 52 weeks Multinational Funding NR Fair	Yes	No	Yes	Modified ITT	Yes
Nauck, 2009 LEAD-1 / LEAD-2 26 weeks Multinational Funding NR	NR	NR	Yes	Modified ITT	NR
Derosa, 2009 The 60's study 15 months Italy Funding NR Fair	No	NR	Yes	Modified ITT	No
McCluskey, 2004 20 weeks US Funding NR Fair	No	No	Yes	Yes	No

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Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Randomization adequate? Yes, No, NR	Allocation concealment adequate? Yes, No, NR	Groups similar at baseline? Yes, No, NR	Outcome assessors masked? Yes, No, NR	Care provider masked? Yes, No, NR	Patient masked? Yes, No, NR	Run-in/Washout? Yes, No, NR
Stewart, 2006 32 weeks Multinational GlaxoSmithKline Fair	NR	NR	Yes	NR	Yes	Yes	Yes
Weissman, 2005 EMPIRE 24 weeks US GlaxoSmithKline Fair	NR	NR	NR	NR	Yes	Yes	Yes
Goldstein, 2006 EMPIRE 24 weeks US GlaxoSmithKline Fair	NR	NR	No	NR	Yes	Yes	Yes
Seck, 2010 104 weeks Multinational Merck Fair Extension of Nauck, 2007 (from previous report)	Yes	Yes	Yes	Yes	NR	Yes	Yes

Evidence Table 6. Key Question 1: Quality assessment of trials for Key Question 1

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Overall attrition high (>20%)? Yes, No, NR	Loss to follow-up differential high (>15%)? Yes, No, NR	Outcome measures (ascertainment) equal, valid, and reliable? Yes, No, Mixed	Intention-to-treat (ITT) analysis? Yes, No, NR, Modified ITT	Post-randomization exclusions? Yes, No, NR
Stewart, 2006 32 weeks Multinational GlaxoSmithKline Fair	Yes	No	Yes	Modified ITT	Yes
Weissman, 2005 EMPIRE 24 weeks US GlaxoSmithKline Fair	Yes	No	Yes	Modified ITT	Yes
Goldstein, 2006 EMPIRE 24 weeks US GlaxoSmithKline Fair	No	No	Yes	Yes	Yes
Seck, 2010 104 weeks Multinational Merck Fair Extension of Nauck, 2007 (from previous report)	Yes	No	Yes	No	No

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Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Randomization adequate? Yes, No, NR	Allocation concealment adequate? Yes, No, NR	Groups similar at baseline? Yes, No, NR	Outcome assessors masked? Yes, No, NR	Care provider masked? Yes, No, NR	Patient masked? Yes, No, NR	Run-in/Washout? Yes, No, NR
Aschner, 2010 24 weeks Multinational Merck Fair	Yes	Yes	Yes	Yes	NR	Yes	Yes
Vilsboll, 2010 24 weeks Multinational Merck Fair	NR	NR	Yes	Yes	NR	Yes	Yes
Dersoa, 2010 52 weeks Italy University of Pavia Fair	NR	NR	Yes	NR	NR	NR	No
Gill, 2010 12 weeks Multinational Eli Lilly Fair	NR	NR	Yes	NR	NR	NR	Yes
Pratley, 2010 26 weeks Multinational Novo Nordisk Fair	Yes	Yes	Yes	Yes	No	No	NR
Apovian, 2010 24 weeks US Eli Lilly Fair	Yes	Yes	Yes	NR	NR	NR	No

Evidence Table 6. Key Question 1: Quality assessment of trials for Key Question 1

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Overall attrition high (>20%)? Yes, No, NR	Loss to follow-up differential high (>15%)? Yes, No, NR	Outcome measures (ascertainment) equal, valid, and reliable? Yes, No, Mixed	Intention-to-treat (ITT) analysis? Yes, No, NR, Modified ITT	Post-randomization exclusions? Yes, No, NR
Aschner, 2010 24 weeks Multinational Merck Fair	No	No	Yes	No	Yes
Vilsboll, 2010 24 weeks Multinational Merck Fair	No	No	Yes	Modified ITT	No
Dersoa, 2010 52 weeks Italy University of Pavia Fair	No	No	Mixed	No	Yes
Gill, 2010 12 weeks Multinational Eli Lilly Fair	No	No	Yes	Yes	No
Pratley, 2010 26 weeks Multinational Novo Nordisk Fair	No	No	Yes	Yes	Yes
Apovian, 2010 24 weeks US Eli Lilly Fair	Yes	No	Yes	Modified ITT	No

Evidence Table 6. Key Question 1: Quality assessment of trials for Key Question 1

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Randomization adequate? Yes, No, NR	Allocation concealment adequate? Yes, No, NR	Groups similar at baseline? Yes, No, NR	Outcome assessors masked? Yes, No, NR	Care provider masked? Yes, No, NR	Patient masked? Yes, No, NR	Run-in/Washout? Yes, No, NR
Derosa, 2010 52 weeks Italy NR Fair	Yes	Yes	Yes	NR	NR	NR	No
DeFronzo, 2010 20 weeks US Eli Lilly Fair	NR	NR	Yes	No	No	No	No
Brackenridge, 2009 Poor	NR	NR	No	NR	Yes	Yes	No
Kadoglou, 2010 14 weeks Greece European Social Fund and National Resources - PYTHAGORAS II & Alexander S Onassis Public Benefit Foundation Fair	Yes	NR	Yes	No	No	No	Yes
Kato, 2009 12 weeks Japan Fair	NR	Yes	Yes	NR	NR	NR	Yes

Evidence Table 6. Key Question 1: Quality assessment of trials for Key Question 1

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Overall attrition high (>20%)? Yes, No, NR	Loss to follow-up differential high (>15%)? Yes, No, NR	Outcome measures (ascertainment) equal, valid, and reliable? Yes, No, Mixed	Intention-to-treat (ITT) analysis? Yes, No, NR, Modified ITT	Post-randomization exclusions? Yes, No, NR
Derosa, 2010 52 weeks Italy NR Fair	No	No	Yes	No	Yes
DeFronzo, 2010 20 weeks US Eli Lilly Fair	Yes	No	Mixed	Yes	No
Brackenridge, 2009 Poor	NR	NR	Mixed	NR	NR
Kadoglou, 2010 14 weeks Greece European Social Fund and National Resources - PYTHAGORAS II & Alexander S Onassis Public Benefit Foundation Fair	No	No	Yes	No	Yes
Kato, 2009 12 weeks Japan Fair	NR	NR	Yes	NR	No

Evidence Table 6. Key Question 1: Quality assessment of trials for Key Question 1

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Randomization adequate? Yes, No, NR	Allocation concealment adequate? Yes, No, NR	Groups similar at baseline? Yes, No, NR	Outcome assessors masked? Yes, No, NR	Care provider masked? Yes, No, NR	Patient masked? Yes, No, NR	Run-in/Washout? Yes, No, NR
Perez, 2009 24 weeks Multinational Takeda Pharmaceuticals Fair	NR	NR	Yes	NR	Yes	Yes	Yes
Petrica, 2009 Poor	NR	NR	Yes	Yes	No	No	No
Gerstein, 2010 18 months Multinational GlaxoSmithKline Fair	Yes	NR	Yes	Yes	Yes	Yes	Yes
DeFronzo, 2010 20 weeks USA Eli Lilly	NR	NR	NR	No	No	No	No
Rigby, 2010 16 weeks Mulitnational Daiichi Sankyo, Inc Fair	NR	NR	Yes	No	No	No	Yes

Evidence Table 6. Key Question 1: Quality assessment of trials for Key Question 1

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Overall attrition high (>20%)? Yes, No, NR	Loss to follow-up differential high (>15%)? Yes, No, NR	Outcome measures (ascertainment) equal, valid, and reliable? Yes, No, Mixed	Intention-to-treat (ITT) analysis? Yes, No, NR, Modified ITT	Post-randomization exclusions? Yes, No, NR
Perez, 2009 24 weeks Multinational Takeda Pharmaceuticals Fair	Yes	No	Yes	Modified ITT	No
Petrica, 2009 Poor	Yes	No	Mixed	No	Yes
Gerstein, 2010 18 months Multinational GlaxoSmithKline Fair	Yes	No	Yes	No	No
DeFronzo, 2010 20 weeks USA Eli Lilly	Yes	No	Mixed	Yes	No
Rigby, 2010 16 weeks Mulitnational Daiichi Sankyo, Inc Fair	No	No	Yes	Modified ITT	Yes

Evidence Table 7. Key Question 2: Studies of pramlintide

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Inclusion and Exclusion Criteria	Overall Sample Size Interventions Group Sizes	Baseline Population Characteristics Mean Age, years Race/Ethnicity % Female	Background Medications
Head-to-head studies				
None				
Active-control studies				
Riddle, 2009 24 weeks US Amylin Pharmaceuticals Fair	Inclusion: 18 - 75 years of age, T2DM, HbA1c > 7% and < 10%, with or without use of any combination of metformin, thiazolidinedione, or sulfonylurea OADs, pramlintide naïve and either insulin naïve or had used <50 units.day of basal insulin for < 6 months, BMI > 25 and < 50 kg/m2, female patients were not pregnant nor lactating and were postmenopausal or using birth control. Exclusion: Poor adherence to diabetes management recommendations, recurrent svere hypoglycemia within the last 6 months, or had a history of hypoglycemia unawareness, gastroparesis, use of exenatide, sitagliptin, antiobesity medications, systemic glucocorticoids, or investigational medications	N=113 (112 analyzed) G1: (pramlintide 120 ug before major meals - two participants reduced dose to 60ug) n=56 G2: (rapid-acting insulin analog 5 units before each meal, titrated every 3-7 days to maintain >70 and <100 before next meal/bedtime) n=56	G1: Age: 55 (11) Race: NR Female 39.3% G2: Age: 54 (10) Race: NR Female 34%	Insulin glargine or detemir, some participants were also taking oral antihyperglycemic drugs

Evidence Table 7. Key Question 2: Studies of pramlintide

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Adverse Events	Changes in Lipid Concentrations	Weight Gain
Head-to-head studies			
None			
Active-control studies			
Riddle, 2009 24 weeks US Amylin Pharmaceuticals Fair	Withdrawals due to AEs G1: 2 (4%) G2: 0 Hypoglycemia G1: 55% G2: 82% Nausea G1: 12 (21%) G2: 0 Serious AEs: 8 events reported in 6 patients G1: 1 (coronary artery disease) G2: 5 (coronary artery disease, congestive heart failure, ischemic cerebral infarction, syncope, noncardiac chest pain, cellulitis, biliary dyskinesia)	NR	

Evidence Table 7. Key Question 2: Studies of pramlintide

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Inclusion and Exclusion Criteria	Overall Sample Size Interventions Group Sizes	Baseline Population Characteristics Mean Age, years Race/Ethnicity % Female	Background Medications
Placebo-controlled trials				
Wysham 2008 16 weeks Amylin Phamaceuticals Fair	Inclusion; T2DM; with or without use of metformin, sulfonylurea and/or TZDs; not achieving glycemic control with insulin glargine; 18-75 years of age; HbA1c 7.0-10.5; BMI 25-45; insulin glargine treatment ≥ 3 months with a stable dose for ≥ 1month, and a stable dose of oral antidiabetic agents for ≥ 2months Exclusion: concurrent participation in a weight loss program or use of antiobesity agents; a history of hypoglycemia unawareness or recurrent severe hypoglycemia during the preceding 6 months; confirmed diagnosis of gastroparesis or any other significant medical condition; female patients were postmenopausal, surgically sterile or used adequate contraception throughout the study.	N=211 randomized G1 (placebo): n=106 G2 (pramlintide): n=105	G1: Age: 55 Race: NR Female 48.1% G2: Age: 55 Race: NR Female 54.3%	Insulin

Evidence Table 7. Key Question 2: Studies of pramlintide

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Adverse Events	Changes in Lipid Concentrations	Weight Gain
Placebo-controlled trials			
Wysham 2008 16 weeks Amylin Phamaceuticals Fair	Hypoglycemia: G1: 47% G2: 44% Nausea: G1: 10% G2: 31%	LDL (mg/dl): G1: -2.3 (SD 2.8) G2: -3.0 (SD 3.3) *P* =0.816, G1 vs. G2 HDL (mg/dl): G1: -0.4 (SD 0.6) G2: -0.9 (SD 0.6) *P* =0.365, G1 vs. G2 TGs (mg/dl): G1: 10 (SD 12) G2: -19 (SD 8) *P* =0.080, G1 vs. G2	Weight gain reported in 346

Evidence Table 8. Key Question 2: Studies of sitagliptin and saxagliptin

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Inclusion and Exclusion Criteria	Overall Sample Size Interventions Group Sizes	Baseline Population Characteristics Mean Age, years Race/Ethnicity % Female	Background Medications
Active-control studies				
Aschner, 2010 24 weeks Multinational Merck Fair	Inclusion: Men and women with type 2 diabetes (18–78 y ears of age)who were treatment na¨ıve (i.e. not taking an antihyperglycaemic agent for at least 16 weeks prior to study entry) with HbA1c 6.5–9.0% Exclusion: Patients with type 1 diabetes, fasting plasma glucose (FPG) <120 mg/dl (6.7 mmol/l) or >250 mg/dl (13.9 mmol/l), unstable cardiac disease, significant renal impairment (creatinine ≥1.4 mg/dl for males or ≥1.3 mg/dl for females or creatinine clearance <60 ml/min), elevated alanine aminotransferase, aspartate aminotransferase, or creatine phosphokinase (more than 2 times upper limit of normal) or triglycerides >600 mg/dl	1050 randomized G1: sitagliptin 100 N= 528 G2: metformin N= 522	G1: Age 56.3, race NR, female 52% G2: Age 55.7, race NR, female 56%	NR

Evidence Table 8. Key Question 2: Studies of sitagliptin and saxagliptin

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Adverse Events	Changes in Lipid Concentrations
Active-control studies		
Aschner, 2010	Withdrawn because of adverse events:	
24 weeks	G1: N=9 (1.7%)	Cholesterol
Multinational	G2: N=19 (3.6%)	G1: +5.5
Merck	Overall adverse events:	G2: +2.2
Fair	G1: 198 (37.5%)	
	G2: 215 (41.2%)	HDL
	Bronchitis	G1: +6.2
	G1: 4; G2: 7	G2: +7.0
	Nasopharyngitis	
	G1: 10; G2: 17	LDL
	URI	G1: +11.2
	G1: 5; G2: 11	G2: +2.5
	UTI	
	G1: 3; G2: 13	Triglycerides
	Hypoglyccemia	G1: -3.7
	G1: 9; G2: 17	G2: -1.2
	Diarrhea	
	G1: 19; G2: 57	
	Nausea	
	G1: 6; G2: 16	
	Abdominal pain	
	G1: 11; G2: 20	
	Vomiting	
	G1: 2; G2: 7	

Evidence Table 8. Key Question 2: Studies of sitagliptin and saxagliptin

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Inclusion and Exclusion Criteria	Overall Sample Size Interventions Group Sizes	Baseline Population Characteristics Mean Age, years Race/Ethnicity % Female	Background Medications
Williams-Herman, 2009 54 weeks Williams-Herman, 2010 104 weeks Multinational Merck Fair	Inclusion: T2DM (18–78 years of age) who were on or not on an oral diabetes mellitus medication at the screening Exclusion: T1DM; unstable cardiac disease; significant renal impairment (glomerular filtration rate<60ml/min) AST, ALT ≥ 2x upper limit of normal	N=885 in 30 week continuation phase (1091 initially randomized) (#s for continuation phase) G1: (placebo/ metformin 1000 bid) n=23 G2: (sitagliptin 100mg qd) n=141 G3: (metformin 500mg bid) n=147 G4: (metformin 1000 bid) n=153 G5: (sitagliptin 50 bid + metformin 500 bid) n=160 G6: (sitagliptin 50mg bid + metformin 1000mg bid) n=161	G1: Age 53.6; Female 51% G2: Age 53.5; Female 48% G3: Age 53.7; Female 52% G4: Age 54.2; Female 55% G5: Age 53.7; Female 47% G6: Age 53.6; Female 59% Race: NR	None

Evidence Table 8. Key Question 2: Studies of sitagliptin and saxagliptin

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Adverse Events	Changes in Lipid Concentrations
Williams-Herman, 2009 54 weeks Williams-Herman, 2010 104 weeks Multinational Merck Fair	Withdrawals due to Aes G1: 11 G2: 12 G3: 9 G4: 11 G5: 6 G6: 5 Overall Aes G1: 97 G2: 105 G3: 114 G4: 129 G5: 130 G6: 126 Hypoglycemia G1: 4 G2: 2 G3: 2 G4: 2 G5: 4 Overall GI events G1: 28 G2: 36 G3: 37 G4: 57 G5: 50 G6 53 Diarrhea G1: 11 G2: 7 G3: 13 G4: 22 G5: 17 G6: 23 Nausea G1: 4 G2: 2 G3: 6 G4: 18 G5: 10 G6: 11 Abdominal Pain G1: 5 G2: 8 G3: 7 G4: 10 G5: 5 G6: 7 Vomiting G1: 1 G2: 1 G3:0 G4: 6 G5: 4 G6: 7 G6: 5	24 week results: G1: TC: +6.2 mg/dl HDL: +2.7 mg/dl LDL: +4.8 mg/dl TG: +0 G2: TC: +2.7 mg/dl HDL: +0.5 mg/dl LDL: +1.6 mg/dl TG: +6.0 mg/dl G3: TC: -1.5 mg/dl HDL: +1.4 mg/dl LDL: -3.2 mg/dl TG: -2.8 mg/dl G4: TC: +0.6 mg/dl HDL: +2.3mg/dl LDL: -3.6 mg/dl TG: -1.8mg/dl G5: TC: -3.2 mg/dl HDL: +1.2 mg/dl LDL: -3.7 mg/dl TG: -9 mg/dl G6: TC: -7.1 mg/dl HDL:+1.8 mg/dl LDL:-5.4 mg/dl TG: -15.5 mg/dl

Evidence Table 8. Key Question 2: Studies of sitagliptin and saxagliptin

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Inclusion and Exclusion Criteria	Overall Sample Size Interventions Group Sizes	Baseline Population Characteristics Mean Age, years Race/Ethnicity % Female	Background Medications
Williams-Herman, 2009 Williams-Herman, 2010 (continued)		Entered extension: 685 original randomization: 1091 Extension sizes: G1: 103 (sitagliptin 100) G2: 107 (met 500 BID) G3: 121 (met 1000 BID) G4: 134 (sit 50 BID + met 500 BID) G5: 122 (sit 50 BID + met 1000 BID)	For Extension Study: (for those included in the efficacy analysis) Race NR G1: Age 54.1, female 42% G2: Age 55.9, female 54% G3: Age 54.3, female 56% G4: Age54.5, female 50% G5: Age 53.9, female 63%	

Evidence Table 8. Key Question 2: Studies of sitagliptin and saxagliptin

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Adverse Events	Changes in Lipid Concentrations
Williams-Herman, 2009 Williams-Herman, 2010 (continued)	For Extension Study (104 weeks): Withdrawn because of adverse events G1: 5 (2.8%) G2: 8 (4.4%) G3: 7 (3.8%) G4: 6 (3.2%) G5: 4 (2.2%) Overall adverse events: G1: 108 G2: 117 G3: 135 G4: 135 G5: 137 Hypoglycemia: G1:N= 2 G2: N=3 G3:N= 4 G4:N= 5 G5:N= 9	54 week results: G1: NR G2: TC: +0.5 mg/dl HDL: +0.1 mg/dl LDL: -1.6mg/dl TG: +15 mg/dl G3: TC: -0 mg/dl HDL: +2.4 mg/dl LDL: -3.0 mg/dl TG: +6 mg/dl G4: TC: -0.2 mg/dl HDL: +3.1 mg/dl LDL: -4.8 mg/dl TG: +24.5 G5: TC: -6.6 mg/dl HDL: +1.7mg/dl LDL: -5.0 mg/dl TG: -8.0 mg/dl G6: TC: -8.8 mg/dl HDL: +2.7 mg/dl LDL:-8.5 mg/dl TG: -15 mg/dl

Evidence Table 8. Key Question 2: Studies of sitagliptin and saxagliptin

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Adverse Events	Changes in Lipid Concentrations
Williams-Herman, 2009 Williams-Herman, 2010 (continued)	For Extension Study (104 weeks): Gastrointestinal Effects: Diarrhea: G1: N= 8 G2: N=14 G3: N=23 G4: N=19 G5: N=25 Nausea G1: N=2 G2: N=6 G3: N=19 G4: N=10 G5: N=12 Abdominal pain G1: N=9 G2: N=7 G3: N=12 G4: N=7 G5: N=9 Vomiting G1: N=1 G2: N=0 G3: N=8 G4: N=4 G5: N-9	

Evidence Table 8. Key Question 2: Studies of sitagliptin and saxagliptin

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Inclusion and Exclusion Criteria	Overall Sample Size Interventions Group Sizes	Baseline Population Characteristics Mean Age, years Race/Ethnicity % Female	Background Medications
Chan, 2008 54 weeks Multinational Merck Fair	Inclusion: T2DM; moderate to severe renal insufficiency (CrCl <50); ages 18+ Exclusion: T1DM; acute renal disease, renal transplant; liver disease; cardiovascular event within 6 months; hepatic transaminase or creatine phosphokinase levels >= two times the upper limit of normal; repeated fasting plasma glucose >15mmol/l or trigycerides >6.8mmol/l	N=91 G1: (25mg or 50mg sitagliptin) n=65 G2: (placebo/5mg-20mg glipizide) n=26	G1: Age: 68.9 (9.8) Race: White 34%; Black 6%; Hispanic 26%; Asian 31% Other 3% Female 52% G2: Age: 65.3 (9.7) Race: White 31%; Black 4%; Hispanic 35%; Asian 27% Other 4% Female 38%	insulin

Evidence Table 8. Key Question 2: Studies of sitagliptin and saxagliptin

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Adverse Events	Changes in Lipid Concentrations
Chan, 2008 54 weeks Multinational Merck Fair	Withdrawals due to AEs G1: n=10 (15.4%); G2: n=4 (15.4%) Note: the numbers reported in Fig 1 differ from those reported in Tab 2. Overall AEs G1: n=52 (80.6%); G2: n=22 (84.6%) Infections G1: n=30 (46.2%); G2: n=13 (50%) Hypoglycemia At week 54 (sita vs P/glip): G1: 3 (4.6%); G2: 6 (23.1%) Congestive heart failure G1: 5; G2: 1 * All patients had coronary artery disease Increased SCr G1 -0.02 SD 0.06 mg/dl G2 +0.69 SD 0.58 mg/dl Anemia: G1: 2; G2: 4 Peripheral edema: G1: 5; G2: 1 Fall: G1: 3 Arthritis: G2: 2 Back or shoulder pain: G1: 1; G2: 4 Dizziness: G1: 4; G2: 1 Lethargy: G1: 3 Cough: G1: 4; G2: 1 Hypertension: G1: 3; G2: 3	(reported Mean change, but baseline NR)

Evidence Table 8. Key Question 2: Studies of sitagliptin and saxagliptin

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Inclusion and Exclusion Criteria	Overall Sample Size Interventions Group Sizes	Baseline Population Characteristics Mean Age, years Race/Ethnicity % Female	Background Medications
Placebo-controlled studies				
Chacra, 2009 CV181-040 24 weeks Multinational Bristol-Myers Squibb and AstraZeneca Fair	Inclusion: Age 18-77 with inadequate glycemic control of T2DM (HbA1c between 7.5% and 10%, inclusive); on a submaximal sulphonylurea dose for at least 2 months; fasting C-peptide >=1.0ng/ml; BMI <= 40kg/m^2 Exclusion: Symptoms of poorly controlled diabetes, history of diabetic ketoacidosis or hyperosmolar non-ketotic coma; insulin therapy within 1 year; cardiovascular event within 6 months or or stage III/IV congestive heart failure and/or known left ventricular ejection fraction <=40%; significant history of renal or liver disease; psychiatric disorder; alcohol or drug abuse within last year; treatment with potent CYP 3A4 inhibitors or inducers; immunocompromised individuals; active liver disease or clinically significant abnormal hepatic, renal, endocrine, metabolic or hematological screening.	N=768 G1: (2.5 mg saxagliptin + 7.4mg (final mean) open-label glyburide) n=248 G2: (5mg saxagliptin + 7.4mg (final mean) open-label glyburide) n=253 G3: (placebo + 2.5mg blinded glyburide + 7.5mgopen-label glyburide; final mean total daily dose = 14.6mg) n=267 Note: glyburide doses were uptitrated in placebo plus glyburide group	Age: G1: 55.4 (9.6) G2: 54.9 (10.0) G3: 55.1 (10.7) Race (%): White: G1: 59.7% G2: 59.7%; G3: 56.9% Black: G1: 2.0% G2: 2.8%; G3: 2.6% Asian: G1: 16.9% G2: 18.2%; G3: 19.1% Other: G1: 21.4% G2: 19.4%; G3: 21.3% % Female: G1: 54.4 G2: 56.5; G3: 53.9	NR

Evidence Table 8. Key Question 2: Studies of sitagliptin and saxagliptin

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Adverse Events	Changes in Lipid Concentrations	
Placebo-controlled studies			
Chacra, 2009 CV181-040 24 weeks Multinational Bristol-Myers Squibb and AstraZeneca Fair	Withdrawals because of AEs: Overall: 11 (1.4%) G1: 1 (0.4%) G2: 6 (2.4%) G3: 4 (1.5%) "Discontinuation" due to AEs: G1: 3 (1.2%) G2: 8 (3.2%) G3: 4 (1.5%) "Discontinuation" due to serious AEs: G1: 0 G2: 1 (0.4%) G3: 1 (0.4%) Overall AEs: G1: 186 (75.0%) G2: 183 (72.3%) G3: 205 (76.8%) Serious AEs: G1: 4 (1.6%); G2: 6 (2.4%); G3: 6 (2.2%) Urinary Tract Infection: G1: 13; G2: 27; G3: 22 Upper Respiratory Tract Infection: G1: 11; G2: 16; G3: 18 Nasopharyngitis: G1: 14; G2: 15; G3: 18	NR	Mean change at 24 weeks, weight: G1 = +0.7kg G2 = +0.8kg G3 = +0.3kg

Evidence Table 8. Key Question 2: Studies of sitagliptin and saxagliptin

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Adverse Events	Changes in Lipid Concentrations
Chacra, 2009 continued	Influenza G1: 13: G2: 10; G3: 16 Hypoglycemia: Reported: G1: 33; G2: 37; G3: 27 Confirmed: G1: 6; G2: 2; G3: 2 Diarrhea: G1: 14; G2: 10; G3: 14 Skin-related: G1: 22; G2: 12; G3: 13 Edema: G1: 1; G2: 1 Cardiac disorder events: G1: 5; G2: 1; G3: 1 Pain (back, head, or extremity): G1: 42; G2: 43; G3: 42 Cough: G1: 13; G2: 10; G3: 13 Hypertension: G1: 9; G2: 16; G3: 6	

Evidence Table 8. Key Question 2: Studies of sitagliptin and saxagliptin

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Inclusion and Exclusion Criteria	Overall Sample Size Interventions Group Sizes	Baseline Population Characteristics Mean Age, years Race/Ethnicity % Female	Background Medications
Rosenstock, 2009 CV181-011 Study 24 weeks US Bristol-Myers Squibb and Astra Zeneca Fair	Inclusion: 18 -77 years of age, T2DM inadequately controlled with diet and exercise (HbA1c >7 and <10% at screening visit), treatment naïve (see comments for definition), fasting C-peptide > 1 ng.mL (>0.33 nmol/L), and a BMI of < 40 kg/m2. Exclusion: symptoms of poorly controlled diabetes, history of diabetic ketoacidosis or hyperosmolar nonketotic coma, cardiovascular event within 6 months prior to study entry or New York Heart Associaten stage III/IV congestive heart failure and/or known left ventricular ejection fraction of <40%, significant renal, liver, or psychiatric history, history of alcohol or drug abuse within the previous year, immunocompromised, active liver disease or clinically significant abnormalities on screening tests of hepatic, renal, endocrine, metabolic, or hematologic function.	N=403 (401 analyzed) G1: (saxagliptin 2.5 mg) n=102 G2: (saxagliptin 5 mg) n=106 G3: (saxagliptin 10 mg) n=98 G4: (placebo) n=95	G1: Age: 53.27 (10.06); White 87.3%, Black 4.9%, Asian 4.9%, Other 2.9%; Female 43.1% G2: Age: 53.91 (11.57); White 87.7%, Black 4.7%, Asian 3.8%, Other 3.8%; Female 49.1% G3: Age: 52.72 (11.27); White 81.6%, Black 6.1%, Asian 6.1; Other 6.1; Female 54.1% G4: Age: 53.91 (12.32); White 83.2%, Black 6.3%, Asian 3.2%, Other 7.4%; Female 50.5%	None

Evidence Table 8. Key Question 2: Studies of sitagliptin and saxagliptin

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Adverse Events	Changes in Lipid Concentrations
Rosenstock, 2009 CV181-011 Study 24 weeks US Bristol-Myers Squibb and Astra Zeneca Fair	Withdrawals because of Serious AEs: G1: 2 (2.0) G2: 0 G3: 1 (1.0) G4: 0 WD because of AEs: G1: 4 (3.9) G2: 3 (2.8) G3: 5 (5.1) G4: 0 Patients experiencing > 1 AE: G1: 76 (74.5) G2: 80 (75.5) G3: 75 (76.5) G4: 68 (71.6) Upper Respiratory Tract Infection: G1:7 (6.9) G2: 9 (8.5) G3: 11 (11.2) G4: 11 (11.6) Urinary Tract Infection: G1: 8 (7.8) G2: 9 (8.5) G3: 4 (4.1) G4: 4 (4.2) Nasopharyngitis: G1: 6 (5.9) G2: 6 (5.7) G3: 6 (6.1) G4: 6 (6.3) Sinusitis: G1: 5 (4.9) G2: 6 (5.7) G3: 6 (6.1) G4: 3 (3.2) Influenza: G1: 4 (3.9) G2: 4 (3.8) G3: 5 (5.1) G4: 1 (1.1)	Modest numerical improvements from baseline to week 24 in total cholesterol were demonstrated in the saxagliptin treatment groups. There were no clear clear effects of saxagliptin on fasting lipid concentrations. Data not shown.

Evidence Table 8. Key Question 2: Studies of sitagliptin and saxagliptin

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Adverse Events	Changes in Lipid Concentrations
Rosenstock, 2009 (continued)	Reported Hypoglycemia: G1: 3 (2.9) G2: 5 (4.7) G3: 8 (8.2) G4: 6 (6.3) Confirmed Hypoglycemia: G1-G4: 0 Diarrhea: G1: 7 (6.9) G2: 1 (0.9) G3: 6 (6.1) G4: 3 (3.2) Pain in Extremity: G1: 8 (7.8) G2: 3 (2.8) G3: 3 (3.1) G4: 4 (4.2) Arthralgia: G1: 1 (1.0) G2: 4 (3.8) G3: 5 (5.1) G4: 1 (1.1) Back Pain: G1: 1 (1.0) G2: 7 (6.6) G3: 0 G4: 5 (5.3) Dizziness: G1: 1 (1.0) G2: 5 (4.7) G3: 1 (1.0) G4: 6 (6.3) Headache: G1: 4 (3.9) G2: 10 (9.4) G3: 11 (11.2) G4: 7 (7.4)	

Evidence Table 8. Key Question 2: Studies of sitagliptin and saxagliptin

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Inclusion and Exclusion Criteria	Overall Sample Size Interventions Group Sizes	Baseline Population Characteristics Mean Age, years Race/Ethnicity % Female	Background Medications
Rosenstock, 2008 12 weeks Multinational Bristol-Myers Squibb Fair	Inclusion: drug-naïve patients; men and non-breastfeeding, non-pregnant women; age 21-70; T2DM; HbA1c 6.8-9.7; BMI<37; screening fasting or random C-peptide >0.5ng/ml; patients aged <35 had to test negative for anti-glutamic acid decardoxylate antibodies Exclusion: T1DM; symptoms of poorly controlled diabetes or a history of ketoacidosis or hyperosmolar coma; congestive heart failure; a history of significant gastrointestinal disease, cardiovascular illness, rapidly progressive renal disease, malignancy, immunodeficiency, asthma or atopic skin disorder; clinically significant abnormalities on screening tests of hepatic, renal, endocrine, metabolic or hematologic function or on chest x-ray or electrocardiogram, use of systemic corticosteroids and cytochrome p450 3A4 inhibitors	N=338 G1: (saxagliptin 2.5mg/day) n=55 G2: (saxagliptin 5mg/day) n=47 G3: (saxagliptin 10mg)/day) n=63 G4: (saxagliptin 20mg/day) n=54 G5: (saxagliptin 40mg/day) n=52 G6: (placebo) n=67	G1: Age: 52.5; White 85%, Black 11%, Other 4%; Female 60% G2: Age: 53.7; White 87%, Black 13%, Other 0%; Female 47% G3: Age: 54.5; White 84%, Black 8%, Other 8%; Female 37% G4: Age: 53.6; White 87%, Black 7%, Other 6%; Female 30% G5: Age: 54.1%; White 92%, Black 4%, Other 4%; Female 42% G6: Age: 55.2; White 87%, Black 10%, Other 3%; Female 37%	None

Evidence Table 8. Key Question 2: Studies of sitagliptin and saxagliptin

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Adverse Events	Changes in Lipid Concentrations
Rosenstock, 2008 12 weeks Multinational Bristol-Myers Squibb Fair	Withdrawals due to AEs: G1: n=0 G2: n=1 G3: n=1 G4: n=1 G5: n=1 G6: n=1 Patients with AEs: G1: n=44 (80%) G2: n=36 (76.6%) G3: n=49 (77.8%) G4: n=47 (87%) G5: n=39 (75%) G6: n=53 (79.1%) Upper Respiratory Tract Infection: G1: n=6 (10.9%) G2: n=3 (6.4%) G3: n=9 (9.5%) G4: n=6 (11.1%) G5: n=0 G6: n=4 (6.0%) Urinary Tract Infection: G1: n=6 (10.9%) G2: n=2 (4.3%) G3: n=4 (6.3%) G4: n=5 (9.3%) G5: n=2 (3.8%) G6: n=5 (7.5%) Nasopharyngitis: G1: n=0 G2: n=2 (4.3%) G3: n=5 (7.9%) G4: n=3 (5.6%) G5: n=6 (11.5%) G6: n=5 (7.5%) Confirmed hypoglycemia: n=0 Nausea: G1: n=1 (1.8%) G2: n=2 (4.3%) G3: n=2 (3.2%) G4: n=2 (3.7%) G5: n=5 (9.6%) G6: n=5 (7.5%)	NR

Evidence Table 8. Key Question 2: Studies of sitagliptin and saxagliptin

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Inclusion and Exclusion Criteria	Overall Sample Size Interventions Group Sizes	Baseline Population Characteristics Mean Age, years Race/Ethnicity % Female	Background Medications
DeFronzo, 2009 Saxagliptin CV181-014 Study 24 weeks Multinational Bristol-Myers Squibb & AstraZeneca Fair	Inclusion: T2DM, inadequate glycemic control (HbA1c >=7.0 and <=10.0%), taking a stable dose of metformin (>=1,500mg but not >2,550mg) for at least 8 weeks before screening, fasting C-peptide concentration >=1.0ng/ml, age 18-77, BMI<=40kg/m^2 Exclusion: Symptoms of poorly controlled DM, history of diabetic ketoacidosis or hyperosmolar nonketonic coma, use of any other antihyperglycemic meds (8 weeks before) or insulin (1 year before), a cardiovascular event within 6 months of study entry, stage III/IV congestive heart failure and/or known left ventricular ejection fraction <40%, chronic or repeated intermittent corticosteroid treatment, history of alcohol or drug abuse within 1 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, assessment of an immunocompromised state, pregnancy, breastfeeding	N=743 G1: (placebo) n=179 G2: (2.5mg saxagliptin) n=192 G3: (5mg saxagliptin) n=191 G4: (10mg saxagliptin) n=181	Age: G1 = 54.8 (10.2); G2 = 54.7 (10.1); G3 = 54.7 (9.6); G4 = 54.2 (10.1) Race: White: G1 = 83.8%; G2 = 79.7%; G3 = 83.2%; G4 = 79.6% Black: G1 = 3.9%; G2 = 4.2%; G3 = 5.8%; G4 = 7.7% Asian: G1 = 2.2%; G2 = 4.2%; G3 = 1.6%; G4 = 2.8% Other: G1 = 10.1%; G2 = 12.0% G3 = 9.4%; G4 = 9.9% Female: G1 = 46.4%; G2 = 56.8%; G3 = 46.1%; G4 = 47.5%	metformin

Evidence Table 8. Key Question 2: Studies of sitagliptin and saxagliptin

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Adverse Events	Changes in Lipid Concentrations
DeFronzo, 2009 Saxagliptin CV181-014 Study 24 weeks Multinational Bristol-Myers Squibb & AstraZeneca Fair	Overall N = 18 G1: n=2 (1.1%) G2: n=5 (2.6%) G3: n=6 (3.1%) G4: n=5 (2.6%) Overall AEs: G1: n=116 G2: n=153 G3: n=134 G4: n=132 Serious AEs: G1: n=5 G2: n=5 G3: n=8 G4: n=5 Nasopharyngitis: G1: n=14 G2: n=18 G3: n=13 G4: n=18 Upper Respiratory Tract Infection: G1: n=9 G2: n=13 G3: n=9 G4: n=15 Urinary Tract Infection: G1: n=8 G2: n=10 G3: n=10 G4: n=9 Influenza: G1: n=13 G2: n=12 G3: n=12 G4: n=10 Hypoglycemia Reported: G1: n=9 G2: n=15 G3: n=10 G4: n=7 Confirmed: G1: n=1 G2: n=1 G3: n=1 G4: n=1 Cardiac death: G1: n=1 Pain (back, head, joint or extremity): G1: n=40 G2: n=42 G3: n=28 G4: n=41 Cough: G1: n=6 G2: n=10 G3: n=6 G4: n=3 Hypertension: G1: n=6 G2: n=11 G3: n=4 G4: n=5	

Evidence Table 8. Key Question 2: Studies of sitagliptin and saxagliptin

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Inclusion and Exclusion Criteria	Overall Sample Size Interventions Group Sizes	Baseline Population Characteristics Mean Age, years Race/Ethnicity % Female	Background Medications
Hollander, 2009 24 weeks US Bristol-Meyers Squibb and AstraZeneca Fair	Inclusion: 18-77 years old; T2DM treated with stable dose of TZD monotherapy for at least 12 weeks prior to screening; HbA1c 7-10.5; fasting C-peptide ≥ 0.3 nmol/L; BMI< 45 Exclusion: history of any anti-hyperglycemic therapy within 12 weeks other than TZD; history of diabetic ketoacidosis; history of hyperosmolar nonketotic coma; symptoms of poorly controlled diabetes; those receiving insulin within 1 year except during hospitalization or gestational diabetes; immunocompromised; treated with potent CYP3A4 inhibitors or inducers; had a cardiovascular event; New York Heart Association class III/IV congestive heart failure; left ventricular ejection fraction < 40%; significant renal, liver or psychiatric history; significant alcohol or drug abuse in the past year; active liver disease; significant abnormalities on screening tests of hepatic, renal, endocrine, metabolic, or hematologic function	N=565 G1: (saxagliptin 2.5mg/day + open-label TZD) n=195 G2: (saxagliptin 5mg/day + open-label TZD) n=186 G3: (placebo + open-label TZD) n=184	G1: Age: 54.9 Race: White 55.9%, Black 2.6%, Asian 34.4%, Other 7.2% Female: 45.6% G2: Age: 53.2 Race: White 53.2%, Black 5.4%, Asian 35.5%, Other 5.9% Female: 52.2% G2: Age: 54.0 Race: White 54.9%, Black 3.8%, Asian 34.2%, Other 7.1% Female: 53.8%	TZD in all groups

Evidence Table 8. Key Question 2: Studies of sitagliptin and saxagliptin

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Adverse Events	Changes in Lipid Concentrations
Hollander, 2009 24 weeks US Bristol-Meyers Squibb and AstraZeneca Fair	Withdrawals due to AEs G1: n=3 (1.5%) G2: n=11 (5.9%) G3: n=6 (3.3%) Overall AEs G1: n=121 G2: n=138 G3: n=123 Upper respiratory infection: G1: n=15 G2: n=17 G3: n=13 Urinary Tract Infection: G1: n=7 G2: n=12 G3: n=12 Reported hypoglycemia: G1: n=8 G2: n=5 G3: n=7 Confirmed hypoglycemia: G1: n=1 G2: n=0 G3: n=0 Cardiac disorder AEs (not otherwise described): G1: n=3 G2: n=10 G3: n=10 Peripheral edema: G1: n=6 G2: n=15 G3: n=8	mean change in total cholesterol at 24 weeks: G1: -3.1mg/dl (SD NR) G2: +0.8mg/dl (SD NR) G3: -4.3mg/dl (SD NR) mean change in LDL at 24 weeks: G1: +1.2 mg/dl (SD NR) G2: +4.3mg/dl (SD NR) G3: -1.2mg/dl (SD NR) mean change in HDL at 24 weeks: G1: -1.2mg/dl (SD NR) G2: 0 mg/dl (SD NR) G3: -0.4mg/dl (SD NR) mean change in TGs at 24 weeks: G1: -13.3mg/dl (SD NR) G2: -27.4mg/dl (SD NR) G3: -12.4mg/dl (SD NR) no statistical testing

Evidence Table 8. Key Question 2: Studies of sitagliptin and saxagliptin

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Inclusion and Exclusion Criteria	Overall Sample Size Interventions Group Sizes	Baseline Population Characteristics Mean Age, years Race/Ethnicity % Female	Background Medications
Hanefeld, 2007 Sitagliptin Study 014 12 weeks Multinational Fair	Inclusion: 21-75 years old; T2DM; currently on monotherapy (except TZDs) with HbA1c 6-9 or not on an anti-diabetic agent with HbA1c 6.5-10 Exclusion: T1DM; unstable cardiac disease; AST, ALT or CPK ≥ 2x upper limit of normal	N=555 randomized, 552 analyzed G1: (placebo) n=111 G2: (sitagliptin 25 mg/day) n=111 G3: (sitagliptin 50 mg/day) n=112 G4: (sitaglitptin 100 mg/day) n=110 G5: (sitagliptin 50 mg bid) n=111	G1: Age: 55.9 Race: White 78.4%, Asian 0.9%, Black 7.2%, Other 13.5% Female: 36.9% G2: Age: 55.1 Race: White 88.3, Asian 0.9%, Black 3.6%, Other 7.2% Female: 48.6% G3: Age: 55.3 Race: White 85.7%, Asian 0%, Black 8.0%, Other 6.3% Female: 54.5% G4: Age: 56.0 Race: White 88.2%, Asian 0%, Black 5.5%, Other 6.4% Female: 44.5% G5: Age: 55.2 Race: White 81.1%, Asian 0.9%, Black 6.3%, Other 11.7% Female: 55.9%	None

Evidence Table 8. Key Question 2: Studies of sitagliptin and saxagliptin

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Adverse Events	Changes in Lipid Concentrations
Hanefeld, 2007	Withdrawals due to AEs	TC (mg/dl):
Sitagliptin Study 014	G1: 8	G1:
12 weeks	G2: 4	change from baseline: -0.1 (-2.5, 2.4)
Multinational	G3: 0	G2:
Fair	G4: 8	change from baseline: 1.5 (-0.9, 4.0)
	G5: 4	change from placebo: 1.6 (-1.8, 5.0)
		G3:
	Overall AEs	change from baseline: 1.1 (-1.3, 3.5)
	G1: 38	change from placebo: 1.2 (-2.2, 4.6)
	G2: 49	G4:
	G3: 50	change from baseline: 3.8 (1.3, 6.2)
	G4: 51	change from placebo: 3.9 (0.4, 7.3)
	G5: 51	G5:
		change from baseline: 2.1 (-0.4, 4.5)
	Nasopharyngitis:	change from placebo: 2.1 (-1.3, 5.6)
	G1: 1.8%	
	G2-G5: 6.3-9.1%	LDL (mg/dl):
		G1:
	Hypoglycemia:	change from baseline: -0.4 (-4.4, 3.7)
	G1: 0	G2:
	G2: 1	change from baseline: 4.9 (0.9, 8.9)
	G3: 1	change from placebo: 5.3 (-0.4, 10.9)
	G4: 2	G3:
	G5: 1	change from baseline: 2.9 (-1.0, 6.9)
		change from placebo: 3.3 (-2.3, 9.0)
	GI Effects:	G4:
	G1: n=15 (13.5%)	change from baseline: 7.4 (3.4, 11.4)
	G2: n=13 (11.8%)	change from placebo: 7.8 (2.1, 13.5)
	G3: n=10 (9.1%)	G5:
	G4: n=10 (9.1%)	change from baseline: 6.2 (2.1, 10.2)
	G5: n=9 (8.1%)	change from placebo: 6.6 (0.9, 12.2)

Evidence Table 8. Key Question 2: Studies of sitagliptin and saxagliptin

Study Characteristics
Author, Year
Trial Name (if app.)
Duration
Country
Funding

Quality	Adverse Events	Changes in Lipid Concentrations
Hanefeld, 2007 cont'd		HDL (mg/dl): G1: change from baseline: 1.1 (-1.6, 3.8) G2: change from baseline: 3.2 (0.6, 5.9) change from placebo: 2.1 (-1.6, 5.9) G3: change from baseline: 6.5 (3.8, 9.1) change from placebo: 5.3 (1.6, 9.1) G4: change from baseline: 5.4 (2.7, 8.1) change from placebo: 4.3 (0.5, 8.1) G5: change from baseline: 3.1 (0.4, 5.8) change from placebo: 1.9 (-1.8, 5.7) TGs (mg/dl): G1: change from baseline: 5.2 (-2.2, 12.7) G2: change from baseline: -3.9 (-11.2, 3.5) change from placebo: -9.1 (-19.5, 1.3) G3: change from baseline: -7.9 (-15.3, -0.6) change from placebo: -13.2 (-23.5, -2.8) G4: change from baseline: 0.8 (-6.6, 8.2) change from placebo: -4.4 (-14.9, 6.0) G5: change from baseline: -1.7 (-9.2, 5.7) change from placebo: -6.9 (-17.4, 3.5)

Evidence Table 8. Key Question 2: Studies of sitagliptin and saxagliptin

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Inclusion and Exclusion Criteria	Overall Sample Size Interventions Group Sizes	Baseline Population Characteristics Mean Age, years Race/Ethnicity % Female	Background Medications
Nonaka, 2008 12 weeks Japan Banyu Pharmaceuticals (Merck) Good	Inclusion: T2DM; ages 20-69; either not on treatment with an oral antihyperglycemic agent or only on a single agent over the 8 weks prior to the screening; HbA1c 6.5-10 in patient not on medication and fasting plasma glucose 126-240 Exclusion: T1DM; treatment with either insulin or pioglitzone in the 8 weeks prior to screening; unstable cardiac disease; elevated serum creatinine; elevations >2-fold the upper limit of normal of AST, ALT or CPK	N=152 G1: (sitagliptin 100mg/day) n=75 G2: (placebo) n=76	G1: Age: 55.6 Japanese 100% Female: 40% G2: Age: 55.0 Japanese 100% Female: 34%	NR

Evidence Table 8. Key Question 2: Studies of sitagliptin and saxagliptin

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Adverse Events	Changes in Lipid Concentrations
Nonaka, 2008 12 weeks Japan Banyu Pharmaceuticals (Merck) Good	Withdrawals due to Aes: G1: 0 G2: 2 Overall Aes: G1: 58.7% G2: 64.5% Hypoglycemia: none Liver function test abnormal: G1: 0 G2: 2 GI Effects: G1: 21.3% G2: 17.1%	NR

Evidence Table 8. Key Question 2: Studies of sitagliptin and saxagliptin

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Inclusion and Exclusion Criteria	Overall Sample Size Interventions Group Sizes	Baseline Population Characteristics Mean Age, years Race/Ethnicity % Female	Background Medications
Mohan, 2009 18 weeks China, India, Korea Merck Good	Inclusion: 18+ years; T2DM diagnosis within past 5 years; HbA1c >=7.5% and <=11.0% if not taking an oral antihyperglycemic agent, or HbA1c >=7.0% and <=10.0% if taking and oral hypoglycemic agent Exclusion: Receipt of insulin or TZD within 12 weeks; pregnant / breastfeeding; type 1 diabetes; unstable cardiac disease; moderate to severe renal insufficiency	N=530 G1: (placebo) n=178 G2: (100mg sitagliptin) n=352	G1: Age = 50.9 (9.3) Chinese = 46%; Indian = 35%; Korean = 19% Female = 40% G2: Age = 50.9 (9.3) Chinese = 46%; Indian = 36%; Korean = 18% Female = 43%	None

Evidence Table 8. Key Question 2: Studies of sitagliptin and saxagliptin

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Adverse Events	Changes in Lipid Concentrations
Mohan, 2009 18 weeks China, India, Korea Merck Good	Withdrawals due to AEs G1: n=4 G2: n=6 Clinical AEs: G1: n patients = 27 (15.2%); G2: n patients = 82 (23.3%) Lab AEs: G1: 7.0% of pts G2: 6.5% of pts Upper Respiratory Tract Infection: G1: 2.8% G2: 2.8% GI effects: G1: 0.6% G2: 5.1%	NR

Evidence Table 8. Key Question 2: Studies of sitagliptin and saxagliptin

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Inclusion and Exclusion Criteria	Overall Sample Size Interventions Group Sizes	Baseline Population Characteristics Mean Age, years Race/Ethnicity % Female	Background Medications
Raz, 2008 30 weeks Multinational Merck Fair	Inclusion: 18 - 78 years of age, currently on metformin monotherapy or any other single oral hypoglycemic agent or being treated with metformin in combination with another oral hypoglycemic agent, and HbA1c was 8.0 - <11.0%. Exclusion: Received treatment with insulin within 8 weeks prior to screening, treatment with a TZD or exenatide within 12 weeks, had type 1 diabetes, a BMI < 20 kg/m2 or > 43 kg/m2, or fasting plasma glucose during run-in that was consistently < 7.2 mmol/L or > 15.6 mmol/L.	N=190 randomized, 187 analyzed G1: (placebo) n=94 G2: (sitagliptin 100mg qd) n=96	G1: Age: 56.1 (9.5) Race: White 47%, Hispanic 25%, Black 1%, Multiracial 25%, Other 2% Female: 58.5% G2: Age: 53.6 (9.5) Race: White 42%, Hispanic 32%, Black 3%, Multiracial 22%, Other 1% Female: 49%	metformin

Evidence Table 8. Key Question 2: Studies of sitagliptin and saxagliptin

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Adverse Events	Changes in Lipid Concentrations
Raz, 2008 30 weeks Multinational Merck Fair	Discontinued because of clinical AE G1: 2 (2.1) G2: 0 Discontinued because of laboratory AE G1: 0 G2: 2 (2.1) One or more clinical AE G1: 56 (59.6) G2: 55 (57.3) One or more drug-related clinical AE G1: 4 (4.3) G2: 5 (5.2) One or more serious clinical AE G1: 5 (5.3) G2: 0 One or more laboratory AE G1: 4 (4.3) G2: 15 (15.6) Respirtatory Tract Infection G1: 3 (3.2) G2: 0 Urinary Tract Infection G1: 3 (3.2) G2: 4 (4.2) Pharyngitis G1: 6 (6.4) G2: 4 (4.2) Nasopharyngitis G1: 7 (7.4) G2: 7 (7.3) Pharyngotonsillitus G1: 1 (1.1) G2: 3 (3.1) Influenza G1: 3 (3.2) G2: 1 (1.0) Hypoglycemia: G1: 0 (1 patient in this group experienced hypoglycemia while on glipizide rescue therapy) G2: 1 (1.0) Gastritis: G1: 3 (3.2) G2: 2 (2.1) Prespecified GI clinical AEs Overall: G1: 7 (7.4) G2: 10 (10.4) Abdominal pain: G1: 0 G2: 2 (2.1) Nausea: G1: 2 (2.1) G2: 2 (2.1) Diarrhea: G1: 5 (5.3) G2: 6 (6.3) Vomiting: G1: 1 (1.1) G2: 0	No significant between-group differences in the fasting blood lipids (TC, HDL, LDL, triglycerides). Data not shown.

Evidence Table 8. Key Question 2: Studies of sitagliptin and saxagliptin

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Inclusion and Exclusion Criteria	Overall Sample Size Interventions Group Sizes	Baseline Population Characteristics Mean Age, years Race/Ethnicity % Female	Background Medications
Seck, 2010 104 weeks Multinational Merck Fair Extension of Nauck, 2007	"Men and women (aged 18–78 years) with T2DM who were either not taking an antihyperglycaemic agent, were taking any oral antihyperglycaemic agent as monotherapy or were taking metformin in combination with another oral antihyperglycaemic agent"	1172 randomized; 519 entered year 2 G1: (sitagliptin 100mg) n=248 G2: (glipizide) n=256	G1: Age: 57.6 Race: White 77.4%; Asian 9.3%, Black 3.6%, Hispanic 5.6%, other 4% Female: 42.7% G2: Age: 57.0 Race: White 78.5%; Asian 8.2%, Black 5.1%, Hispanic 5.1% other 3.1% Female: 37.1%	metformin

Evidence Table 8. Key Question 2: Studies of sitagliptin and saxagliptin

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Adverse Events	Changes in Lipid Concentrations
Seck, 2010 104 weeks Multinational Merck Fair Extension of Nauck, 2007	Number withdrawn because of AEs: G1: n=23 (3.9%) G2: n=29 ((5%) Overall AEs: G1: 452 (76.9%) G2: 480 (82.2%) Cystitis: G1: 8 G2: 1 Nasopharyngitis: G1: 71 G2: 61 Urinary Tract Infection: G1: 44 G2: 25 Upper Respiratory Tract Infection: G1: 73 G2: 79 Sinusitis: G1: 26 G2: 18 Hypoglycemia: G1: 31 (5.3%) G2: 199 (34.1%)	

Evidence Table 8. Key Question 2: Studies of sitagliptin and saxagliptin

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Inclusion and Exclusion Criteria	Overall Sample Size Interventions Group Sizes	Baseline Population Characteristics Mean Age, years Race/Ethnicity % Female	Background Medications
Vilsboll, 2010 24 weeks Multinational Merck Fair	Inclusion: at least 21 years of age, had a body mass index (BMI) >20 kg/m2 and <43 kg/m2, were taking insulin (≥15 IU/day; long- or intermediate-acting or premixed insulin) alone or in combination with metformin (at a dose of at least 1500 mg/day), and had inadequate glycaemic control (HbA1c 7.5–11% at screening) Exclusion: type 1 diabetes, fasting plasma glucose (FPG) <130 mg/dl, unstable cardiac disease (including new or worsening signs or symptoms of coronary heart disease within 3 months of study entry or any of the following within 6 months of study entry: acute coronary syndrome, stroke or ischaemic event; coronary artery intervention, or NYHA Class II-IV congestive heart failure), significant renal impairment (creatinine clearance<50 ml/min), elevated (more than twofold the upper limit of normal) alanine aminotransferase (ALT) or aspartate aminotransferase (AST), or elevated triglycerides (>600 mg/dl), treatment with oral antihyperglycaemic agents (except metformin) or exenatide within 8–12 weeks of study entry	N = 641 G1: sitagliptin 100mg N=322 G2: placebo N=319	G1: Age 58.3, white 71%, black 6%, asian 17%, other 6%, female 51% G2: Age 57.2, white 69%, black 7%, asian 19%, other 5%, female 47%	insulin +/- metformin

Evidence Table 8. Key Question 2: Studies of sitagliptin and saxagliptin

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Adverse Events	Changes in Lipid Concentrations
Vilsboll, 2010 24 weeks Multinational Merck Fair	Withdrawn because of adverse events: G1: 11 (3.4%) G2: 4 (1.3%) Overal adverse events: G1: 168 G2: 137 influenza: G1: 4%; G2: 3.8% nasopharyngitis G1: 3.1%; G2: 2.5% URI G1: 3.1%; G2: 3.4% UTII G1: 2.8%; G2: 1.9% Hypoglycemia G1: 50; G2: 25	

Evidence Table 9. Key Question 2: Studies of exenatide and liraglutide

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Inclusion and Exclusion Criteria	Overall Sample Size Interventions Group Sizes	Baseline Population Characteristics Mean Age, years Race/Ethnicity % Female	Background Medications
Head-to-head studies				
Buse, 2009 LEAD-6 26 weeks Multinational Novo Nordisk Fair	Inclusion: Aged 18 - 80 with T2DM, HbA1c between 7 - 11 %, BMI ≤ 45kg, on stable treatment with maximally tolerated doses of metformin, sulfonylurea, or both for at least 3 months Exclusion: Previous insulin treatment (except short-term treatment for intercurrent illness), previous exposure to exenatide or liraglutide, impaired liver or renal function, clinically significant cardiovascular disease, retinopathy or maculopathy requiring acute treatment, hypertension (>180/100 mm Hg), or cancer	N=464 G1: (liraglutide 1.8 mg qd) n=233 G2: (exenatide 10 ug bid) n=231	G1: Age: 56.3 Race: White 93%, Asian/ Pacific Islander <1%, Black (including African American) 6%, Hispanic or Latin American 14%, Other 1% Female: 51% G2: Age: 57.1 Race: White 91%, Asian/ Pacific Islander 2%, Black (including African American) 5%, Hispanic or Latin American 11%, Other 2% Female: 45%	metformin with or without sulfonylurea

Evidence Table 9. Key Question 2: Studies of exenatide and liraglutide

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Adverse Events	Changes in Lipid Concentrations
Head-to-head studies		
Buse, 2009 LEAD-6 26 weeks Multinational Novo Nordisk Fair	Total Withdrawals because of AEs: G1: 23 (9.9) G2: 31 (13.4) Cancers/Neoplasms: G1: 1 (0.4%) G2: 0 Serious AEs (Infections and Infestations): G1: 2 (0.9) G2: 1 (0.4) Any Severity (Infections and Infestations): G1: 78 (33.2) G2: 85 (36.6) Bronchitis: G1: 12 (5.1) G2: 16 (6.9) Nasopharyngitis: G1: 27 (11.5) G2: 31 (13.4) Upper Respiratory Tract Infection: G1: 15 (6.4) G2: 14 (6.0) Major Hypoglycemia: G1: 0 G2: 2	Change from baseline, data are least square means (SE): TC mmol/L G1: -.20 (0.07) G2: -0.09 (0.07) Estimated Treatment Difference: -0.11 (-0.23 to 0.02), *P* =0.0946 LDL Cholesterol mmol/L G1: -0.44 (0.06) G2: -0.40 (0.06) Estimated Treatment Difference: -0.04 (-0.15 to 0.06), *P* value=0.4412 HDL Cholesterol mmol/L G1: -0.04 (0.02) G2: -0.05 (0.02) Estimated TreatmentDifference: 0.01 (-0.02 to 0.04), *P* =0.5105 Triglycerides G1: -0.41 (0.10) G2: -0.23 (0.10) Estimated Treatment Difference: -0.18 (-0.37 to 0.00), *P* =0.0485

Evidence Table 9. Key Question 2: Studies of exenatide and liraglutide

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Adverse Events	Changes in Lipid Concentrations
Buse, 2009 continued	Minor Hypoglycemia: G1: 60 (26) G2: 78 (34) Minor Hypoglycemia in subgroups using metformin: G1: 4 (6) n=64 G2: 7 (11) n=63 Minor Hypoglycemia in subgroups using sulfonylurea with or w/o metformin: G1: 56 (33) n=171 G2: 71 (42) n=169 Serious GI AEs: G1: 8 (3.4) G2: 5 (2.2) Any Severity GI AEs: G1: 107 (45.5) G2: 99 (42.7) Constipation: G1: 12 (5.1) G2: 6 (2.6) Diarrhea: G1: 29 (12.3) G2: 28 (12.1) Dyspepsia: G1: 21 (8.9) G2: 11 (4.7) Nausea: G1: 60 (25.5) G2: 65 (28) Vomiting: G1: 14 (6.0) G2: 23 (9.9)	

Evidence Table 9. Key Question 2: Studies of exenatide and liraglutide

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Inclusion and Exclusion Criteria	Overall Sample Size Interventions Group Sizes	Baseline Population Characteristics Mean Age, years Race/Ethnicity % Female	Background Medications
Pratley, 2010 26 weeks Multinational Novo Nordisk Fair	Inclusion: 18-80 y; T2DM; HbA1c 7.5-10.0%;BMI ≤ 45.0 kg/m2; treatmed with metformin (≥1500 mg/d) for ≥ 3 mo Exclusion: Prior treatment with any antihperglycemic drug (except metformin) within 3 mo; Recurrent major hypoglycemia; hypoglycemic unawareness; present use of any drug that could affect glucose (except metformin); contraindication to trial drugs; cardiovascular disease; cancer	N = 665 G1: liraglutide (1.2mg/d) n=225 G2: liraglutide (1.8 mg/d) n=221 G3: sitagliptin (100mg/d) n=219	G1: Age 55.9; Caucasian 82%, Hispanic/Latino 17%, Black 10%, Asian 3%, Other 5%; Female 48% G2: Age 55.0; Caucasian 91%, Hispanic/Latino 16%, Black 5%, Asian 1%, Other 4%; Female 48% G3: Age 55.0; Caucasian 87%, Hispanic/Latino 15%, Black 7%, Asian 2%, Other 4%; Female 45%	metformin

Evidence Table 9. Key Question 2: Studies of exenatide and liraglutide

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Adverse Events	Changes in Lipid Concentrations
Pratley, 2010 26 weeks Multinational Novo Nordisk Fair	Number of withdrawals because of AEs: G1: 14 (6.3%) G2: 15 (6.9%) G3: 4 (1.8%) Serious AEs: G1: n=6 (3%) G2: n=6 (3%) G3: n=4 (2%) Severe AEs: G1: n=7 (3%) G2: n=7 (3%) G3: n=8 (4%) AE in >5% of participants in any treatment group: G1: 146 (66%) G2: 159 (73%) G3: 127 (58%) Severe GI AEs: G1: 3 (1%) G2: 3 (1%) G3: 4 (2%) GI AEs: G1: 73 (33%) G2: 88 (40%) G3: 46 (21%)	TC, mg/dL (95%CI): G1: -1.16 (-6.56, 3.09) G2: -6.56 (-10.81, -2.70) G3: -0.77 (-5.02, 3.47) Estimated Treatment Differences: G1 vs. G3: -0.39 (-6.18, 5.02), *P* =0.8458 G2 vs. G3: -6.18 (-11.58, -0.39), *P* =0.0332 LDL Cholesterol, mg/dL (95% CI): G1: 3.09 (-0.39, 6.56) G2: 1.93 (-1.54, 5.41) G3: 5.02 (1.54, 8.49) Estimated Treatment Differences: G1 vs. G3: -1.93 (-6.56, 2.70), *P* =0.4414 G2 vs. G3: -3.09 (-7.72, 1.54), *P* =0.2055 HDL Cholesterol, mg/dL (95%CI) G1: 0.00 (-0.77, 0.77) G2: 0.00 (-0.77, 1.16) G3: 0.00 (-0.77, 0.77) Estimated Treatment Differences: G1 vs. G3: 0.00 (-1.16, 1.16), *P* =0.9507 G2 vs. G3: 0.00 (-1.16, 1.16), *P* =0.9225

Evidence Table 9. Key Question 2: Studies of exenatide and liraglutide

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Adverse Events	Changes in Lipid Concentrations
Pratley, 2010 continued	Neoplasms (benign, malingant, and unspecified): G1: 1 (<1%) G2: 0 G3: 1 (<1%) Infections and Infestations: Severe: G1: 1 (<1%) G2: 1 (<1%) G3: 1 (<1%) AEs: G1: 62 (28%) G2: 59 (27%) G3: 63 (29%) Nasopharngitis: G1: 21 (10%) G2: 28 (13%) G3: 26 (12%) Influenza: G1: 13 (6%) G2: 2 (1%) G3: 5(2%)	Triglycerides, mg/dL (95%CI) G1: -16.81 (-33.63, 0.00) G2: -38.05 (-53.98, -22.12) G3: -35.40 (-51.33, -19.47) Estimated Treatment Differences: G1 vs. G3: 18.58 (-3.54, 40.71), *P* =0.0962 G2 vs. G3: -2.65 (-24.78, 18.58), *P* =0.8021

Evidence Table 9. Key Question 2: Studies of exenatide and liraglutide

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Adverse Events	Changes in Lipid Concentrations
Pratley, 2010 continued	Major Hypoglycemic Event: G1: 1 G2: 0 G3: 0 Minor Hypoglycemia: G1: 12 (5%) G2: 11 (5%) G3: 10 (5%) Nausea: G1: 46 (21%) G2: 59 (27%) G3: 10 (5%) Vomiting: G1: 17 (8%) G2: 21 (10%) G3: 9 (4%) Diarrhea: G1: 16 (7%) G2: 25 (11%) G3: 10 (5%) Constipation: G1: 10 (5%) G2: 11 (5%) G3: 6 (3%) Dyspepsia: G1: 7 (3%) G2: 14 (6%) G3: 5 (2%)	

Evidence Table 9. Key Question 2: Studies of exenatide and liraglutide

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Inclusion and Exclusion Criteria	Overall Sample Size Interventions Group Sizes	Baseline Population Characteristics Mean Age, years Race/Ethnicity % Female	Background Medications
Active-control studies				
Bergenstal, 2009 Novo-Log Mix vs Exenatide Study Group 24 weeks United States Novo Nordisk Poor	Inclusion: T2DM >6 months, age >18 and <80 years, HbA1c >8%, insulin naïve (received no insulin for more than 2 weeks of daily use in the preceding 6 months), had received at least 1500 mg/day metformin and a sulfonylurea at at least half the maximum dose for 3 months before screening Exclusion: Significant cardiac disease within 12 months prior to the study, hepatic insufficiency, renal insufficiency, used thiazolidinediones, alpha-glucosidase inhibitors or meglitinides within 6 months before the study, had a history of an eating disorder or were receiving current treatment with a weight-reducing diet.	N=372 G1: (exenatide 5ug bid increased to 10ug bid) n=124 G2: (biphasic insulin aspart 30 qd started at 12 IU qd and adjusted as indicated) G3: (biphasic insulin aspart 30 bid started at 12 IU divided in to two doses and adjusted as indicated)	G1: Age: 52.5 (10.62) Race: American Indian/Alaska Native 10.5%, Asian 1.6%, Black 19.4%, White 63.7%, Other 4.8% Female: 51.6% G2: Age: 51.8 (10.90) Race: American Indian/Alaska Native 8.1%, Asian 2.4%, Black 18.5%, White 67.7%, Other 3.2% Female: 51.6% G3: Age: 53.4 (9.96) Race: American Indian/Alaska Native 8.9%, Asian 1.6%, Black 26.6%, White 59.7%, Other 3.2% Female: 52.4%	metformin and sulfonylurea

Evidence Table 9. Key Question 2: Studies of exenatide and liraglutide

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Adverse Events	Changes in Lipid Concentrations
Active-control studies		
Bergenstal, 2009 Novo-Log Mix vs Exenatide Study Group 24 weeks United States Novo Nordisk Poor	Number of withdrawals because of Aes: G1: 9 (7.3) G2: 1 (0.8) G3: 6 (4.8) Hypoglycemia: Serious Events: G1: NR G2: NR G3: 1 Major Events: G1: 0 G2: 4 G3: 6 Combined Hypoglycemic Events (major, minor, symptoms only): G1: 29% G2: 56% G3: 61% The percent of subjects reporting minor hypoglycemic events was significantly greater in the biphasic insulin aspart 30 qd and bid groups vs. the exenatide group: 39.3 v 20.2%, *P* =0.0013 (biphasic insulin aspart 30 qd v exenatide) 52.1 v 20.2%,*P* =0.0001 (biphasic insulin aspart 30 bid v exenatide)	NR

Evidence Table 9. Key Question 2: Studies of exenatide and liraglutide

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Adverse Events	Changes in Lipid Concentrations
Bergenstal, 2009 continued	GI effects: G1: 29% G2: 9% G3: 8% Cardiac Arrhythmia Leading to Death: G3: 1 Hypokalemia: G3: 1 Events in G1 included: rash, gastric reflux, nausea or vomiting, elevated blood sugar, dizziness, nervousness, worsening asthma Events in G2 included: psoriasis Events in G3 included: worsening neuropathy, drooping of upper left eyelid, shoulder and neck pain, diarrhea and nausea, shingles	

Evidence Table 9. Key Question 2: Studies of exenatide and liraglutide

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Inclusion and Exclusion Criteria	Overall Sample Size Interventions Group Sizes	Baseline Population Characteristics Mean Age, years Race/Ethnicity % Female	Background Medications
DeFronzo, 2010 20 weeks US Eli Lilly Fair	Inclusion: age 18 –75 years, BMI 25–40 kg/m2, stable body weight for at least 6 months prior to screening, A1C 6.8–10.0%, stable dose of metformin for at least 6 weeks prior to screening and no treatment with any other antidiabetic medication, and absence of islet cell autoantibodies. Exclusion: NR	N=137 G1: (exenatide) n=45 G2: (rosiglitazone + exenatide) n=47 G3: (rosiglitazone) n=45	Age: 56 Race: White 61% Female: 49%	metformin

Evidence Table 9. Key Question 2: Studies of exenatide and liraglutide

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Adverse Events	Changes in Lipid Concentrations
DeFronzo, 2010 20 weeks US Eli Lilly Fair	Number of withdrawals because of (specified) AEs: G1: 2 (nausea) G2: 2 (nausea), 1 (vomiting), and 1 (breast cancer) G3: 1 (peripheral edema) Overall AEs: G1: -2.8 (0.5) G2: -1.2 (0.5) G3: +1.5 (0.5) G1 vs.G2: *P* =0.038 G1 vs. G3: *P* <0.001 G3 vs. G2: *P* <0.001 Hypoglycemia: G1: 2 (4%) G2: 2 (4%) G3: 0 Nausea: G1: 47% G2: 47% G3: 4% Vomiting: G1: 22% G2: 19% G3: 0 Diarrhea: G1: 7 % G2: 21% G3: 4% Pedal Edema: G1: 8 (18%) G2: 14 (30%) G3: 21 (47%) G3 vs. G1: *P* =0.007 G2 vs. G1 or G3: *P* =NS	Change in Fasting (SE) TC: G1: -0.13 (0.12) G2: +0.26 (0.11) G3: +0.44 (0.12) G1 vs. G2: *P* =0.020 G1 vs. G3: *P* <0.001 G3 vs. G2: *P* =0.276 HDL: G1: 0.02 (0.03) G2: 0.05 (0.03) G3: 0.06 (0.03) G1 vs. G2: *P* =0.566 G1 vs. G3: *P* =0.445 G3 vs. G2: *P* =0.840 LDL: G1: -0.05(0.10) G2: 0.10 (0.10) G3: 0.33 (0.10) Exe vs. Exe+rosi *P* =0.308 Exe vs. rosi *P* =0.008 Rosi vs. Exe+rosi *P* =0.096 Triglycerides: G1: -0.34 (0.17) G2: 0.00 (0.16) G3: 0.07 (0.17) G1 vs. G2: *P* =0.140 G1 vs. G3: *P* =0.079 G3: vs. G2: *P* =0.752

Evidence Table 9. Key Question 2: Studies of exenatide and liraglutide

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Inclusion and Exclusion Criteria	Overall Sample Size Interventions Group Sizes	Baseline Population Characteristics Mean Age, years Race/Ethnicity % Female	Background Medications
Russel-Jones, 2009 LEAD-5 26 weeks Multinational Novo Nordisk Good	Inclusion: 18–80 years old, with type 2 diabetes treated with oral glucose-lowering drugs (OGLAs) (94–95% combination therapy) for at least 3 months ; HbA1c level of 7.5–10% if on OGLA monotherapy or 7–10% if on OGLA combination therapy, and BMI ≤ 45kg/m2. Exclusion: Insulin within 3 months prior to the trial (except for short-term treatment for intercurrent illness); impaired hepatic or renal function, clinically significant cardiovascular disease, proliferative retinopathy or maculopathy, hypertension (≥180/100 mmHg) or cancer; pregnant; experienced recurrent hypoglycaemia or hypoglycaemia unawareness; were seropositive for hepatitis B antigen or hepatitis C antibody; or used any drugs except for OGLAs that could affect blood glucose levels	N=581 G1: (liraglutide 1.8mg) n=232 G2: (placebo) n=115 G3: (insulin glargine, dose titrated to fasting blood sugar) n=234	Age: G1: 57.6 G2: 57.5 G3: 57.5 Ethnicity: NR % Female: G1: 43 G2: 51 G3: 40	All patients on metformin 2g and glimepiride 4mg

Evidence Table 9. Key Question 2: Studies of exenatide and liraglutide

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Adverse Events	Changes in Lipid Concentrations
Russel-Jones, 2009 LEAD-5 26 weeks Multinational Novo Nordisk Good	Number of withdrawals because of AEs: Overall: 16 (2.95%) G1: 11 (4.78%) G2: 1 (0.09%) G3: 5 (2.16%) Major Hypoglycemic Event (events/patient/year): G1: 0.06 events/patient/year G2: 0 G3: 0 Minor Hypoglycemic Event (events/patient/year): G1: 1.2 events/patient/year G2: 1.0 events/patient/year G3: 1.3 events/patient/year Nausea: G1: 32 G2: 4 G3: 3 *P* <0.0001 Diarrhea: G1: 23 G2: 6 G3: 3 *P* <0.0001	NR

Evidence Table 9. Key Question 2: Studies of exenatide and liraglutide

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Adverse Events	Changes in Lipid Concentrations
Russel-Jones, 2009 continued	Dyspepsia: G1: 15 G2: 1 G3: 4 *P* =0.0042 Vomiting: G1: 15 G2: 4 G3: 1 *P* =0.0005 Nasopharyngitis: G1: 21 G2: 10 G3: 26 *P* =0.6864 Headache: G1: 22 G2: 9 G3: 13 *P* =0.2687 Change in Systolic Blood Pressure: G1: 4.0 mmHg reduction G2: 1.4 mmHg reduction; treatment difference −2.53 mmHg, 95% CI −5.36, 0.29; *P* =0.0791 G3: 0.54 mmHg increase; treatment difference −4.51 mmHg, 95% CI −6.82, −2.20; *P* =0.0001	

Evidence Table 9. Key Question 2: Studies of exenatide and liraglutide

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Inclusion and Exclusion Criteria	Overall Sample Size Interventions Group Sizes	Baseline Population Characteristics Mean Age, years Race/Ethnicity % Female	Background Medications
Garber, 2009 LEAD-3 Mono 52 weeks US and Mexico Novo Nordisk Fair	Inclusion: 18–80 years, BMI of 45 kg/m² or less, with T2DM; treated with diet and exercise (36·5% of patients randomised) or up to half the highest dose of oral antidiabetic drug monotherapy (63·5%) including sulphonylureas, meglitinides, aminoacid derivatives, biguanides, α-glucosidase inhibitors, and thiazolidinediones (1500 mg metformin or 30 mg pioglitazone were allowed) for at least 2 months; a screening HbA1c value of 7–11% if treated with diet and exercise or 7–10% with oral antidiabetic monotherapy. Exclusion: insulin treatment during the previous 3 months (except short-term treatment for intercurrent illness), treatment with systemic corticosteriods, hypoglycaemia unawareness or recurrent severe hypoglycaemia, and impaired liver function (aspartate aminotransferase or alanine aminotransferase concentrations ≥2.5 times upper normal range.	N=746 G1: (liraglutide 1.2 mg) n=251 G2: (liraglutide 1.8 mg) n=247 G3: (glimepiride 8 mg) n=248	Age: G1: 53.7 G2: 52.0 G3: 53.4 Race/Ethnicity: White % G1: 80 G2: 75 G3: 77 Black % G1: 14 G2: 12 G3: 12 Asian % G1: 2 G2: 6 G3: 4 Other % G1: 5 G2: 7 G3: 7 % Female: G1: 53 G2: 51 G3: 46	None

Evidence Table 9. Key Question 2: Studies of exenatide and liraglutide

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Adverse Events	Changes in Lipid Concentrations
Garber, 2009 LEAD-3 Mono 52 weeks US and Mexico Novo Nordisk Fair	Number of withdrawals because of AEs: G1: 25 (10.0) G2: 18 (7.3) G3: 15 (6.0) Infections and Infestations: G1: 119 (47%) G2: 102 (41%) G3: 90 (36%) Influenza: G1: 17 (7%) G2: 20 (8%) G3: 9 (4%) Nasopharyngitis: G1: 17 (7%) G2: 9 (4%) G3: 13 (5%) Sinusitis: G1: 15 (6%) G2: 13 (5%) G3: 15 (6%) Upper Respiratory Tract Infection: G1: 23 (9%) G2: 24 (10%) G3 14 (6%)	NR

Evidence Table 9. Key Question 2: Studies of exenatide and liraglutide

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Adverse Events	Changes in Lipid Concentrations
Garber, 2009 continued	Urinary Tract Infection: G1: 20 (8%) G2: 10 (4%) G3: 10 (4%) Major (requiring third party intervention): G1: 0 G2: 0 G3: 0 Minor: G1: 0.3 events/patient/year G2: 0.25 events/patient/year G3: 1.96 events/patient/year GI disorders: G1: 122 (49%) G2: 126 (51%) G3: 64 (26%) Constipation: G1: 21 (8%) G2: 28 (11%) G3: 12 (5%) Diarrhea: G1: 39 (16%) G2: 46 (19%) G3: 22 (9%) Flatulence: G1: 4 (2%) G2: 13 (5%) G3: 4 (2%)	

Evidence Table 9. Key Question 2: Studies of exenatide and liraglutide

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Adverse Events	Changes in Lipid Concentrations
Garber, 2009 continued	Nausea: G1:69 (27%) G2: 72 (29%) G3:21 (8%) Vomiting: G1: 31 (12%) G2: 23 (9%) G3: 9 (4%) Injury, poisoning, and procedural complications: G1: 22 (9%) G2: 24 (10%) G3: 29 (12%) Investigations: G1: 16 (6%) G2: 23 (9%) G3: 18 (7%) Metabolism and nutrition disorders: G1: 38 (15%) G2: 35 (14%) G3: 28 (11%) Musculoskeletal and connective tissue disorders: G1: 48 (19%) G2: 46 (19%) G3: 38 (15%) Back pain: G1: 14 (6%) G2: 11 (5%) G3: 11 (4%)	

Evidence Table 9. Key Question 2: Studies of exenatide and liraglutide

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Adverse Events	Changes in Lipid Concentrations
Garber, 2009 continued	Nervous system disorders: G1: 56 (22%) G2: 49 (20%) G3: 55 (22%) Dizziness: G1: 13 (5%) G2: 16 (6%) G3: 13 (5%) Headache: G1: 27 (11%) G2: 18 (7%) G3: 23 (9%) Psychiatric disorders: G1: 21 (8%) G2: 21 (9%) G3: 14 (5%) Respiratory, thoracic, and mediastinal disorders: G1: 21 (8%) G2: 28 (11%) G3: 28 (11%) Skin and subcutaneous tissue disorders: G1: 23 (9%) G2: 24 (10%) G3: 17 (7%) Vascular disorders: G1: 11 (4%) G2: 15 (6%) G3: 17 (7%) Hypertension: G1: 7 (3%) G2: 8 (3%) G3: 15 (6%)	

Evidence Table 9. Key Question 2: Studies of exenatide and liraglutide

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Inclusion and Exclusion Criteria	Overall Sample Size Interventions Group Sizes	Baseline Population Characteristics Mean Age, years Race/Ethnicity % Female	Background Medications
Madsbad, 2004 12 weeks Scandanavia and the UK Novo Nordisk Fair	Inclusion: Men and women age 30 years or more; T2DM diagnosis (according to American Diabetes Association criteria); BMI 40 kg/m2 or less, were being treated with diet or an oral hypoglycemic agent (OHA), and had an HbA1c 9.5% or less (OHA) or 7.5–10.0% (diet) Exclusion: Liver or renal disease, heart failure, unstable angina pectoris, myocardial infarction within the previous 12 months, concomitant treatment with thiazolidinediones or other investigational drugs, or other significant conditions likely to affect a patient's diabetes and/or ability to complete the trial. Women who were pregnant, breast-feeding, or not using an adequate method of contraception	N=193 (190 in ITT) G1: liraglutide 0.045 mg n=26 G2: liraglutide 0.225 mg n= 24 G3: liraglutide 0.45 mg n=27 G4: liraglutide 0.60 mg n=30 G5: liraglutide 0.75 n=28 G6: placebo N = 29 G7: glimepiride n=26	Age: G1: 53 (9.0) G2: 58 (7.5) G3: 57 (11.3) G4: 57 (7.7) G5: 58 (9.7) G6: 57 (9.4) G7: 57 (9.2) Race/Ethnicity: NR % Female: G1: 15% G2: 38% G3: 33% G4: 33% G5: 43% G6: 31% G7: 38%	None

Evidence Table 9. Key Question 2: Studies of exenatide and liraglutide

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Adverse Events	Changes in Lipid Concentrations
Madsbad, 2004 12 weeks Scandanavia and the UK Novo Nordisk Fair	Number of withdrawals because of AEs: G1: 0 G2: 1 (4.2%) G3: 0 G4: 1 (3.3%) G5: 1 (3.6%) G6: 0 G7: 0 Overall WDs: 3/190 or 1.6% Overall Adverse Events: G1-G5: All liraglutide 60% (81/135) G6: 55% (16/29) G7: 35% (9/26) Hypoglycemia: Minor hypoglycemia blood glucose < 2.8 mmol/L G1: 0 G2: 0 G3: 0 G4: 1 (3.3%) G5: 0 G6: NR G7: 4 (15.3%)	

Evidence Table 9. Key Question 2: Studies of exenatide and liraglutide

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Adverse Events	Changes in Lipid Concentrations
Madsbad, 2004 continued	Nausea: G1-G5: 10 (7.4%) G2: 1 (3.4%) G3: NR Diarrhea: G1-G5: 5 (3.7%) G6: 0 G7: 0 Vomitting: G1-G5: 3 (2.2%) G6: 0 G7: 1 (3.8%) Constipation: G1-G5: 3 (2.2%) G6: 0 G7: 0	

Evidence Table 9. Key Question 2: Studies of exenatide and liraglutide

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Inclusion and Exclusion Criteria	Overall Sample Size Interventions Group Sizes	Baseline Population Characteristics Mean Age, years Race/Ethnicity % Female	Background Medications
Nauck, 2009 LEAD-2 26 weeks Multinational Novo Nordisk Fair	Inclusion: 18–80 years of age, had A1C between 7 and 11% (prestudy oral antidiabetic agents (OAD) monotherapy for 3 months) or between 7 and 10% (prestudy combination OAD therapy for 3 months); BMI 40 kg/m2 or less Exclusion: Insulin during the previous 3 months (except short-term treatment)	N=1091 (1087 in ITT) G1: liraglutide 0.6 mg n=242 G2: liraglutide 1.2 mg n=240 G3: liraglutide 1.8 mg n=242 G4: glimepiride 4 mg n=242 G5: placebo n=121	Age: G1: 56 G2: 57 G3: 57 G4: 57 G5: 56 Race/Ethnicity %: Caucasian: G1: 84, G2: 88, G3: 88, G4: 89, G5: 88 Black: G1: 2, G2: 4, G3: 2, G4: 2, G5: 3 Asian/Pacific Islander: G1: 13, G2: 8, G3: 7, G4: 9, G5: 7 Other: G1: 2, G2: 1, G3: 2, G4: 1, G5: 3 % Female: G1: 38 G2: 46 G3: 41 G4: 43 G5: 40	metformin

Evidence Table 9. Key Question 2: Studies of exenatide and liraglutide

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Adverse Events	Changes in Lipid Concentrations
Nauck, 2009 LEAD-2 26 weeks Multinational Novo Nordisk Fair	Number of withdrawals because of AEs: G1: 11(5) G2: 23 (10) G3: 29 (12) G4: 8 (3) G5: 2 (2) Hypoglycemia: Minor G1: ~7 G2: ~7 G3: ~ 7 G4: 41 G5: ~ 4 0.03– 0.14 events/year for the placebo and liraglutide groups and 1.23 events/year for the glimepiride) that was significantly less for all three liraglutide groups than for the glimepiride group (*P* <0.001). *No major hypoglycemia was reported in any of the groups Overall GI AEs: G1: 85 G2: 96 G3: 106 G4: 41 G5: 21 Diarrhea: G1: 24 G2: 19 G3: 36 G4: 10 G5: 5	NR

Evidence Table 9. Key Question 2: Studies of exenatide and liraglutide

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Inclusion and Exclusion Criteria	Overall Sample Size Interventions Group Sizes	Baseline Population Characteristics Mean Age, years Race/Ethnicity % Female	Background Medications
Placebo-controlled studies				
Apovian, 2010 24 weeks US Eli Lilly Fair	Inclusion: 8-75 years of age withn T2DM, treated for at least 6 weeks with a stable dose of metformin or a sulfonylurea, hemoglobin A1c (HbA1c) 6.6%-10.0%, body mass index 25-39.9 kg/m2, and history of stable body weight (not varying by >5% for at least 6 months Exclusion: Use of exogenous insulin, alpha-glucosidase inhibitors, a thiazolidinedione, weight loss agents within 6 months before study entry, evidence of poorly controlled hypertension within the previous 3 months, or history or presence of cardiac disease within 3 years	N=194 G1: exenatide n=96 G2: placebo n=98	Age: G1: 54.5 G2: 55.1 Ethnicity: NR % Female: G1: 63 G2: 62	Yes

Evidence Table 9. Key Question 2: Studies of exenatide and liraglutide

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Adverse Events	Changes in Lipid Concentrations
Placebo-controlled studies		
Apovian, 2010 24 weeks US Eli Lilly Fair	Number of withdrawals because of AEs: G1: 4.2% G2: 5.1% *P* =1.0 Hypoglycemia: Events per patient year G1: 7.1 (1.4) G2: 4.6 (1.4) *P* =0.127 (No events were severe) Nausea % (n): G1: 45% (43) G2: 19% (19) *P* <0.001 Vomitting % (n): D1: 22% (21) D2: 9% (9) *P* =0.017 Weight Gain: G1: -6.2 kg G2: -4.0 kg	Fasting Triglyceride (mmol/l): Baseline: G1: 1.62 (0.07) G2: 1.78 (0.07) After treatment: G1: 1.93 (0.11) G2: 1.92 (0.11) *P* =0.065

Evidence Table 9. Key Question 2: Studies of exenatide and liraglutide

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Inclusion and Exclusion Criteria	Overall Sample Size Interventions Group Sizes	Baseline Population Characteristics Mean Age, years Race/Ethnicity % Female	Background Medications
Gao, 2009 16 weeks Multiple, Asia Amylin Pharmaceuticals and Eli Lilly Good	Inclusion: Age 21-75, T2DM, treated with stable dose of metformin and/or sulfonylurea for at least 3 months, inadequate glycemic control (HbA1c >=7.0% and <=11.0%), BMI>21kg/m^2 and <35kg/m^2 Exclusion: Previous participation in any study using exenatide or GLP-1 analogs, participation in any study within 30 days, contraindications for metformin or sulfonylurea, treated with exogenous insulin for >1 week within 3 months, use of weight loss drugs within 1 month	N=472 randomized, 466 analyzed G1: (5ug [1st 4 weeks] to 10ug [12 weeks] exenatide twice daily + oral antidiabetic agents) n=234 G2: (placebo + oral antidiabetic agents) n=232	G1: Age 55 (9) Race: All Asian/Indian Female: 52% G2: Age 54 (9) Race: 100% Asian/Indian Female: 59%	metformin alone or metformin + sulfonylurea (usual dose)

Evidence Table 9. Key Question 2: Studies of exenatide and liraglutide

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Adverse Events	Changes in Lipid Concentrations
Gao, 2009 16 weeks Multiple, Asia Amylin Pharmaceuticals and Eli Lilly Good	Discontinuation due to AE: G1: 23 (9.8%); G2: 3 (1.3%) Any AEs: G1: n patients = 134 G2: n patients = 84 Upper Respiratory Tract Infection: G1: 4 G2: 5 Hypoglycemia: Reported: G1: 83 G2: 21 Documented: G1: 41 G2: 10 Severe: G1: 2 G2: 1 Nausea/vomiting/abdominal distention/anorexia/dyspepsia: G1: 119 G2: 13 Dizziness: G1: 14 G2: 4 Nasopharyngitis: G1: 17 G2: 12 Anorexia: G1: 9 G2: 1 Fever: G1: 6 G2: 4 Pain (joint, head): G1: 9 G2: 8	NR

Evidence Table 9. Key Question 2: Studies of exenatide and liraglutide

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Inclusion and Exclusion Criteria	Overall Sample Size Interventions Group Sizes	Baseline Population Characteristics Mean Age, years Race/Ethnicity % Female	Background Medications
Gill, 2010 12 weeks Multinational Eli Lilly Fair	Inclusion: 18-75 y; Stable metformin dose for 30 days or TZD for 120 days; BMI >25 and < 40 kg/m2; HbA1c 6.5-9.5%; Body weight with ≤ 10% variation for 3 mo; stable antihypertensive regimens maintained ≥ 6wk Exclusion: History of clinically significant cardiac disease or cardiac disease within one year; Clinically significant arrhythmia; Resting heart rate <60 or>100 beats/minute; repeated systolic blood pressure > 1600 mm Hg or diastolic blood pressure > 100 mm Hg; current treatment with beta blockers	N=54 G1: exenatide (5-10mg/bid) n=28 G2: placebo n=26	G1: Age: 57 Race: Caucasian 86%, African 7%, East Asian 4%, Hispanic 4% Female: 32% G2: Age: 54 Race: Caucasian 96%, African 0%, East Asian 4%, Hispanic 0% Female: 58%	"metformin (stable dose 30 days) or TZD (stable dose for 120 days)"

Evidence Table 9. Key Question 2: Studies of exenatide and liraglutide

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Adverse Events	Changes in Lipid Concentrations
Gill, 2010 12 weeks Multinational Eli Lilly Fair	Number of withdrawals because of AEs: G1: 0 G2: 1 (3.8%) Hypoglycemia (Percentage of patients reporting): G1: 7% G2: 4%	NR

Evidence Table 9. Key Question 2: Studies of exenatide and liraglutide

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Inclusion and Exclusion Criteria	Overall Sample Size Interventions Group Sizes	Baseline Population Characteristics Mean Age, years Race/Ethnicity % Female	Background Medications
Kadowaki, 2009 12 weeks Japan Amylin Pharmaceuticals and Eli Lilly Fair	Inclusion: 20-75 years, T2DM, weight >=50kg, been managing DM with sulfonylurea alone, sulfonylurea plus a biguanide, or sulfonylurea plus a TZD for at least 3 months, treatment with a-glucosidase inhibitor or meglitinide included after discontinuation; suboptimal glycemic control (HbA1c from 7%-10% for patients on sulfonylurea alone or sulfonylurea plus biguanide; 6.5-9.5% for patients treated with a-glucosidase inhibitor or meglitinide) Exclusion: Treatment with any exogenous insulin or drug directly affecting GI motility within last 3 months, clinically significant renal or hepatic disease, blood pressure >=160/100mm/Hg, hospitalization for cardiac disease within 1 year, clinically significant history of or active digestive disease within 1 year, active or untreated malignancy or remission from clinical malignancy for <5 years, hyperglycemia (self-monitored blood glucose >=250mg/dL fasting or >=350mg/dL anytime), >1 severe hypoglycemic episode requiring assistance within 3 months, pregnancy, no reliable birth control	N=153 randomized; 151 included in full analysis G1: (placebo + sulfonylurea/ sulfonyurea+biguanide/ sulfonylurea+TZD) n=40 G2: (2.5ug exenatide twice daily + sulfonylurea/ sulfonyurea+biguanide/ sulfonylurea+TZD) n=38 G3: (5ug exenatide twice daily + sulfonylurea/ sulfonyurea+biguanide/ sulfonylurea+TZD) n=37 G4: (5ug for 4 weeks then 10ug exenatide twice daily + sulfonylurea/ sulfonyurea+biguanide/ sulfonylurea+TZD) n=38	Age: G1: 60.5 (10.2) G2: 62.2 (7.8) G3: 60.7 (9.8) G4: 57.8 (10.4) Race: 100% Japanese Female: G1: 25.0% G2: 29.7% G3: 32.4% G4: 37.8%	sulfonylurea alone or with biguanise or TZD; patients using an a-glucosidase inhibitor or a meglitinide derivative could be included but were required to discontinue them before starting study drug

Evidence Table 9. Key Question 2: Studies of exenatide and liraglutide

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Adverse Events	Changes in Lipid Concentrations
Kadowaki, 2009 12 weeks Japan Amylin Pharmaceuticals and Eli Lilly Fair	Discontinued due to AE: G1: 1 (2.5%) G2: 3 (8.1%) G3: 4 (10.8%) G4: 5 (13.5%) AEs reported in >=10% of patients in any treatment group: G1: 22 G2: 35 G3: 55 G4: 72 Mild or moderate hypoglycemia: G1: 4 G2: 10 G3: 16 G4: 20 *No patients with severe hypoglycemia during the study Nausea/vomiting/constipation/diarrhea/ stomach discomfort/abdominal distention: G1: 3 G2: 13 G3: 24 G4: 27 Anorexia: G1: 0 G2: 0 G3: 1 G4: 5 Nasopharyngitis: G1: 11 G2: 9 G3: 3 G4: 7 Decreased appetite: G1: 0 G2: 0 G3: 3 G4: 5 Blood glucose decreased (separate from hypoglycemia): G1: 4 G2: 10 G3: 16 G4: 20	None

Evidence Table 9. Key Question 2: Studies of exenatide and liraglutide

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Inclusion and Exclusion Criteria	Overall Sample Size Interventions Group Sizes	Baseline Population Characteristics Mean Age, years Race/Ethnicity % Female	Background Medications
Moretto, 2008 24 weeks United States, Puerto Rico, Romania, Russia, and India Amylin Pharamceuticals and Eli Lilly and Company Good	Inclusion: >18 years of age, T2DM, BMI of 25 to 45 kg/m2, manage T2DM with diet and exercise consistent with local standards of medical care, have HbA1c between 6.5% and 10.0%. (Female patients eligible if they were postmenopausal, surgically sterile, or using contraceptives for >12 weeks before screening and continuing throughout the study.) Exclusion: Ever been treated with an antidiabetic agent; blood pressure >160/>110mm Hg, history or presence of clinically significant cardiac disease within the year prior to inclusion in the study, history of renal transplant or active renal or hepatic disease, received any medication for weight loss within 12 weeks prior to screening.	N=232 G1: (exenatide 5 ug bid) n=77 G2: (exenatide 10 bid) n=78 G3: (placebo) n=78 randomized, 77 analyzed	G1: 54 (10); White 65%, Asian 29%, Hispanice 6%, Black, 0%; Female 48% G2: 55 (10); White 72%, Asian 23%, Hispanic 1%, Black, 4%; Female 38% G3: 53 (9); White 66%, Asian 27%, Hispanice 3%, Black, 4%; Female 45%	None

Evidence Table 9. Key Question 2: Studies of exenatide and liraglutide

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Adverse Events	Changes in Lipid Concentrations
Moretto, 2008 24 weeks United States, Puerto Rico, Romania, Russia, and India Amylin Pharamceuticals and Eli Lilly and Company Good	Withdrawals due to AEs: G1: N=0 G2: N=2 G3: N=0 Overall 57/232 (25%) patients reported one or more AEs: G1: 16/77 (21%) G2: 26/78 (33%) G3: 15/77 (19%) Hypoglycemia: G1: 4/77 (5%) G2: 3/78 (4%) G3: 1/77 (1%) Nausea: G1: 2 (3%) G2: 10 (13%) G3: 0 Vomiting: G1: 3 (4%) G2: 3 (4%) G3: 0 Dyspepsia: G1: 0 G2: 4 (5) G3: 0 Diarrhea: G1: 0 G2: 2 (3%) G3: 0 Headache: G1: 4 (5%) G2: 2 (3%) G3: 3 (4%) Inlfluenza: G1: 3 (4%) G2: 5 (6%) G3: 3 (4%) Back Pain: G1: 3 (4%) G2: 2 (3%) G3: 1 (1%) Nasopharyngitis: G1: 2 (3%) G2: 4 (5%) G3: 1 (1%)	Change from Baseline: G1: TC = -0.2 (1.6) HDL = 1.3 (0.4) LDL = -2.0 (1.3) G2: TC = -1.1 (1.6) HDL = 0.4 (0.4) LDL = -1.3 (1.4) G3: TC = 3.4 (1.6) HDL = 0.5 (0.4) LDL = 1.4(1.3)

Evidence Table 9. Key Question 2: Studies of exenatide and liraglutide

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Inclusion and Exclusion Criteria	Overall Sample Size Interventions Group Sizes	Baseline Population Characteristics Mean Age, years Race/Ethnicity % Female	Background Medications
Seino, 2008 14 weeks Japan Novo Nordisk Good	Inclusion: T2DM treated with diet therapy with or without oral antidiabetic drug (OAD) monotherapy, HbA1c 7.0% and <10.0%, to be aged between 20 and 75 years and to have BMI <30 Exclusion: Insulin or insulin sensitizer within 16 weeks, or systemic corticosteroids, impaired hepatic or renal function;, congestive heart failure (New York Heart Association class III or IV), unstable angina pectoris or myocardial infarction within 12 months, uncontrolled hypertension (systolic blood pressure > 160 mmHg or diastolic blood pressure >100 mmHg), non-stabilised proliferative retinopathy or maculopathy.	N=226 G1: liraglutide 0.1 mg n=45 G2: liraglutide 0.3 mg n=46 G3: liraglutide 0.6 mg n=45 G4: liraglutide 0.9 mg n=44 G5: placebo n=46	Age: G1: 56.5 SD 8.4 G2: 56.8 SD 8.8 G3: 60.0 SD 7.0 G4: 55.5 SD 7.6 G5: 57.5 SD 8.7 Race/Ethnicity: NR % Female G1: 31 G2: 30 G3: 38 G4: 30 G5: 37	None

Evidence Table 9. Key Question 2: Studies of exenatide and liraglutide

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Adverse Events	Changes in Lipid Concentrations
Seino, 2008 14 weeks Japan Novo Nordisk Good	Withdrawals due to AEs: G1: 0 G2: 0 G3: 0 G4: 1 (2%) G5: 1 (2%) *Overall 154 (68%) No hypoglycemia GI Effects: G1: 8 (18%) G2: 7 (15%) G3: 14 (31%) G4: 13 (30%) G5: 11 (24%) Mean change from baseline (kg): G1: -0.05 G2: +0.13 G3: -0.10 G4: -0.48 G5: -0.95 Liraglutide-placebo mean, 95% CI: G1: 0.87, 0.19 to 1.55 G2: 1.08, 0.41 to 1.75 G3: 0.84, 0.16 to 1.51 G4: 0.46, -0.22 to 1.14 G5: NA	NR

Evidence Table 9. Key Question 2: Studies of exenatide and liraglutide

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Inclusion and Exclusion Criteria	Overall Sample Size Interventions Group Sizes	Baseline Population Characteristics Mean Age, years Race/Ethnicity % Female	Background Medications
Vilsboll, 2007 14 weeks Denmark, France, the Netherlands, Slovakia Novo Nordisk Fair	Inclusion: Age >=18 years; T2DM; HbA1c >=7.5% and <=10.0% (diet) or >=7.0% and <=9.5% (mono-oral antidiabetes drug); BMI<=40 (from a related article) Exclusion: NR	N=165 randomized, 163 exposed G1: (1.90mg liraglutide) n=41 G2: (1.25mg liraglutide) n=42 G3: (0.65mg liraglutide) n=40 G4: (placebo) n=40	G1: Age: 55.4 (11.4) Race: NR Female: 27% G2: Age: 53.8 (10.7) Race: NR Female: 45% G3: Age: 56.5 (9.3) Race: NR Female: 33% G4: Age: 57.7 (8.2) Race: NR Female: 53%	None

Evidence Table 9. Key Question 2: Studies of exenatide and liraglutide

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Adverse Events	Changes in Lipid Concentrations
Vilsboll, 2007 14 weeks Denmark, France, the Netherlands, Slovakia Novo Nordisk Fair	Withdrawals due to AEs: All: 7 (4%) G1: 2 (5%) G2: 1 (2%) G3: 1 (2.5%) G4: 3 (7.5%) Any GI event: G1: N=15 G2: N=12 G3: N=15 G4: N=9 Constipation: G1: N=1 Tachyopnea / GERD: G1: N=1 Nausea: G1: N=4 G2: N=1 G3: N=4 G4 N=1 Diarrhea: G1-G3: N=26 G4: N=5 Vomiting: G1-G3: N=4 G4: N=0 Injection site rash: G2 = 1 Increased blood glucose: G4: N=2 Hyperglycemia/nausea: G4: N=1 Influenza: G1: N=1 G4: N=1	Lipids (total, LDL, HDL, VLDL): NS Triglycerides (%, vs placebo) at 14 wks): G1 = -22% [35, -6] G2 = -15% [-30, 2] (NS) G3 = -19% [-33, -2]

Evidence Table 9. Key Question 2: Studies of exenatide and liraglutide

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Inclusion and Exclusion Criteria	Overall Sample Size Interventions Group Sizes	Baseline Population Characteristics Mean Age, years Race/Ethnicity % Female	Background Medications
Zinman, 2009 LEAD-4 26 weeks US and Canada Novo Nordisk Fair	Inclusion: T2DM, 18–80 years, had A1C between 7 and 11% (prestudy oral antidiabetic drug (OAD) monotherapy for 3 months) or 7–10% (prestudy combination OAD therapy for 3 months), and had BMI 45 kg/m2 Exclusion: Insulin treatment in previous 3 months(except shortterm treatment for intercurrent illness)	N=821 screened/enrolled N=533 randomized G1: Liraglutide 1.2 mg n= 178 G2: Liraglutide 1.8 mg n= 178 G3: Placebo n = 177	G1: Age: 55 Race %: Caucasian 81, Black 15, Asian 1, Indian 1, Other 2 Female: 43% G2: Age: 55 Race %: Caucasian 83, Black 10, Asian 3, Indian 1, Other 3 Female: 49% G3: Age: 55 Race %: Caucasian 84, Black 10, Asian 2, Indian 1, Other 3 Female: 38%	metformin and rosiglitazone

Evidence Table 9. Key Question 2: Studies of exenatide and liraglutide

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Adverse Events	Changes in Lipid Concentrations
Zinman, 2009 LEAD-4 26 weeks US and Canada Novo Nordisk Fair	Withdrawals due to Aes: G1: 11 G2: 27 G3: 6 Minor hypoglycemia: G1: 16 G2: 14 G3: 9 Events per year: G1: 0.4 G2: 0.6 G3: 0.2 G2 vs. G3: *P* =0.004 GI Events: G1: 80 G2: 100 G3 34 Peripheral Edema: G1: 9 G2: 3 G3: 14	TC: G1: -8.11 G2: -7.72 G3: -0.77 LDL: G1: -10.81 G2: -8.88 G3: -3.86 G1 vs G3: *P* <0.05 HDL: G1: -1.16 G2: -1.54 G3: -1.16 TG: G1: -33.62 G2: -28.31 G3: -11.5 G1 vs G3: *P* <0.05

Evidence Table 10. Key Question 2: Studies of rosiglitazone and pioglitazone

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Inclusion and Exclusion Criteria	Overall Sample Size Interventions Group Sizes	Baseline Population Characteristics Mean Age, years Race/Ethnicity % Female	Background Medications
Head-to-head studies				
Brackenridge, 2009 Poor	data not abstracted because of poor quality rating			
Deeg, 2007 GLAI 24 weeks US Eli Lilly & Takeda Fair	Inclusion; aged 35 years with T2DM; fasting triglyceride levels ≥150 mg/dl and <600 mg/dl; fasting LDL cholesterol levels <130 mg/dl; fasting serum C-peptide levels ≥ 1 ng/ml; and A1C values ≥7%, ≤ 11% if naıve to previous oral antihyperglycemic medication therapy; or A1C values ≥7%, ≤9.5% if previously treated with OAM monotherapy. Exclusion: treatment with insulin within 60 days of screening, combination oral antihyperglycemic medication therapy, any lipid-altering agent, and any weight loss agent	Overall: N=735 Original study: G1: n=369 G2: n=366 With lipid results: G1: (pioglitazone 30mg daily for 12 weeks, then pioglitazone 45mg daily for 12 weeks) n=333 G2: (rosiglitazone 4mg daily for 12 weeks, then rosiglitazone 4mg bid for 12 weeks) n=325	Baseline characteristics of original study population - not population in this analysis: G1: Age 55.9, SD 10.5 Race: White 64.8%, Hispanic 28.5%, Asian 2.7%, African 2.4% Other 1.6% Female: 46.1% G2: Age: 56.3, SD 11.3 Race: White 59.8%, Hispanic 32.2% Asian 3.3% African 2.7%, other 1.9% Female: 45.1%	None reported

Evidence Table 10. Key Question 2: Studies of rosiglitazone and pioglitazone

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Adverse Events	Changes in Lipid Concentrations	Weight Gain
Head-to-head studies			
Brackenridge, 2009 Poor			
Deeg, 2007 GLAI 24 weeks US Eli Lilly & Takeda Fair	NR	G1: least squares means (95% CI) TC: +9.6 (5.8, 13.5) LDL: +12.5 (9.3, 15.7) HDL: +5.2 (4.2, 6.1) TG: -46.7 (-62.5, -31) G2: TC: +28.5 (24.6, 32.3) LDL: +21.4 (18.1, 24.6) HDL: +2.3 (1.4, 3.3) TG: +12.3 (-3.5, 28.1) G1 vs G2: *P* <0.001 for all comparisons	NR

Evidence Table 10. Key Question 2: Studies of rosiglitazone and pioglitazone

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Inclusion and Exclusion Criteria	Overall Sample Size Interventions Group Sizes	Baseline Population Characteristics Mean Age, years Race/Ethnicity % Female	Background Medications
Chogtu, 2009 12 weeks India Funding NR Poor	Inclusion: both genders; age 30-70; T2DM; perscribed glimeperide and required an add-on therapy for poor glycemic control, normotensive, not on antihypertensive or hypolipidaemic drugs Exclusion: NR	N=63 patients randomized G1: (pioglitazone, titrated dose + glimeperide 2mg/day) n=28 G2: (rosiglitazone, titrated dose + glimeperide 2mg/day) n=28	NR	glimepiride

Evidence Table 10. Key Question 2: Studies of rosiglitazone and pioglitazone

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Adverse Events	Changes in Lipid Concentrations	Weight Gain
Chogtu, 2009 12 weeks India Funding NR Poor	NR	data available in graph only. From the text: Lipid profile parameters showed significant differences between the two groups. TC in the pioglitazone and rosiglitazone groups changed and the difference between the two groups was significant (p = 0.004) (Fig. 2). TG in the pioglitazone group (p = 0.0006) decreased significantly in comparison to the rosiglitazone group (p = 0.255) at 12 weeks with a p-value of 0.002. LDL cholesterol levels also showed a significant decrease (p = 0.005) at the end of the study in the pioglitazone group, compared to the rosiglitazone group. HDL cholesterol increased non-significantly (p = 0.83) in the pioglitazone group as compared to the rosiglitazone group, in which there was a decrease in the HDL levels (p = 0.03). However, the intergroup change in the HDL cholesterol levels was not statistically significant (p > 0.05) (Fig. 2).	NR

Evidence Table 10. Key Question 2: Studies of rosiglitazone and pioglitazone

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Inclusion and Exclusion Criteria	Overall Sample Size Interventions Group Sizes	Baseline Population Characteristics Mean Age, years Race/Ethnicity % Female	Background Medications
Beysen, 2008 20 weeks US Funding NR Fair	Inclusion: T2DM; HbA1c > 7.5 or fasting glucose > 180mg/dl; not controlled with metformin alone or metformin in combination with sulfonylurea; hypertriglyceridemia (150-400mg/dl) Exclusion: pregnancy; ALT>1.5 times normal upper limit; creatinine > 1.4mg/dl; congestive heart failure; history of coronary artery, pulmonary or neurological disesae; treatment with insulin; treatment with statin or fibric acid derivative within 2 months of study	N=12 patients randomized G1: (rosiglitazone 15-30mg/day x 4 weeks, 45mg/day x 16 weeks) n=6 G2: (pioglitazone 4mg/day x 4 weeks, 8mg/day x 16 weeks) n=6	G1: Age: 56 Race: NR Female: 66.7% G2: Age: 53 Race: NR Female: 50%	NR

Evidence Table 10. Key Question 2: Studies of rosiglitazone and pioglitazone

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Adverse Events	Changes in Lipid Concentrations	Weight Gain
Beysen, 2008 20 weeks US Funding NR Fair	Fasting AST, Mean Change (SD): G1: 0 (4) G2: -2 (5) Fasting ALT, Mean Change (SD): G1: -6 (6) G2: -4 (6)	TC: G1: 37.84 mg/dL (SD NR) G2: -1.93 mg/dL (SD NR) LDL: G1: 29.34 mg/dL (SD NR) G2: 7.34 mg/dL (SD NR) HDL: G1: 1.54 mg/dL (SD NR) G2: -3.09 mg/dL (SD NR)	G1: 3.0 (3.4) kg G2: 4.9 (4.2) kg

Evidence Table 10. Key Question 2: Studies of rosiglitazone and pioglitazone

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Inclusion and Exclusion Criteria	Overall Sample Size Interventions Group Sizes	Baseline Population Characteristics Mean Age, years Race/Ethnicity % Female	Background Medications
Vijay, 2009 16 weeks India UGC, India Fair	Inclusion: HbA1c > 8%; cardiovascular risk factors; age 30-70; BMI <36; stable body weight for 3 months prior to study Exclusion: Hepatic or other preexisting chronic disease; any smoking in 6 months prior to study; previous use of insulin or thiazonlidinediones; history of stroke; patients taking glucocorticoids or other drugs that affect glucose metabolism, lipid lowering drugs, alcohol, or psychoactive substances.	N=50 G1: (pioglitazone 30-45mg/day) n=20 G2: (rosiglitazone 4-8mg/day) n=20 G3: (controls (sulfonylureas/other secretagogues)) n=10	G1: Age: 48.1 Race/Ethnicity: NR Female: NR G2: Age: 47.75 Race/Ethinicity: NR Female: NR G3: Age: 49.7 Race/Ethnicity: NR Female: NR *Study reports that overall the male/female ratio was 3:2	NR

Evidence Table 10. Key Question 2: Studies of rosiglitazone and pioglitazone

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Adverse Events	Changes in Lipid Concentrations	Weight Gain
Vijay, 2009 16 weeks India UGC, India Fair	NR	TC (mg/dl): G1: -20.1 (SD 9.7) *P* =0.00, G1 vs. baseline G2: 6.20 (SD NR) *P* =0.40, G2 vs. baseline G3: 17.6 (SD NR) *P* =0.002, G3 vs. baseline *P* =0.00, G1 vs. G2 LDL (mg/dl): G1: -13.66 (SD 6.7) *P* =0.00, G1 vs. baseline G2: 5.39 (SD NR) *P* =0.39, G2 vs. baseline G3: 11.27 (SD NR) *P* =0.00, G3 vs. baseline *P* =0.00, G1 vs. G2 and G3 HDL (mg/dl): G1: 4.7 (SD 1.4) *P* =0.00, G1 vs. baseline G2: 3.25 (SD NR) *P* =0.010, G2 vs. baseline G3: -1.72 (SD NR) *P* =0.01, G3 vs. baseline *P* =0.01, G1 vs. G2 TGL (mg/dl): G1: -33 (SD 8.7) *P* =0.00, G1 vs. baseline G2: -25.3 (SD NR) *P* =0.013, G2 vs. baseline G3: 22.5 (SD NR) *P* =0.00, G3 vs. baseline *P* =0.38, G1 vs. G2	G1: 1.15kg (SD 0.40) *P* =0.00, G1 vs. baseline G2: 0.7kg (SD 0.3) *P* =0.80, G2 vs. baseline G3: -0.13kg (SD NR) *P* =0.38, G3 vs. baseline NR, G1 vs. G2 vs. G3

Evidence Table 10. Key Question 2: Studies of rosiglitazone and pioglitazone

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Inclusion and Exclusion Criteria	Overall Sample Size Interventions Group Sizes	Baseline Population Characteristics Mean Age, years Race/Ethnicity % Female	Background Medications
Oz, 2008 12 weeks Turkey Funding NR Fair	Inclusion: Newly diagnosed T2DM (<6 months) Exclusion: Impaired hepatic function or renal function; Serious cardiovascular disease including heart failure, history of myocardial infarction or stroke; Pregnant or breastfeeding women; Severe anemia	N=35 G1: (pioglitazone 30mg/day) n=14 G2: (rosiglitazone 4mg/day) n=11 G3: (placebo + medical nutrition therapy): n=10	Age: 55.2 Race/Ethnicity: NR Female: 49% *NR by individual groups	NR

Evidence Table 10. Key Question 2: Studies of rosiglitazone and pioglitazone

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Adverse Events	Changes in Lipid Concentrations	Weight Gain
Oz, 2008 12 weeks Turkey Funding NR Fair	Withdrawals due to AEs = 0	TC: (mg/dl): G1: -10.17 (SD NR) G2: -8.3 (SD NR) G3: 0.3 (SD NR) NS, all groups vs. baseline LDL (mg/dl): G1: -15.3 (SD NR) G2: -3.3 (SD NR) G3: 8.7 (SD NR) NS, all groups vs. baseline HDL (mg/dl): G1: -2.1 (SD NR) G2: -1.8 (SD NR) G3: -2.7 (SD NR) NS, all groups vs. baseline TGL (mg/dl): G1: -82.6 (SD NR) *P* =0.004, G1 vs. baseline G2: -13.8 (SD NR) G3: -27.6 (SD NR) NS, G2/G3 vs. baseline	BMI: G1: -0.1 (SD NR) G2: -0.4 (SD NR) G3: -1.0 (SD NR) *P* =0.013, G3 vs. baseline NS, G1/G2 vs. baseline NR, G1 vs. G2 vs. G3

Evidence Table 10. Key Question 2: Studies of rosiglitazone and pioglitazone

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Inclusion and Exclusion Criteria	Overall Sample Size Interventions Group Sizes	Baseline Population Characteristics Mean Age, years Race/Ethnicity % Female	Background Medications
OZ Gul, 2010 12 weeks Turkey Funding NR Fair	Inclusion: Newly diagnosed T2DM (<6 months) naïve to prior antidiabetic therapy Exclusion: Taking statins, ACE inhibitors, ARBs; Acute complications with need for insulin therapy; Impaired hepatic function or renal function; Severe anemia; Serious cardiovascular disease including heart failure, history of myocardial infarction or stroke; Pregnant or breastfeeding women.	N=60 G1: (pioglitazone 30mg/day) n=19 G2: (rosiglitazone 4mg/day) n=20 G3: (placebo + medical nutrition therapy) n=21	Age: 56.4 Race/Ethnicity: 100% Turkish Female: 42% *NR by individual groups	None

Evidence Table 10. Key Question 2: Studies of rosiglitazone and pioglitazone

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Adverse Events	Changes in Lipid Concentrations	Weight Gain
OZ Gul, 2010 12 weeks Turkey Funding NR Fair	NR	TC (mg/dl): G1: -10.7 (SD NR) G2: -3.6 (SD NR) G3: -0.7 (SD NR) NS, all groups vs. baseline LDL (mg/dl): G1: 6.1 (SD NR) G2: 2.2 (SD NR) G3: 2.3 (SD NR) NS, all groups vs. baseline HDL (mg/dl): G1: 1.2 (SD NR) G2: -1.1 (SD NR) G3: -0.1 (SD NR) NS, all groups vs. baseline TGL (mg/dl): G1: -44.5 (SD NR) *P* =0.011, G1 vs. baseline G2: -22.7 (SD NR) G3: -23.2 (SD NR) NS, G2/G3 vs. baseline	BMI: G1: 0.1 (SD NR) G2: -0.1 (SD NR) G3: -0.8 (SD NR) NS, all groups vs. baseline NR, G1 vs. G2 vs. G3

Evidence Table 10. Key Question 2: Studies of rosiglitazone and pioglitazone

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Inclusion and Exclusion Criteria	Overall Sample Size Interventions Group Sizes	Baseline Population Characteristics Mean Age, years Race/Ethnicity % Female	Background Medications
Active-control studies				
DeFronzo, 2010 20 weeks USA Eli Lilly Fair	Inclusion: age 18 –75 years, BMI 25–40 kg/m2, stable body weight for at least 6 months prior to screening, A1C 6.8–10.0%, stable dose of metformin for at least 6 weeks prior to screening and no treatment with any other antidiabetic medication, and absence of islet cell autoantibodies. Exclusion: NR	N = 137 G1: Exenatide 10mcg N = 45 G2: Exenatide 10mcg + Rosiglitazone 4mcg N = 47 G3: Rosglitazone 4mg N = 45	Baseline characteristics not reported for each arm. For entire study population: Mean age 56 yrs 61% white 49% female	Metformin

Evidence Table 10. Key Question 2: Studies of rosiglitazone and pioglitazone

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Adverse Events	Changes in Lipid Concentrations	Weight Gain
Active-control studies			
DeFronzo, 2010 20 weeks USA Eli Lilly Fair	Number withdrawn because of adverse events G1: 2; G2: 5; G3: 1 Overall advese events NR Severe hypoglycemia: G1: 0; G2: 1; G3: 0 Any confirmed hypoglycemia: G1: 2 (4%) G2: 2 (4%) G3: 0 Pedal Edema G1: 8 (18%) G2: 14 (30%) G3: 21 (47%) Exenaide vs. rosiglitazone P = 0.007 Rosiglitazone or exenatide vs. Exenatide+rosiglitazone P = NS	Change in Fasting (SEM) mg/dL Total Cholesterol G1: -5.02 (4.63) G2: +10.03 (4.25) G3: +16.99 (4.63) Exenatide vs. Exenatide+rosiglitazone P = 0.020 Exenaide vs. rosiglitazone P < 0.001 Rosiglitazone vs. Exenatide+rosiglitazone P = 0.276 HDL G1: 0.77 (1.16) G2: 1.93 (1.16) G3: 2.32 (1.16) Exenatide vs. Exenatide+rosiglitazone P = 0.566 Exenaide vs. rosiglitazone P =0.445 Rosiglitazone vs. Exenatide+rosiglitazone P = 0.840 LDL G1: -1.93 (3.86) G2: 3.86 (3.86) G3: 12.74 (3.86) Exenatide vs. Exenatide+rosiglitazone P = 0.308 Exenaide vs. rosiglitazone P = 0.008 Rosiglitazone vs. Exenatide+rosiglitazone P = 0.096	see KQ1

Evidence Table 10. Key Question 2: Studies of rosiglitazone and pioglitazone

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Adverse Events	Changes in Lipid Concentrations	Weight Gain
DeFronzo, 2010		Triglcerides	
cont'd	Nausea	G1: -13.13 (6.56)	
	G1: 47%	G2: 0.00 (6.18)	
	G2: 47%	G3: 2.70 (6.56)	
	G3: 4%	Exenatide vs. Exenatide+rosiglitazone P = 0.140	
		Exenaide vs. rosiglitazone P = 0.079	
	Vomiting	Rosiglitazone vs. Exenatide+rosiglitazone P = 0.752	
	G1: 22%		
	G2: 19%		
	G3: 0		
	Diarrhea		
	G1: 7 %		
	G2: 21%		
	G3: 4%		

Evidence Table 10. Key Question 2: Studies of rosiglitazone and pioglitazone

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Inclusion and Exclusion Criteria	Overall Sample Size Interventions Group Sizes	Baseline Population Characteristics Mean Age, years Race/Ethnicity % Female	Background Medications
Gerstein, 2010 APPROACH 18 months Multinational GlaxoSmithKline Fair	Inclusion: 30-80y; established T2DM; clinically indicated coronary angiography or percutaneous coronary intervention; ≥ atherosclerotic plaque with 10%-50% luminal narrowing in a coronary artery that had not undergone intervention and if their DM was treated with either lifesly approaches alone or with oral agents. Exclusion: ST-segment elevation myocardial infarction in past 30 days; coronary artery bypass graft surgery; severe valvular heart disease; left ventricular efection fraction <40%; any heart failure NY Heart Association class I-IV; systolic blood pressure >170 mmHG or diastolic blood pressure > 100 mm Hg; serum creatinine ≥ 1.5 mg/dL for men; serum creatinine ≥ 1.4 mg/dL for women; active liver disease	N = 672 G1: Glipizide (10-15mg/d) N = 339 G2: Rosiglitazone (4-8mg/d) N = 333	G1: Age 60.2, Race NR, Female 34.2% G2: Age 61.8, Race NR, Female 30.0% Age, G1 vs. G2, p = 0.03	Metformin max 2550 mg/d and once-daily basal insulin or both if needed to maintain a HbA1c of ≤ 7%

Evidence Table 10. Key Question 2: Studies of rosiglitazone and pioglitazone

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Adverse Events	Changes in Lipid Concentrations	Weight Gain
Gerstein, 2010 APPROACH 18 months Multinational GlaxoSmithKline Fair	Number withdrawn because of adverse events G1: 8 (2.3%) G2: 5 (1.5%) Died before follow-up IVUS G1: 6 (1.8%) G2: 7 (2.1%) No. of Patients (%) G1: 96 (28%) G2: 27 (8%) G1 vs. G2, p < 0.0001 Events [No. of Patients with event (%)]requiring change or stop in study medication: Hypoglycemia G1: 12 (4%) G2: 0 (0%) G1 vs. G2, p = 0.0004 Severe hypoglycemia G1: 3 (<1%) G2: 0 (0%) G1 vs. G2, p = 0.25	HDL - C(mg/dL), mean change: G1 +2.6 G2: +6.2 G1 vs. G2, p < 0.0001 LDL-c (mg/dL), mean change: G1: -7.8 G2: +2.8 G1 vs. G2, p = 0.002 Triglycerides (mg/dL) G1: -9.3 G2: -14.2 G1 vs. G2, p = 0.14	Mean change (kg): G1: 1.4 G2: 2.6 G1 vs. G2, p = 0.02

Evidence Table 10. Key Question 2: Studies of rosiglitazone and pioglitazone

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Adverse Events	Changes in Lipid Concentrations	Weight Gain
Gerstein, 2010 cont'd	Diarrhea, No. of Patients (%) G1: 17 (5%) G2: 12 (4%) G1 vs. G2, p = 0.45 Congestive heart failure No. of Patients (%) G1: 3 (0.9%) G2: 8 (2.4%) G1 vs. G2, p = 0.14) Fractures No. of patients (%) G1: 2 (<1%) G2: 6 (2%) G1 vs. G2, p = 0.17		
Gerstein, 2010 cont'd	Peripheral edema, No. of patients (%) G1: 24 (7%) G2: 29 (9%) G1 vs. G2, p = 0.48 Events [No. of Patients with event (%)]requiring change or stop in study medication: Peripheral Edema: G1: 1 (<1%) G2: 2 (<1%) G1 vs. G2, p = 0.62		

Evidence Table 10. Key Question 2: Studies of rosiglitazone and pioglitazone

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Inclusion and Exclusion Criteria	Overall Sample Size Interventions Group Sizes	Baseline Population Characteristics Mean Age, years Race/Ethnicity % Female	Background Medications
Kadoglou, 2010 14 weeks Greece European Social Fund and National Resources - PYTHAGORAS II & Alexander S Onassis Public Benefit Foundation Fair	Inclusion: 50-70 y; T2DM; treated with metformin (850 mg/d) alone for ≥ 4 mo; HbA1c > 6.5%; BMI > 25 kg/m2 Exclusion: Creatinine > 2mg/dL; Alanine amino transferase > 3 times higher than the upper normal limit; congestive heart failure (NY Heart Association II-IV); Prior TZD treamtent; >5% change in body weight for up to 4 mo prior study initiation.	N = 100 G1: Rosiglitazone(8 mg/d) + Metformin (850 mg/d) N= 50 analyzed = 49 G2: Metformin (titration from 850 mg/d - 2550 mg/d) N = 50 analyzed = 48	G1: Age 62, Race NR, Female 74% G2: Age 62.7, Race NR, Female 67%	Metformin 850 mg/d

Evidence Table 10. Key Question 2: Studies of rosiglitazone and pioglitazone

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Adverse Events	Changes in Lipid Concentrations	Weight Gain
Kadoglou, 2010 14 weeks Greece European Social Fund and National Resources - PYTHAGORAS II & Alexander S Onassis Public Benefit Foundation Fair	Withdrawals due to peripheral edema: G1: 1 (2%) G2: 0 (0%)	Total Cholesterol (mg/dL): G1: 10.1 SD NR, p = 0.232 G2: -10.1 SD NR, p = 0.268 G1 vs. G2, p = 0.157 Triglycerides (mg/dL): G1:16.2 SD NR, p = 0.407 G2: -25.2 SD NR, p = 0.64 G1 vs. G2, p = 0.191 HDL-C (mg/dL): G1:1.7 SD NR, p = 0.187 G2: 0.7 SD NR, p = 0.500 G1 vs. G2, p = 0.625 LDL-C (mg/dL): G1: 5.2 SD NR, p = 0.505 G2: -2.5 SD NR, p = 0.784 G1 vs. G2, p = 0.577	BMI (kg/m2) G1: 0.84 SD NR, p = 0.032 G2: -0.79 SD NR, p = 0.13 G1 vs. G2, p < 0.001

Evidence Table 10. Key Question 2: Studies of rosiglitazone and pioglitazone

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Inclusion and Exclusion Criteria	Overall Sample Size Interventions Group Sizes	Baseline Population Characteristics Mean Age, years Race/Ethnicity % Female	Background Medications
Kato, 2009 12 weeks Japan NR Fair	Inclusion: Recent diagnosis of T2DM associated with metabolic syndrome; Abdominal ultrasound determining fatty liver; no history of treamtne with oral antihyperglycemic drugs, antihyperlipidemic drugs, or antihypertensive drugs. Exclusion: Diabetic retinopathy, nephropathy, or neuropathy whose condition was unstable or underwent sudden progression; Aspartate aminotransferase or alanin aminotransferase > 1.5 times the upper limit of normal level; serum creatinine > 133 µmol/L; anemia; myocardial infar4ction; angina pectoris; congestive heart failure; history of cerebrovascular disease.	N = 50 G1:Pioglitazone (15mg/d) N = 25 G2: Metformin (500 mg/d) N = 25	G1: Age 51.4, Race NR, Female 52% G2: Age 58.6, Race NR, Female 44%	All patients received diet therapy and exercise therapy. Parameters: total energy intake within 1200-1800kcal, fat ration of caloric intake to < 25-30% and to do ≥ 150 min of exercise per wk.

Evidence Table 10. Key Question 2: Studies of rosiglitazone and pioglitazone

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Adverse Events	Changes in Lipid Concentrations	Weight Gain
Kato, 2009 12 weeks Japan NR Fair	Overall adverse events G1: 2 patients with edema G2: No significant adverse events Liver function test abnormalities ALT Percent Change (95% CI) from baseline G1: -26.9% (15.7%, 36.8%) G2: 4.1% (-31.1%, 24.0%) G1 vs. G2, p <0.05 AST Percent Change (95%CI) from baseline G1: -12.9% (2.7%, 23.1%) G2: -2.7% (9.0%, 15.0%) G1 vs. G2, p = NS	Triglycerides Calculated Change from baseline mg/dL G1: -17.70 mg/dL SD NR, p < 0.05 G2: -10.62 mg/dL SD NR, p = NR Triglycerides Percent change from baseline (95% CI) G1: -5.4% (-5.1%, 16.4%) G2: -0.7% (-14.7%, 32.4%) G1 vs. G2, p = NS LDL Cholesterol Calculated Change from baseline mg/dL G1: 0.36 mg/dL SD NR, p = NR G2: -1.54 mg/dL SD NR, p = NR LDL Cholesterol Percent change from baseline (95% CI) G1: -2.1% (-9.2%, 6.4%) G2: 0.0% (-7.1%, 7.9%) G1 vs. G2, p = NS HDL Cholesterol Calculated Change from baseline mg/dL G1: 9.27 mg/dL SD NR, p = NR G2: 5.80 mg/dL SD NR, p = NR HDL Cholesterol Percent change from baseline (95% CI) G1: -18.2% (9.6%, 26.2%) G2: -10.9% (5.4%, 16.5%) G1 vs. G2, p = NS	BMI (kg/m2) Change from baseline to 12 weeks G1: 0.1, SD NR G2: -0.9, SD NR Rate of Change (95%CI) G1: 0.2% (-1.4%, 1.7%) G2: -3.3% (-4.5%, -2.0%) G1 vs. G2, p <0.01

Evidence Table 10. Key Question 2: Studies of rosiglitazone and pioglitazone

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Inclusion and Exclusion Criteria	Overall Sample Size Interventions Group Sizes	Baseline Population Characteristics Mean Age, years Race/Ethnicity % Female	Background Medications
Papathanassiou, 2009 6 months Greece Funding NR Fair	Inclusion: T2DM treated only with metformin for 6 months prior to study; HbA1c > 6.5%; normal liver enzymes and renal function Exclusion: History of coronary artery, cerebrovascular, or peripheral vascular disease; chronic heart failure; liver or renal disease; anemia; thyroid dysfunction; and the new onset of any medications within the previous 8 weeks.	N=28 G1: (glimepiride 4mg/day) n=14 G2: (pioglitazone 30mg/day) n=14	G1: Age: 63.6 Race/Ethnicity: NR Female: 78.6% G2: Age: 62.8 Race/Ethnicity: NR Female: 78.6%	metformin

Evidence Table 10. Key Question 2: Studies of rosiglitazone and pioglitazone

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Adverse Events	Changes in Lipid Concentrations	Weight Gain
Papathanassiou, 2009 6 months Greece Funding NR Fair	Withdrawals due to AEs: G1: n=1 (2.6%) G2: n=1 (2.6%)	TC (mg/dl): G1: 9.27 (SD 28.19) G2: 2.32 (SD 32.82) *P* =0.854, G1 vs. G2 LDL (mg/dl): G1: 7.34 (SD 23.55) G2: -3.47 (SD 30.50) *P* =0.661, G1 vs. G2 HDL (mg/dl): G1: -2.70 (SD 8.49) G2: 5.41 (SD 7.72) *P* =0.036, G1 vs. G2 TGL (mg/dl): G1: 22.12 (SD 46.90) G2: 0.88 (SD 29.20) *P* =0.208, G1 vs. G2	BMI: G1: 0.15 (SD 1.5) G2: 0.23 (SD 0.82) *P* =0.985, G1 vs. G2

Evidence Table 10. Key Question 2: Studies of rosiglitazone and pioglitazone

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Inclusion and Exclusion Criteria	Overall Sample Size Interventions Group Sizes	Baseline Population Characteristics Mean Age, years Race/Ethnicity % Female	Background Medications
Perez, 2009 24 weeks Multinational Takeda Fair	Inclusion: 18 y; TWDM; baseline HbA1c ≥ 7.5% but ≤ 10.0%; treatment -naïve; BMI ≤ 45 kg/m2; received counseling on lifestyle modification for T2DM including diet and exercise Exclusion:Type 1 diabetes; NY Heart Association Class II or IV heart failure; history of myocardial infarction, cerebrovascular accident, percutaneous coronary intervention, coronary arter bypass graft, transient ischemic attach within 6 mo; serum creatinine level males ≥ 1.5 mg/dL; serum creatinine level females ≥ 1.4 mg/dL; triglyceride level >500mg/dL; ALT level > 2.5 times upper limit of normal; active liver disease; jaundice; discontinuation from TZD or metformin therapy due to lack of efficacy; clinical or laboratory signs of intolerance of TZD or metformin; pregnant; intent to become pregnant; lactating during the study period.	N = 600 G1: Pioglitazone (15mg) + Metformin (850mg) bid: N = 201 G2: Pioglitazone (15mg) bid M = 189 G3: Metformin (850mg) bid N = 210	Overall: Age 54.1, American Indian 32%, Asian 2.2%, Black 6.5%, White 89.0%, Multiracial 29.7%, Hispanic/Latino 25.5%, Non-hispanic/non-Latino 20.7% Female 57.7% G1: Age 54.7, American Indian 31.3%, Asian 1.5%, Black 6.0%, White 91.5%, Multiracial 30.3%, Hispanic/Latino 24.4%, Non-hispanic/non-Latino 20.9% Female 55.2% G2: Age 54.0, American Indian 32.8%, Asian 2.6%, Black 6.9%, White 87.3%, Multiracial 29.6%, Hispanic/Latino 25.9%, Non-hispanic/non-Latino 19.0% Female 65.1% G3: Age 53.7, American Indian 31.9%, Asian 2.4%, Black 6.7%, White 88.1%, Multiracial 29.0%, Hispanic/Latino 26.2%, Non-hispanic/non-Latino 21.9% Female 53.3%	None

Evidence Table 10. Key Question 2: Studies of rosiglitazone and pioglitazone

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Adverse Events	Changes in Lipid Concentrations	Weight Gain
Perez, 2009 24 weeks Multinational Takeda Fair	Number withdrawn because of adverse events Overall: 22 (3.7%) G1: 6 (3.0%) G2: 6 (3.2%) G3: 10 (4.8%) Overall adverse events Overall: 766 events (312 patients) Numbers (%) of patients: G1: 102 (50.7%) G2: 99 (52.1%) G3: 111 (53.1%) Hypoglycemia G1: 1.0% G2: 0.5% G3: 1.4% Gastrointestinal events: G1: 17.9% G2: 10.5% G3: 25.8% Diarrhea (numbers (5) of patients): G1: 18 (9.0%) G2: 5 (2.6%) G3: 32 (15.3%) Abdominal Pain: G1: 4 (2.0%) G2: 3 (1.6%) G3: 7 (3.3%)	NR	Change in weight G1: 0.69 kg G2: 1.64 kg G3: -1.28 kg

Evidence Table 10. Key Question 2: Studies of rosiglitazone and pioglitazone

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Adverse Events	Changes in Lipid Concentrations	Weight Gain
Perez, 2009 cont'd	Peripheral Edema, Number (%) of patients: G1: 6 (3.0%) G2: 8 (4.2%) G3: 3 (1.4%) Headache, Number (%) of patients: G1: 11 (5.5%) G2: 5 (2.6%) G3: 10 (4.8%) Phayngitis, Number (%) of patients: G1: 8 (4.0%) G2: 5 (2.6%) G3: 7 (3.3%) Urinary tract infection, Number (%) of patients: G1: 6 (3.0%) G2: 5 (2.6%) G3: 9 (4.3%)		

Evidence Table 10. Key Question 2: Studies of rosiglitazone and pioglitazone

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Adverse Events	Changes in Lipid Concentrations	Weight Gain
Perez, 2009 cont'd	Back Pain, Number (%) of patients: G1: 4 (2.0%) G2: 8 (4.2%) G3: 6 (2.9%) Glycosylated hemoglobin increased, Number (%) of patients: G1: 2 (1.0%) G2: 7 (3.7%) G3: 7 (3.3%) Nasopharyngitis, Number (%) of patients: G1: 8 (4.0%) G2: 3 (1.6%) G3: 5 (2.4%) Bronchitis, Number (%) of patients: G1: 5 (2.5%) G2: 7 (3.7%) G3: 3 (1.4%) Dizziness, Number (%) of patients: G1: 6 (3.0%) G2: 3 (1.6%) G3: 4 (1.9%) Insomnia, Number (%) of patients: G1: 6 (3.0%) G2: 2 (1.1%) G3: 2 (1.0%)		

Evidence Table 10. Key Question 2: Studies of rosiglitazone and pioglitazone

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Inclusion and Exclusion Criteria	Overall Sample Size Interventions Group Sizes	Baseline Population Characteristics Mean Age, years Race/Ethnicity % Female	Background Medications
Petrica, 2009 Poor	data not abstracted because of poor quality rating			
Rigby, 2010 16 weeks Multinational Daiichi Sankyo Fair	Inclusion: Male and female; 18-80; T2DM diagnosis; HbA1c 7.0% - 10.0%; Taking a dose of metformin 1500-2550 mg/d; LDl cholesterol ≥ 60 mg/dL; Triglycerides < 500 mg/dL	N = 169 G1: Rosiglitazone (4mg/d) N = 56 G2: Sitagliptin (100 mg/d) N = 56 G3: Colesevelam (3.75 g/d) N = 57	 G1: Age 54.7; White 28.6%, Black 3.6%, Asian 0%, Hispanic 67.9%, Multiple 0%, Other 0%; Female 58.9% G2: Age 54.8; White 23.2%, Black 1.8%, Asian 0%, Hispanic 73.2%, Multiple 0%, Other 1.8%; Female 64.3%	Metformin (1500-2550 mg/d)

Evidence Table 10. Key Question 2: Studies of rosiglitazone and pioglitazone

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Adverse Events	Changes in Lipid Concentrations	Weight Gain
Petrica, 2009 Poor			
Rigby, 2010 16 weeks Multinational Daiichi Sankyo Fair	Number withdrawn because of adverse events G1: 1(1.8%) G2: 1 (1.8%) Percentage of patients with AE G1: 46.4% G2: 48.2% Patients who withdrew because of hypoglycemia (5) G1: 1 (1.8%) G2: 0 (0%) Cholelithiasis, No. of patients (%) G1: 0 G2: 1 (1.8%) Decreased appetite, No. of patients who withdrew because of AE (%) G1: 0 G2: 1 (1.8%)	LDL, least-squares mean percentage changes G1: 7.6, $p < 0.05$ G2: 7.7, $p \leq 0.01$ Total Cholesterol, least-squares mean percentage changes G1: 7.8, $p \leq 0.01$ G2: 2.2, p = NR Tryclycerides, median change (%) G1: 24.2 $p \leq 0.001$ G2: -1.2, p = NR HDL, least-squares mean percentage changes G1: -3.1, p = NR G2: -2.1, p = NR	NR

Evidence Table 10. Key Question 2: Studies of rosiglitazone and pioglitazone

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Inclusion and Exclusion Criteria	Overall Sample Size Interventions Group Sizes	Baseline Population Characteristics Mean Age, years Race/Ethnicity % Female	Background Medications
Van der Meer, 2009 PIRAMID 24 weeks The Netherlands Eli Lilly, Takeda Good	Inclusion: Men with uncomplicated T2DM; ages 45-65; HbA1c 6.5-8.5; BMI 25 to 32; Blood pressure lower than 150/85 Exclusion: Any clinically significant disorder; particularly any history of cardiovascular or liver disease or diabetes-related complications; any prior use of thiazolidinediones or insulin.	N=78 G1: (pioglitazone 30mg/day) n=39 G2: (metformin 2000mg/day) n=39	G1: Age: 56.8 Race/Ethnicity: NR Female: 0% G2: Age: 56.4 Race/Ethinicity: NR Female: 0%	glimepiride monotherapy, titrated during the 10-week run-in period

Evidence Table 10. Key Question 2: Studies of rosiglitazone and pioglitazone

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Adverse Events	Changes in Lipid Concentrations	Weight Gain
Van der Meer, 2009 PIRAMID 24 weeks The Netherlands Eli Lilly, Takeda Good		TC (mg/dl): G1: 3.86 (SD NR) G2: -15.44 (SD NR) *P* =0.042, G1 vs. G2 LDL (mg/dl): G1: 0 (SD NR) G2: -11.58 (SD NR) *P* =0.107, G1 vs. G2 HDL (mg/dl): G1: 6.18 (SD NR) G2: -4.25 (SD NR) *P* =0.009, G1 v G2 TGL (mg/dl): G1: 0 (SD NR) G2: 17.70 (SD NR) *P* =0.596, G1 v G2	NR

Evidence Table 10. Key Question 2: Studies of rosiglitazone and pioglitazone

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Inclusion and Exclusion Criteria	Overall Sample Size Interventions Group Sizes	Baseline Population Characteristics Mean Age, years Race/Ethnicity % Female	Background Medications
Schernthaner, 2004 Quarter Study 12 months Multinational Funding NR Good	Inclusion: age 35–75 ; T2DM; inadequately treated with diet alone, HbA1c between 7.5% and 11% with stable or worsening glycemic control for at least 3 months Exclusion: prior use of glucose-lowering pharmacotherapy; specific contraindications to either drug	N=1199 randomized G1: (pioglitazone 30-45mg/day + placebo) n=597 G2: (metformin up to 850mg-2550mg/day + placebo) n=597	G1: Age: 57 Race: NR Female: 47.4% G2: Age: 56 Race: NR Female: 42.2%	None

Evidence Table 10. Key Question 2: Studies of rosiglitazone and pioglitazone

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Adverse Events	Changes in Lipid Concentrations	Weight Gain
Schernthaner, 2004 Quarter Study 12 months Multinational Funding NR Good	Withdrawals due to AEs: G1: n=42 (7%) G2: n=39 (7%) Overall AEs: G1: 16 patients G2: 346 patients Bronchitis G1: 11 (1.8%) G2: 14 (2.3%) Influenza G1: 14 (2.4%) G2: 22 (3.7%) Nasopharyngitis G1: 25 (4.2%) G2: 19 (3.2%) Liver toxicity: G1: 2 G2: 1 ALT >3x ULN: G1: 0.9% G2: 2.2% Diarrhea: G1: 19 (3.2%) G2: 66 (11.1% Nausea: G1: 14 (2.3%) G2: 25 (4.2%) Edema: G1: 40 G2: 11	TC: NR LDL (mg/dl): G1: +10.42 (SD NR) G2: -4.63 (SD NR) *P* <0.001, G1 vs. G2 TGL (mg/dl): G1: -45.86 (SD NR) G2: -26.55 (SD NR) *P* <0.001, G1 vs. G2 HDL (mg/dl): G1: +6.18 (SD NR) G2: +3.09 (SD NR) *P* <0.001, G1 vs. G2	G1: 1.9kg (SD NR) G2: 2.5 kg (SD NR)

Evidence Table 10. Key Question 2: Studies of rosiglitazone and pioglitazone

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Inclusion and Exclusion Criteria	Overall Sample Size Interventions Group Sizes	Baseline Population Characteristics Mean Age, years Race/Ethnicity % Female	Background Medications
Kusaka, 2008 4 months Japan Funding NR Fair	Inclusion: T2DM; inadequate glucose control Exclusion: cardiovascular disease; apparent liver or kidney disease; severe diabetic complications	N=35 patients randomized G1: (metformin 750mg/day) n=17 G2: (pioglitazone 15-30mg/day) n=16	G1: Age: 60 Race: NR Female: 41.2% G2: Age: 64 Race: NR Female: 43.8%	Patients stayed on sulfonylurea if on them (82% and 75%, respectively)

Evidence Table 10. Key Question 2: Studies of rosiglitazone and pioglitazone

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Adverse Events	Changes in Lipid Concentrations	Weight Gain
Kusaka, 2008 4 months Japan Funding NR Fair	Withdrawals due to AEs: G1: 0 G2: 1 (5.9%) Overall AEs: G1: 0 G2: 2 Hypoglycemia: G1: 0 G2: 0	TC: NR Mean change in LDL at 4 months: G1: -11.6mg/dl (SD NR) G2: 0mg/dl (SD NR) NS from baseline, G1&G2 Mean change in DL: G1: 0mg/dl (SD NR) G2: +7.7mg/dl (SD NR) NS from baseline, G1 *P* =0.0097, G2 vs. baseline Mean change in TGs: G1: +17.7mg/dl (SD NR) G2: +17.7mg/dl (SD NR) NS from baseline, G1&G2	BMI mean change at 4 months: G1: 0 (SD NR) G2: +0.9 (SD NR) *P* =0.0026, G2 vs. baseline G1 vs. G2, NR

Evidence Table 10. Key Question 2: Studies of rosiglitazone and pioglitazone

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Inclusion and Exclusion Criteria	Overall Sample Size Interventions Group Sizes	Baseline Population Characteristics Mean Age, years Race/Ethnicity % Female	Background Medications
Nissen, 2008 PERISCOPE 18 months Multinational Takeda Pharmaceuticals Fair	Inclusion: age 35-85; HbA1c 6.0-9.0 (if taking glucose-lowering meds) and 6.5-10.0 (if not); one angiographic stenosis at least 20% narrowing; a "target vessel" for ultrasound was required to have less than 50% obstruction throughout a 40mm or longer segment Exclusion: T1DM; 3 or more antidiabetic meds; received any TZD within 12 weeks; serum creatinine > 2.0mg/dL; triglycerides > 500mg/dl; blood pressure >160/100 despite therapy; active liver disease; left main coronary artery stenosis more than 50%	N=547 patients randomized G1: (glimepiride titrated) n=273 randomized, 181 included in primary analysis G2: (pioglitazone titrated) n=274 randomized, 179 included in primary analysis	G1: Age: 59.7 Race: White 80.6%, Black 9.9%, Asian 5.9%, Native American 3.7% Female 34.1% G2: Age: 60.0 Race: White 83.3%, Black 11.1%, Asian 4.4%, Native American 1.1% Female 31.1%	Patients stayed on baseline therapy (unless a TZD or sulfonylurea)

Evidence Table 10. Key Question 2: Studies of rosiglitazone and pioglitazone

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Adverse Events	Changes in Lipid Concentrations	Weight Gain
Nissen, 2008 PERISCOPE 18 months Multinational Takeda Pharmaceuticals Fair	Hypoglycemia: G1: 101 (37.0%) G2: 41 (15.2%) *P* <0.001, G1 vs. G2 ALT > 3 times normal limit: G1: 3 G2: 2 *P* >0.99, G1 vs. G2 Hospitalization for congestive heart failure: G1: 5 G2: 4 *P* >0.99, G1 vs. G2 Fractures G1: 0 (0%) G2: 8 (3.0%) *P* =0.004, G1 vs. G2 Angina: G1: 33 G2: 19 *P* =0.05, G1 vs. G2 Peripheral edema: G1: 30 G2: 48 *P* =0.02, G1 vs. G2 Hypertension: G1: 24 G2: 13 *P* =0.07, G1 vs. G2	Mean change in TC (95% CI): G1: 1.16mg/dl (-2.9, 5.3) G2: 2.5mg/dl (-3.3, 8.3) *P* =0.39, G1 vs. G2 Mean change in LDL (95% CI): G1: 1.1mg/dl (-2.4, 4.6) G2: 2.1mg/dl (-1.5, 5.8) *P* =0.69, G1 vs. G2 Mean change in HDL (95% CI): G1: 0.9mg/dl (-0.3, 2.1) G2: 5.7mg/dl (4.4, 7.0) *P* <0.001, G1 vs. G2 Mean change in TGs: G1: 3.3mg/dl (-10.7, 11.7) G2: -16.3mg/dl (-27.7, -11.0) *P* <0.001, G1 vs. G2	Median weight change (95% CI): G1: 1.6 (0.8, 2.4) G2: 3.6 (2.8, 4.4) *P* <0.001, G1 vs. G2

Evidence Table 10. Key Question 2: Studies of rosiglitazone and pioglitazone

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Inclusion and Exclusion Criteria	Overall Sample Size Interventions Group Sizes	Baseline Population Characteristics Mean Age, years Race/Ethnicity % Female	Background Medications
Marre, 2003 LEAD-1SU 26 weeks Multinational Novo Nordisk Fair	Inclusion: T2DM treated with oral glucose-lowering agents (OGLAs) for ≥ 3 months; 18–80 years of age; HbA1c 7.0–11.0% (previous OGLA monotherapy) or 7.0–10.0% (previous OGLA combination therapy); BMI ≤ 45.0 kg/m 2. Exclusion: Insulin within 3 months, impaired liver or renal function, uncontrolled hypertension (≥ 180/100 mmHg), cancer or used any drugs apart from OGLAs likely to affect glucose concentrations	N=1041 G1: liraglutide 0.6 mg n=233 G2: liraglutide 1.2 mg n=228 G3: liraglutide 1.8 mg n=234 G4: placebo n=114 G5: rosiglitizone n=232	Age: 56 Race/Ethnicity: NR % Female: G1: 46 G2: 55 G3: 47 G4: 53 G5: 53	Glimepiride (2-4 mg)

Evidence Table 10. Key Question 2: Studies of rosiglitazone and pioglitazone

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Adverse Events	Changes in Lipid Concentrations	Weight Gain
Marre, 2003 LEAD-1SU 26 weeks Multinational Novo Nordisk Fair	Withdrawals due to AEs: G1: 5 (2.1) G2: 11 (4.8) G3: 9 (3.8) G4: 6 (5.3) G5: 7 (3.0) Hypoglycemia: Major: G3: 1 Minor: G1: 12 G2: 21 G3: 19 G4: 3 G5: 10 Events per subject-year: G1: 0.17 G2: 0.51 G3: 0.47 G4: 0.17 G5: 0.12 G2 vs. G5: *P* =0.0024 G3 vs. G5: *P* =0.0065 G2 vs. G4: *P* =0.048 Pancreatitis: G1: 1 G2: 0 G3: 0 G4: 0 G5: 0 Serious AEs: G1: 7 G2: 9 G3: 12 G4: 3 G5: 7	NR	G1: +0.7 kg G2: +0.3 kg G3: -0.2 kg G4: -0.1 kg G5: +2.1 kg G1 and G2 and G3 vs. G5: *P* <0.0001

Evidence Table 10. Key Question 2: Studies of rosiglitazone and pioglitazone

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Inclusion and Exclusion Criteria	Overall Sample Size Interventions Group Sizes	Baseline Population Characteristics Mean Age, years Race/Ethnicity % Female	Background Medications
Pop-Busui, 2009 6 months US GlaxoSmithKline, Eli Lilly, Research Foundations Fair	Inclusion: Subjects with T2DM without known coronary artery disease; HbA1c between 6% and 9%; treatment with diet/exercise or sulfonylurea therapy or insulin < 20 U/d; If previously on metformin, 4-wk washout period prior to study. Exclusion: NR	N=27 G1: (rosiglitazone 8mg/day) n=14 G2: (glyburide 10mg/day) n=13	Age: 49.5 Race/Ethnicity: NR Female: 48% *NR by individual groups	NR
Turkmen Kemal, 2007 Poor	data not abstracted because of poor quality rating			

Evidence Table 10. Key Question 2: Studies of rosiglitazone and pioglitazone

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Adverse Events	Changes in Lipid Concentrations	Weight Gain
Pop-Busui, 2009 6 months US GlaxoSmithKline, Eli Lilly, Research Foundations Fair	Hypoglycemia: G1: 0 G2: 3 Chest discomfort: G1: 1 G2: 0	TC (mg/dl): G1: -11 (SD NR) G2: -22 (SD NR) LDL (mg/dl): G1: -13 (SD NR) G2: -11 (SD NR) HDL (mg/dl): G1: 4 (SD NR) G2: 0 (SD NR) TGL (mg/dl): G1: -19 (SD NR) G2: -53 (SD NR) NS, G1 vs. G2 for all lipid measures	NR
Turkmen Kemal, 2007 Poor			

Evidence Table 10. Key Question 2: Studies of rosiglitazone and pioglitazone

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Inclusion and Exclusion Criteria	Overall Sample Size Interventions Group Sizes	Baseline Population Characteristics Mean Age, years Race/Ethnicity % Female	Background Medications
von Bibra, 2008 16 weeks (32-week cross-over) Germany Funding NR Fair	Inclusion: T2DM of relative short duration; taking metformin monotherapy; age 35-75; BMI 25-35; HbA1c 6.5-9%; no major complications of macrovascular disease; normal left ventricular function by 2-dimensional echocardiography; blood pressure normal or <140/90 if treated; cholesterol <250 mg/dL; triglyceride <250mg/dL; no microvascular complications and no albuminuria Exclusion: Atrial fibrillation; ischemic heart disease; severe left ventricular hypertrophy; history or signs of heart failure; hepatic, or renal insufficiency	N=12 G1: (rosiglitazone 8mg/day) n=12 G2: (glimpiride 3mg/day) n=12	Age: 59 Race/Ethnicity: NR Female: 33.3%	metformin and other previous medications continued

Evidence Table 10. Key Question 2: Studies of rosiglitazone and pioglitazone

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Adverse Events	Changes in Lipid Concentrations	Weight Gain
von Bibra, 2008 16 weeks (32-week cross-over) Germany Funding NR Fair	Withdrawals due to AEs: n=1 (8.3%) Overall Aes: G1: AE=1 G2: AE=1 Hypoglycemia: G1: n=0 G2: n=1 Peripheral edema: G1: n=1 G2: n=0	TC (mg/dl): G1: 14 (SD NR) *P* =0.330, G1 vs. baseline G2: -6 (SD NR) *P* =0.357, G2 vs. baseline LDL (mg/dl): G1: 12 (SD NR) *P* =0.388, G1 vs. baseline G2: -1 (SD NR) *P* =0.621, G2 vs. baseline HDL (mg/dl): G1: 2 (SD NR) *P* =0.404, G1 vs. baseline G2: 1 (SD NR) *P* =0.498, G2 vs. baseline TGL (mg/dl): G1: -6 (SD NR) *P* =0.846, G1 vs. baseline G2: -12 (SD NR) *P* =0.375, G2 vs. baseline	NR

Evidence Table 10. Key Question 2: Studies of rosiglitazone and pioglitazone

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Inclusion and Exclusion Criteria	Overall Sample Size Interventions Group Sizes	Baseline Population Characteristics Mean Age, years Race/Ethnicity % Female	Background Medications
Home, 2009 RECORD 7 year study, mean follow up time 5.5 years Multinational GlaxoSmithKline Fair	Inclusion: age between 40-75; BMI > 25; being on maximum tolerated doses of metformin or a sulfonylurea monotherapy Exclusion: hospitalizations for a major cardiovascular event in prior 3 months; planned cardiovascular intervention; presence, history or treatment for heart failure	N=4458 randomized G1: (addition of rosiglitazone) n=2,220 G1a: (rosiglitazone + metformin) n=1,117 G1b: (rosiglitazone + sulfornylurea) n=1,103 G2: (metformin + sulfonylurea) n=2,227 G2a: (background metformin) n=1,105 G2b: (background sulfonylurea) n=1,122	G1a: Age: 57.0 Race: White 98.9%, Other 1.1% Female: 46.2% G1b Age: 59.8 Race: White 99.3%, Other 0.7% Female: 51.0% G2a: Age: 57.2 Race: White 98.4%; Other 1.6% Female: 47.1% G2b: Age: 59.7 Race: White 99.1%; Other 0.9% Female: 49.4%	all patients stayed on their metformin or sulfonylurea that they used as monotherapy

Evidence Table 10. Key Question 2: Studies of rosiglitazone and pioglitazone

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Adverse Events	Changes in Lipid Concentrations	Weight Gain
Home, 2009 RECORD 7 year study, mean follow up time 5.5 years Multinational GlaxoSmithKline Fair	Overall Malignancies: G1: 126 (5.7%) G2: 148 (6.6%) *P* =0.20, G1 vs. G2 Prostate Cancer: G1: 15 (1.3%) G2: 21 (1.8%) *P* =0.41 Breast Cancer: G1: 11 (1.0%) G2: 17 (1.6%) *P* =0.34 Colon Cancer: G1: 10 (0.5%) G2: 14 (0.6%) *P* =0.54 Infections: G1: 139 (6.3%) G2: 157 (7.0%) *P* =0.32, G1 vs. G2 Serious hypoglycemia: G1: 15 (0.7%) G2: 6 (0.3%) *P* =0.076 Deaths and Hospitializations: G1: 61 G2: 29 HR: 2.10 (1.35-3.27) Patients with Heart Failure: G1: 82 (3.7%) G2: 42 (1.9%) *P* =0.0003	Mean change at 5 years total: NR LDL: G1a: -12.7 (SD 1.5) G2a: -19.3 (SD 1.2) *P* =0.0001, G1a vs. G2a G1b: -8.5 (SD 1.5) G2b: -20.5 (SD 1.2) *P* <0.0001, G1b bs. G2b HDL: G1a: 4.6 (SD 0.4) G2a: 1.5 (SD 0.4) *P* <0.0001, G1a vs. G2a G1b: 4.2 (SD 0.4) G2b: 2.7 (SD 0.4) *P* =0.002, G1b vs. G2b TGs: G1a: -12.4 (SD 3.5) G2a: -1.8 (SD 4.4) *P* =0.046, G1a vs. G2a G1b: -11.5 (SD 3.5) G2b: -12.4 (SD 3.5) *P* =0.82, G1b vs. G2b	Mean weight change at 5 years: G1a: 3.8kg (SD 0.24) G2a: 0.0 (SD 0.2) *P* <0.0001, G1a vs. G2a G1b: 4.1kg (SD 0.2) G2b: -1.5kg (SD 0.2) *P* <0.0001, G1b vs. G2b

Evidence Table 10. Key Question 2: Studies of rosiglitazone and pioglitazone

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Adverse Events	Changes in Lipid Concentrations	Weight Gain
Home, 2009 (continued)	GI Effects: G1: 133 (6.0%) G2: 119 (5.3%) *P* =0.39, G1 vs. G2 Fracture: G1: 225 G2: 132 RR: 1.57 (1.26-1.97) Serious Macular Edema: G1: 0 (0.0%) G2: 0 (0.0%) Non-serious Macular Edema: G1: 7 G2: 3 *P* =NR		

Evidence Table 10. Key Question 2: Studies of rosiglitazone and pioglitazone

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Inclusion and Exclusion Criteria	Overall Sample Size Interventions Group Sizes	Baseline Population Characteristics Mean Age, years Race/Ethnicity % Female	Background Medications
Kiyici, 2009 12 months Turkey Funding NR Fair	Inclusion: age 30-65; baseline HbA1c<8; BMI < 40 Exclusion: usage of any medications for T2DM before study; presence of cardiovascular, gastrointestinal, hepatic, renal, rhematologic, neoplastic, infectious or other endocrine diseases (except hyperlipidemia), micro or macrovascular complications of diabetes, previous history of substance abuse	N=50 randomized G1: (medical nutrition therapy) n=15 G2: (metformin + medical nutrition therapy) n=16 G3: (rosiglitazone + medical nutrition therapy) n=19	G1: Age: 52.1 Race: NR Female: NR G2: Age: 52.4 Race: NR Female: NR G3: Age: 50.7 Race: NR Female: NR	none

Evidence Table 10. Key Question 2: Studies of rosiglitazone and pioglitazone

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Adverse Events	Changes in Lipid Concentrations	Weight Gain
Kiyici, 2009 12 months Turkey Funding NR Fair	NR	Mean change in TC at 12 months: G1: -7.7 mg/dl (SD NR) G2: -7.7mg/dl (SD NR) G3: 0mg/dl (SD NR) NS differences between groups Change in LDL: G1: -3.9mg/dl (SD NR) G2: -7.7mg/dl (SD NR) G3: -3.9mg/dl (SD NR) NS differences between groups Change in HDL: G1: +3.9mg/dl (SD NR) G2: 0 mg/dl (SD NR) G3: +7.7mg/dl (SD NR) *P* <0.05, G1 vs. G2 *P* <0.05, G2 vs. G3 Change in TGs: G1: -26.5mg/dl (SD NR) G2: -8.8mg/dl (SD NR) G3: -17.7mg/dl (SD NR) NS differences between groups	Mean change in BMI at 12 monhts: G1: -0.4 (SD NR) G2: -0.9 (SD NR) G3: +1.0 (SD NR) *P* <0.05, G1 vs. G3 *P* <0.05, G2 vs. G3

Evidence Table 10. Key Question 2: Studies of rosiglitazone and pioglitazone

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Inclusion and Exclusion Criteria	Overall Sample Size Interventions Group Sizes	Baseline Population Characteristics Mean Age, years Race/Ethnicity % Female	Background Medications
Scott, 2008 18 weeks Multinational Merck Fair	Inclusion: age 18-75; taking metformin monotherapy >1500mg/day for a t least 10 weeks prior to screening; HbA1c 7-11% Exclusion: T1DM; insulin use within 8 weeks of the screening visit; contraindications for use of TZDs or metformin; impaired renal function, ALT or AST levels more than 2-fold the upper limit of normal, fasting glucose values >270mg/dl	N=273 randomized G1: (placebo) n=92 G2: (sitagliptin 100mg/day) n=94 G3: (rosiglitazone 8mg/day) n=87	G1: Age: 55.3 Race: White 61%, Asian 39%, Other 0% Female: 41% G2: Age: 55.2 Race: White 61%, Asian 38%, Other 1% Female 45% G3: Age: 54.8 Race: White 59%, Asian 38%, Other 3% Female 37%	metformin

Evidence Table 10. Key Question 2: Studies of rosiglitazone and pioglitazone

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Adverse Events	Changes in Lipid Concentrations	Weight Gain
Scott, 2008 18 weeks Multinational Merck Fair	Withdrawals due to AEs: G1: N=1 (1.1%) G2: N=3 (3.2%) G3: N=2 (2.3%) Patients with AEs: G1: N=27 (30%) G2: N=37 (39%) G3: N=38 (44%) Hypoglycemia: G1: N=2 (2%) G2: N=1 (1%) G3: N=1 (1%) GI Effects: G1: N=8 (9%) G2: N=8 (9%) G3: N=6 (7%) Edema: G1: N=1 G2: N=1 G3: N=4	TC (mg/dl): G1: 17.4 (SDNR) G2: 8.1 (SDNR) G2 mean % change vs. G1: -6.3 (-11.8, -0.9) G3: 26.2 (SD NR) G3 mean % change vs. G1: 5.1 (-0.3, 10.6) G3 mean % change vs. G2: 11.5 (6.0, 16.9) LDL (mg/dl): G1: 12.8 (SD NR) G2: 9.2 (SD NR) G2 mean % change vs. G1: -5.3 (-14.5, 3.9) G3: 20.4 (SD NR) G3 mean % change vs. G1: 9.5 (0.2-18.7) G3 mean % change vs. G2: 14.8 (5.7-23.9) HDL (mg/dl): G1: 0.6 (SD NR) G2: 1.8 (SD NR) G2 mean % change vs. G1: 2.5 (-1.8, 6.8) G3: 3.5 (SD NR) G3 mean % change vs. G1: 7.4 (3.1, 11.7) G3 mean % change vs. G2: 4.9 (0.6, 9.2) TGs (mg/dl): G1: 20.4 (SD NR) G2: -14.5 (SD NR) G2 mean % change vs. G1: -16.7 (-27.9, 5.5) G3: -1.8 (SD NR) G3 mean % change vs. G1: 1.2 (-10.1, 12.6) G3 mean % change vs. G2: 17.9 (6.7, 29.2)	see KQ1

Evidence Table 10. Key Question 2: Studies of rosiglitazone and pioglitazone

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Inclusion and Exclusion Criteria	Overall Sample Size Interventions Group Sizes	Baseline Population Characteristics Mean Age, years Race/Ethnicity % Female	Background Medications
Hamann, 2008 52 weeks Multinational Funding NR Fair	Inclusion: BMI ≥ 25 T2DM; HbA1c 7-10; received metfromin for at least 8 weeks prior to screening Exclusion: used any oral diabetic drug other than metformin in last 12 weeks; insulin at any time other than pregnancy or emergency; history of metabolic acidosis; edema requiring treatment; anemia; renal or hepatic disease; known congestive heart failure; unstable or severe angina; history of myocardial infarction; angioplasty; coronary artery bypass graft; stroke within 3 months; left ventricular dysfunction within 6 monhts; fasting C-peptide ≤ 0.5nmol/L; systolic blood pressure > 170; diastolic > 100	N=818 entered run-in, 596 randomized G1: (rosiglitazone 4mg/day + metformin 2g/day) n=294 G2: (sulfonylurea (glibenclamide 5mg/day or glicazide 80mg/day + metformin 2g/day) n=288 All medications uptitrated	G1: Age: 58.5 Race: white 94%, other 6% Female: 47% G2: Age 59.3 Race: white 95%, other 5% Female: 48%	metformin

Evidence Table 10. Key Question 2: Studies of rosiglitazone and pioglitazone

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Adverse Events	Changes in Lipid Concentrations	Weight Gain
Hamann, 2008 52 weeks Multinational Funding NR Fair	Withdrawals due to AEs: G1: n=11 (3.7%) G2: n=12 (4.0%) Number of subjects with AEs: G1: 165 (56%) G2: 175 (58%) Hypoglycemia: Proportion of subjects: G1: 6% G2: 30% *P* <0.001, G1 vs. G2 Total number of hypoglycemic events: G1: 58 G2: 482 GI effects: G1: 38 (13%) G2: 54 (18%) Edema: G1: 12 G2: 3 Serious AEs: G1: 16 G2: 11	Mean change in TC at 52 weeks: G1: +11.19mg/dl (SD NR) G2: -10.42mg/dl (SD NR) Mean change in HDL at 52 weeks: G1:+4.63mg/dl (SD NR) G2:+1.16 (SD NR) Mean change in LDL at 52 weeks: G1: +5.02mg/dl (SD NR) G2: -6.18 mg/dl (SD NR) Mean change in TGs at 52 weeks: G1: -17.7mg/dl (SD NR) G2: -28.01mg/dl (SD NR) No statistical testing done	NR

Evidence Table 10. Key Question 2: Studies of rosiglitazone and pioglitazone

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Inclusion and Exclusion Criteria	Overall Sample Size Interventions Group Sizes	Baseline Population Characteristics Mean Age, years Race/Ethnicity % Female	Background Medications
Giles, 2008 6 months Multinational Takeda Pharmaceuticals Fair	Inclusion: Participants were ≥18 years of age with HbA1c ≥7.0%, BMI ≤48 kg/m2, New York Heart Association functional class II or III heart faiure, left ventricular ejection fraction ≤40% at screening, receiving sulfonylurea therapy (±insulin) for ≥30 days before screening, or discontinued metformin therapy within 30 days of screening. Exclusion: naïve to antidiabetic therapy; serum creatinine > 2.0mg/dl (males) or >1.8mg/dl (females); systolic blood pressure > 150 or diastolic > 100; myocardial infarction in last 3 months; coronary angioplasty or bypass graft; unstable angina; transient ischemic attack or stroke; severe/advanced peripheral vascular disease	N=518 patients randomized G1: (pioglitazone) n=262 G2: (glyburide) n=256	G1: Age: 64.2 Race: White 68.7%, Other NR Female: 29.8% G2: Age: 63.4 Race: White 66.4, Other NR Female: 23.0%	some patients were on insulin (stratified randomization by use)

Evidence Table 10. Key Question 2: Studies of rosiglitazone and pioglitazone

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Adverse Events	Changes in Lipid Concentrations	Weight Gain
Giles, 2008 6 months Multinational Takeda Pharmaceuticals Fair	Withdrawals because of AEs: G1: 9.16% G2: 5.46% Percent with AEs: G1: 74.0% G2: 74.6% Bronchitis: G1: 2.7% G2: 5.5% Pneumonia: G1: 1.9% G2: 1.6% Hypoglycemia G1: 9.5% G2: 16.0% Diarrhea: G1: 5.3% G2: 3.5% Worsened/aggravated congestive heart failure: G1: 15.6% G2: 10.2% AND G1: 3.8% G2: 2.0%	Change in TC: NR LDL: G1: +6.9mg/dl (SD NR) G2: -2.4 (SD NR) *P* =0.016, G1 vs. G2 HDL: G1: +4.8mg/dl G2: -0.8mg/dl *P* <0.001, G1 vs. G2 TG: G1: -36.8mg/dl G2: +7.6mg/dl *P* <0.001, G1 vs. G2	G1: 2.1 kg G2: 1.23kg

Evidence Table 11. Key Question 2: Studies of fixed-dose combination products and dual therapy

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Inclusion and Exclusion Criteria	Overall Sample Size Interventions Group Sizes	Baseline Population Characteristics Mean Age, years Race/Ethnicity % Female	Background Medications
Active-control studies				
McCluskey, 2004 20 weeks US Funding NR Fair	Inclusion: T2DM ≥ 1 year; age 18-80; managed on rosiglitazone 4 or 8mg for at least 2 months; HbA1c 7.5-9.5; BMI 26-42; fasting C-peptide ≥ 0.27 nmol/L; fasing plasma glucose 126-235 mg/dl Exclusion: require insulin therapy; receiving other sulfonylureas; history of sulfonylurea hypersensitivity; rosiglitazone dose increased within 2 months; body weight increases >2% (for patients weighing ≤ 250 lbs. or >3% (for patients weighing > 250 lbs.) during the stabilization period; clinically abnormal baseline values	N=40 patients randomized G1: (Glimeperide 8mg/day + rosiglitazone 4 or 8mg/day) n=25 G2: (placebo + rosiglitazone 4 or 8mg/day) n=15	G1: Age: 60.2 Race: White 96%, Other 4% Female 56% G2: Age: 50.8 Race: White 80%, Other 20% Female 60%	NR

Evidence Table 11. Key Question 2: Studies of fixed-dose combination products and dual therapy

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Adverse Events	Changes in Lipid Concentrations	Weight Gain
Active-control studies			
McCluskey, 2004 20 weeks US Funding NR Fair	Number of withdrawals because of Aes: G1: 0 G2: 0 Episodes of Hypoglycemia: G1: 59 G2: 4 *P* <0.013, G1 vs. G2 Episodes of Severe Hypoglycemia: G1: 0 G2: 0	TC mean change from baseline: G1: -3.3 mg/dl (SD 3.1) G2: 1.4 mg/dl (SD 4.3) NS, G1 vs. G2 LDL mean change from baseline: G1: 0.2 mg/dl (SD 2.3) G2: -0.1 (3.4 mg/dl) NS, G1 vs. G2 HDL mean change from baseline: G1: 0.6mg/dl (SD 0.5) G2: -0.3 mg/dl (SD 0.7) NS, G1 vs. G2 TGs mean change from baseline: G1: -7.5 mg/dl (SD 10.0) G2: 21.6 mg/dl (SD 13.7) NS, G1 vs. G2	Mean weight change from baseline: G1: +5.1kg (SD NR) G2: + 2.4kg (SD NR) NS, G1 vs. G2

Evidence Table 11. Key Question 2: Studies of fixed-dose combination products and dual therapy

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Inclusion and Exclusion Criteria	Overall Sample Size Interventions Group Sizes	Baseline Population Characteristics Mean Age, years Race/Ethnicity % Female	Background Medications
Stewart, 2006 32 weeks Multinational GlaxoSmithKline Fair	Inclusion: 18-70 years old; T2DM; drug naïve subjects with fasting plasma glucose 7-9 mmol/l and HbA1c 7.0-9.0 mmol/l or treated with monotherapy with fasting plasma glucose 6-8mmol/l and HbA1c 6.5-8.0. Prior to visit 2 all subjects must have had fasting plasma glucose 7.0-9.0 mmol/l Exclusion: prior exposure to TZDs within 6 months; use of insulin; unstable or severe angina; coronary insufficiency; NewYork Heart Association I-IV congestive heart failure; blood pressure > 170/100 while on anti-hypertensive treatment	N=526 patients randomized, 509 in ITT population G1: (rosiglitazone titrated up to 8mg day/ metformin titrated to 2000mg day) n=254 G2: (metformin titrated up to 3000mg) n=272	G1: Age 58.9 Race: White 98%, Asian 1%, Hispanic <1%, African American 0%, Native Hawaiian/other Pacific Islander 0% Female 45% G2: Age: 59.0 Race: White 99%, Asian <1%, Hispanic <1%, African American <1%, Native Hawaiian/other Pacific Islander <1% Female 44%	None

Evidence Table 11. Key Question 2: Studies of fixed-dose combination products and dual therapy

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Adverse Events	Changes in Lipid Concentrations	Weight Gain
Stewart, 2006 32 weeks Multinational GlaxoSmithKline Fair	Reported 5% withdrawals due to AEs in both groups Withdrawals due to GI disorders: G1: 11 (4%) G2: 7 (3%) *P* =NR Number experiencing AEs: G1: 62% G2: 59% *P* =NR Serious AEs: G1: 10 (4%) G2: 10 (4%) *P* =NR Hypoglycemia: G1: 17 (7%) G2: 10 (4%) Severe Hypoglycemia: G1: 1 G2: 0 GI AE similar in both groups, 33% Reduced incidence of diarrhea: G1: 8% G2: 18%	TC (mg/dl): G1: 10.42 (SD NR) G2: -11.58 (SD NR) *P* <0.0001, G1 vs. G2 LDL (mg/dl): G1: 5.41 (SD NR) G2: -8.49 (SD NR) *P* <0.0001, G1 vs. G2 HDL (mg/dl): G1: 3.09 (SD NR) G2: 0.77 (SD NR) *P* =0.0027, G1 vs. G2 TGs (mg/dl): G1: 0 (SD NR) G2: -15.04 (SD NR) *P* =0.0410, G1 vs. G2	NR

Evidence Table 11. Key Question 2: Studies of fixed-dose combination products and dual therapy

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Adverse Events	Changes in Lipid Concentrations	Weight Gain
Stewart, 2006 (continued)	Edema: G1: 6 (2%) G2: 0 (0%) *P* =NR Reductions in mean Hb: G1: -0.75 (.07) g/dl G2: -0.34 (0.07) g/dl *P* <0.0001 Reductions in Hct: G1: -0.02 (0.002) G2: -0.01 (0.002) *P* <0.0001		

Evidence Table 11. Key Question 2: Studies of fixed-dose combination products and dual therapy

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Inclusion and Exclusion Criteria	Overall Sample Size Interventions Group Sizes	Baseline Population Characteristics Mean Age, years Race/Ethnicity % Female	Background Medications
Weissman, 2005 EMPIRE 24 weeks US GlaxoSmithKline Fair	Inclusion: age 18-75; T2DM; HbA1c 6.5-8.5 for subjects with prior treatment, 7-10 for drug naïve subjects; fasting plasma glucose 7.0-15.0mmol/l; BMI ≥ 27; previous therapy could include diet, exercise or oral therapy (acarbose, sulfonylurea, metformin or metformin + sulfonylurea); metformin dose must have been ≤ 1000mg/day for at least 3 months prior to study; subjects must have stopped TZD at least 3 months prior to screening Exclusion: uncontrolled hypertension; congestive heart failure requiring treatment; severe angina; anemia or severe edema associated with TZDs; active or chronic metabolic acidosis; clinically significant renal or hepatic disease; prior insulin use within 3 months; subjects non-compliant with metformin up-titration	N=766 randomized, 709 in ITT population G1: (rosiglitazone titrated to 8mg/day + metformin 1000mg/day) n=358 ITT G2: (metformin titrated to 2000mg/day) n=351 ITT	G1: Age: 55.5 Race/Female: NR G2: Age: 55.7 Race/Female: NR	NR

Evidence Table 11. Key Question 2: Studies of fixed-dose combination products and dual therapy

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Adverse Events	Changes in Lipid Concentrations	Weight Gain
Weissman, 2005 EMPIRE 24 weeks US GlaxoSmithKline Fair	Withdrawals because of AEs: G1: 28 (7.3%) G2: 37 (9.6%) Withdrawals due to Gi-related AEs (all randomized population): All GI Disorders: G1: 3.1%; G2: 6.8% Diarrhea: G1: 1.6%; G2: 4.2% Abdominal pain: G1: 1.0%; G2: 2.3% Specific Adverse Events Anemia: G1: 6 (1.6%) G2: 0 Edema: G1: 18 (4.7%) G2: 5 (1.3%)	TC (mg/dl): G1: +20.5 (SD NR) G2: -2.2 (SD NR) LDL (mg/dl): G1: +12.2 (SD NR) G2: -3.5 (SD NR) HDL (mg/dl): G1: +4.1 (SD NR) G2: +1.6 (SD NR) TGs (mg/dl): G1: +11.8 (SD NR) G2: -2.4 (SD NR)	G1: +1.79kg (SD 4.15) *P* <0.0001, G1 vs. baseline G2: -1.78kg (SD 3.50) *P* <0.0001, G2 vs. baseline

Evidence Table 11. Key Question 2: Studies of fixed-dose combination products and dual therapy

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Adverse Events	Changes in Lipid Concentrations	Weight Gain
Weissman, 2005 continued	Hypoglycemia: G1: 4 G2: 4 Abnormal Hepatic function: G1: 1 (withdrew) G2: 0 ITT population: G1: 100 (27.9%) G2: 136 (38.7%) All randomized population: Diarrhea: G1: NR G2: 63 (16.4%) Abdominal pain: G1: NR G2: 43		

Evidence Table 11. Key Question 2: Studies of fixed-dose combination products and dual therapy

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Inclusion and Exclusion Criteria	Overall Sample Size Interventions Group Sizes	Baseline Population Characteristics Mean Age, years Race/Ethnicity % Female	Background Medications
Goldstein, 2006 EMPIRE 24 weeks US GlaxoSmithKline Fair	Inclusion: Age 18-75; HbA1c of 6.5-8.5% for subjects having received prior combination treatment and 7-10% for drug-naive or monotherapy subjects; fasting plasma glucose 126-270mg/dL; BMI >=27kg/m2; previous treatment with either diet & exercise or with oral therapy with metformin (<=1,000mg/day for at least 3 months prior to study), either as monotherapy or in combination with a sulfonylurea. Exclusion: Uncontrolled hypertension; congestive heart failure requiring treatment, severe angina, clinically significant renal or hepatic disease; active or chronic metabolic acidosis; receipt of insulin or TZD in 3 months prior to study; history of anemia or severe edema associatyed with TZD therapy; non-compliance with metformin during run-in period.	N=122 G1: (rosiglitazone 4mg/day up-titrated to 8mg/day at week 8 + metformin 1,000mg day) n=71 G2: (metformin 1,500mg/day up-titrated to 2,000mg/day at week 8) n=51	Age: G1: 54.6 G2: 56.0 Race (%): Caucasian: G1: 71.8 G2: 66.7 Black: G1: 7.0 G2: 5.9 Hispanic: G1: 16.9 G2: 25.5 Other: G1: 4.2 G2: 2.0 % Female: G1: 49.3 G2: 35.3	NR

Evidence Table 11. Key Question 2: Studies of fixed-dose combination products and dual therapy

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Adverse Events	Changes in Lipid Concentrations	Weight Gain
Goldstein, 2006 EMPIRE 24 weeks US GlaxoSmithKline Fair	Overall AEs: G1: 36 G2: 23 Viral Infection: G1: 5 G2: 1 Upper Respiratory Tract Infection: G1: 10 G2: 6 Dyspespsia: G1: 6 G2: 3 Flatulence: G1: 6 G2: 1 Abdominal pain: G1: 4 G2: 4 Constipation: G1: 4 G2: 0 Diarrhea: G1: 4 G2: 6 Nausea: G1: 2 G2: 4 Injury: G1: 2 G2: 4	NR	NR

Evidence Table 12. Key Question 2: Quality assessment of trials for Key Question 2

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Randomization adequate? Yes, No, NR	Allocation concealment adequate? Yes, No, NR	Groups similar at baseline? Yes, No, NR	Outcome assessors masked? Yes, No, NR	Care provider masked? Yes, No, NR	Patient masked? Yes, No, NR	Run-in/Washout? Yes, No, NR
Buse, 2009 LEAD-6 26 weeks Mulitnational Novo Nordisk Fair	Yes	Yes	Yes	Yes	Yes	Yes	No
Bergenstal, 2009 Novo-Log Mix vs Exenatide Study Group 24 weeks United States Novo Nordisk Poor	Yes	Yes	Yes	No	No	No	No
Russel-Jones, 2009 LEAD-5 Multinational Novo Nordisk Good	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Garber, 2009 LEAD-3 MoNo 52 weeks US and Mexico Novo Nordisk Fair	Yes	NR	Yes	NR	NR	Yes	Yes

Evidence Table 12. Key Question 2: Quality assessment of trials for Key Question 2

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Overall attrition high (>20%)? Yes, No, NR	Loss to follow-up differential high (>15%)? Yes, No, NR	Outcome measures (ascertainment) equal, valid, and reliable? Yes, No, Mixed	Intention-to-treat (ITT) analysis? Yes, No, NR, Modified ITT	Post-randomization exclusions? Yes, No, NR	Adverse events pre-specified and defined? Yes, No, NR	Ascertainment techniques adequately described? Yes, No, NR
Buse, 2009 LEAD-6 26 weeks Mulitnational Novo Nordisk Fair	Yes	No	Yes	No	Yes	No	Yes
Bergenstal, 2009 Novo-Log Mix vs Exenatide Study Group 24 weeks United States Novo Nordisk Poor	Yes	No	Yes	NR	Yes	No	Yes
Russel-Jones, 2009 LEAD-5 Multinational Novo Nordisk Good	No	No	Yes	Yes	NR	Yes	Yes
Garber, 2009 LEAD-3 MoNo 52 weeks US and Mexico Novo Nordisk Fair	Yes	No	Yes	Yes	NR	Yes	No

Evidence Table 12. Key Question 2: Quality assessment of trials for Key Question 2

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Ascertainment techniques equal, valid, and reliable? Yes, No, Mixed	Adequate duration of follow-up? Yes, No, NR	Overall quality assessment for harms Good, Fair, Poor
Buse, 2009 LEAD-6 26 weeks Mulitnational Novo Nordisk Fair	Yes	Yes	Fair
Bergenstal, 2009 Novo-Log Mix vs Exenatide Study Group 24 weeks United States Novo Nordisk Poor	Yes	Yes	Fair
Russel-Jones, 2009 LEAD-5 Multinational Novo Nordisk Good	Yes	Yes	Good
Garber, 2009 LEAD-3 MoNo 52 weeks US and Mexico Novo Nordisk Fair	No	Yes	Fair

Evidence Table 12. Key Question 2: Quality assessment of trials for Key Question 2

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Randomization adequate? Yes, No, NR	Allocation concealment adequate? Yes, No, NR	Groups similar at baseline? Yes, No, NR	Outcome assessors masked? Yes, No, NR	Care provider masked? Yes, No, NR	Patient masked? Yes, No, NR	Run-in/Washout? Yes, No, NR
Madsbad, 2004 12 weeks Scandanavia and the UK Novo Nordisk Fair	NR	NR	Yes	NR	NR	Yes	Yes
Deeg, 2007 GLAI 24 weeks US Eli Lilly & Takeda Fair	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Chogtu, 2009 12 weeks India Funding NR Poor	Yes	Yes	Yes	NR	No	No	No
Beysen, 2008 20 weeks US Funding NR Fair	NR	NR	Yes	No	No	No	No
Vijay, 2009 16 weeks India UGC, India Fair	Yes	NR	Yes	NR	NR	NR	No

Evidence Table 12. Key Question 2: Quality assessment of trials for Key Question 2

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Overall attrition high (>20%)? Yes, No, NR	Loss to follow-up differential high (>15%)? Yes, No, NR	Outcome measures (ascertainment) equal, valid, and reliable? Yes, No, Mixed	Intention-to-treat (ITT) analysis? Yes, No, NR, Modified ITT	Post-randomization exclusions? Yes, No, NR	Adverse events pre-specified and defined? Yes, No, NR	Ascertainment techniques adequately described? Yes, No, NR
Madsbad, 2004 12 weeks Scandanavia and the UK Novo Nordisk Fair	No	Yes	Yes	Modified ITT	No	No	Yes
Deeg, 2007 GLAI 24 weeks US Eli Lilly & Takeda Fair	No	No	Yes	Yes	No	Yes	Yes
Chogtu, 2009 12 weeks India Funding NR Poor	No	NR	Yes	No	Yes	No	No
Beysen, 2008 20 weeks US Funding NR Fair	No	No	Yes	NR	Yes	No	Yes
Vijay, 2009 16 weeks India UGC, India Fair	NR	NR	Yes	NR	NR	Yes	Yes

Evidence Table 12. Key Question 2: Quality assessment of trials for Key Question 2

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Ascertainment techniques equal, valid, and reliable? Yes, No, Mixed	Adequate duration of follow-up? Yes, No, NR	Overall quality assessment for harms Good, Fair, Poor
Madsbad, 2004 12 weeks Scandanavia and the UK Novo Nordisk Fair	Mixed	Yes	Fair
Deeg, 2007 GLAI 24 weeks US Eli Lilly & Takeda Fair	Yes	Yes	Good
Chogtu, 2009 12 weeks India Funding NR Poor	Mixed	Yes	Poor
Beysen, 2008 20 weeks US Funding NR Fair	Yes	Yes	Fair
Vijay, 2009 16 weeks India UGC, India Fair	Yes	Yes	Fair

Evidence Table 12. Key Question 2: Quality assessment of trials for Key Question 2

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Randomization adequate? Yes, No, NR	Allocation concealment adequate? Yes, No, NR	Groups similar at baseline? Yes, No, NR	Outcome assessors masked? Yes, No, NR	Care provider masked? Yes, No, NR	Patient masked? Yes, No, NR	Run-in/Washout? Yes, No, NR
Oz, 2008 12 weeks Turkey Funding NR Fair	NR	NR	Yes	NR	NR	NR	No
OZ Gul, 2010 12 weeks Turkey Funding NR Fair	NR	NR	NR	Yes	NR	NR	No
Papathanassiou, 2009 6 months Greece Funding NR Fair	Yes	No	Yes	NR	No	No	No
Van der Meer, 2009 PIRAMID 24 weeks The Netherlands Eli Lilly, Takeda Good	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Schernthaner, 2004 Quarter Study 12 months Multinational Funding NR Good	Yes	Yes	Yes	Yes	NR	Yes	No

Evidence Table 12. Key Question 2: Quality assessment of trials for Key Question 2

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Overall attrition high (>20%)? Yes, No, NR	Loss to follow-up differential high (>15%)? Yes, No, NR	Outcome measures (ascertainment) equal, valid, and reliable? Yes, No, Mixed	Intention-to-treat (ITT) analysis? Yes, No, NR, Modified ITT	Post-randomization exclusions? Yes, No, NR	Adverse events pre-specified and defined? Yes, No, NR	Ascertainment techniques adequately described? Yes, No, NR
Oz, 2008 12 weeks Turkey Funding NR Fair	Yes	No	Yes	NR	No	Yes	Yes
OZ Gul, 2010 12 weeks Turkey Funding NR Fair	NR	No	Yes	NR	No	Yes	Yes
Papathanassiou, 2009 6 months Greece Funding NR Fair	No	No	No	Yes	NR	Yes	Yes
Van der Meer, 2009 PIRAMID 24 weeks The Netherlands Eli Lilly, Takeda Good	No	No	Yes	NR	No	NR	No
Schernthaner, 2004 Quarter Study 12 months Multinational Funding NR Good	No	No	Yes	Modified ITT	Yes	NR	No

Evidence Table 12. Key Question 2: Quality assessment of trials for Key Question 2

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Ascertainment techniques equal, valid, and reliable? Yes, No, Mixed	Adequate duration of follow-up? Yes, No, NR	Overall quality assessment for harms Good, Fair, Poor
Oz, 2008 12 weeks Turkey Funding NR Fair	Yes	Yes	Fair
OZ Gul, 2010 12 weeks Turkey Funding NR Fair	Yes	Yes	Fair
Papathanassiou, 2009 6 months Greece Funding NR Fair	Yes	Yes	Fair
Van der Meer, 2009 PIRAMID 24 weeks The Netherlands Eli Lilly, Takeda Good	Yes	Yes	Fair
Schernthaner, 2004 Quarter Study 12 months Multinational Funding NR Good	Mixed	Yes	Fair

Evidence Table 12. Key Question 2: Quality assessment of trials for Key Question 2

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Randomization adequate? Yes, No, NR	Allocation concealment adequate? Yes, No, NR	Groups similar at baseline? Yes, No, NR	Outcome assessors masked? Yes, No, NR	Care provider masked? Yes, No, NR	Patient masked? Yes, No, NR	Run-in/Washout? Yes, No, NR
Kusaka, 2008 4 months Japan Funding NR Fair	NR	NR	Yes	No	No	No	No
Nissen, 2008 PERISCOPE 18 months Multinational Takeda Pharmaceuticals Fair	Yes	Yes	Yes	Yes	Yes	Yes	No
Marre, 2003 LEAD-1SU 26 weeks Multinational Novo Nordisk Fair	NR	NR	Yes	NR	NR	Yes	Yes
Pop-Busui, 2009 6 months US GlaxoSmithKline, Eli Lilly, Research Foundations Fair	NR	NR	No	NR	NR	NR	Yes

Evidence Table 12. Key Question 2: Quality assessment of trials for Key Question 2

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Overall attrition high (>20%)? Yes, No, NR	Loss to follow-up differential high (>15%)? Yes, No, NR	Outcome measures (ascertainment) equal, valid, and reliable? Yes, No, Mixed	Intention-to-treat (ITT) analysis? Yes, No, NR, Modified ITT	Post-randomization exclusions? Yes, No, NR	Adverse events pre-specified and defined? Yes, No, NR	Ascertainment techniques adequately described? Yes, No, NR
Kusaka, 2008 4 months Japan Funding NR Fair	No	No	Yes	No	Yes	NR	No
Nissen, 2008 PERISCOPE 18 months Multinational Takeda Pharmaceuticals Fair	Yes	No	Yes	No	Yes	Yes	Yes
Marre, 2003 LEAD-1SU 26 weeks Multinational Novo Nordisk Fair	No	No	Yes	Yes	Yes	Yes	No
Pop-Busui, 2009 6 months US GlaxoSmithKline, Eli Lilly, Research Foundations Fair	No	No	Yes	NR	NR	NR	No

Evidence Table 12. Key Question 2: Quality assessment of trials for Key Question 2

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Ascertainment techniques equal, valid, and reliable? Yes, No, Mixed	Adequate duration of follow-up? Yes, No, NR	Overall quality assessment for harms Good, Fair, Poor
Kusaka, 2008 4 months Japan Funding NR Fair	Mixed	Yes	Fair
Nissen, 2008 PERISCOPE 18 months Multinational Takeda Pharmaceuticals Fair	Yes	Yes	Fair
Marre, 2003 LEAD-1SU 26 weeks Multinational Novo Nordisk Fair	No	Yes	Fair
Pop-Busui, 2009 6 months US GlaxoSmithKline, Eli Lilly, Research Foundations Fair	Yes	Yes	Fair

Evidence Table 12. Key Question 2: Quality assessment of trials for Key Question 2

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Randomization adequate? Yes, No, NR	Allocation concealment adequate? Yes, No, NR	Groups similar at baseline? Yes, No, NR	Outcome assessors masked? Yes, No, NR	Care provider masked? Yes, No, NR	Patient masked? Yes, No, NR	Run-in/Washout? Yes, No, NR
von Bibra, 2008 16 weeks (32-week cross-over) Germany Funding NR Fair	NR	No	Yes	Yes	NR	NR	Yes
Home, 2009 RECORD 7 year study, mean follow up time 5.5 years Multinational GlaxoSmithKline Fair	Yes	Yes	Yes	No	No	No	No
Kiyici, 2009 12 months Turkey Funding NR Fair	NR	NR	Yes	No	No	No	No
Scott, 2008 18 weeks Multinational Merck Fair	NR	NR	Yes	NR	Yes	Yes	Yes
Hamann, 2008 52 weeks Multinational Funding NR Fair	Yes	Yes	Yes	NR	Yes	Yes	Yes

Evidence Table 12. Key Question 2: Quality assessment of trials for Key Question 2

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Overall attrition high (>20%)? Yes, No, NR	Loss to follow-up differential high (>15%)? Yes, No, NR	Outcome measures (ascertainment) equal, valid, and reliable? Yes, No, Mixed	Intention-to-treat (ITT) analysis? Yes, No, NR, Modified ITT	Post-randomization exclusions? Yes, No, NR	Adverse events pre-specified and defined? Yes, No, NR	Ascertainment techniques adequately described? Yes, No, NR
von Bibra, 2008 16 weeks (32-week cross-over) Germany Funding NR Fair	No	No	Yes	No	Yes	NR	No
Home, 2009 RECORD 7 year study, mean follow up time 5.5 years Multinational GlaxoSmithKline Fair	No	No	Yes	Modified ITT	Yes	Yes	Yes
Kiyici, 2009 12 months Turkey Funding NR Fair	No	No	Yes	NR	No	NR	Yes
Scott, 2008 18 weeks Multinational Merck Fair	No	No	Yes	Modified ITT	Yes	Yes	Yes
Hamann, 2008 52 weeks Multinational Funding NR Fair	Yes	No	Yes	Modified ITT	Yes	NR	No

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Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Ascertainment techniques equal, valid, and reliable? Yes, No, Mixed	Adequate duration of follow-up? Yes, No, NR	Overall quality assessment for harms Good, Fair, Poor
von Bibra, 2008 16 weeks (32-week cross-over) Germany Funding NR Fair	No	Yes	Fair
Home, 2009 RECORD 7 year study, mean follow up time 5.5 years Multinational GlaxoSmithKline Fair	Yes	Yes	Fair
Kiyici, 2009 12 months Turkey Funding NR Fair	Yes	Yes	Fair
Scott, 2008 18 weeks Multinational Merck Fair	Yes	Yes	Fair
Hamann, 2008 52 weeks Multinational Funding NR Fair	Yes	Yes	Fair

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Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Randomization adequate? Yes, No, NR	Allocation concealment adequate? Yes, No, NR	Groups similar at baseline? Yes, No, NR	Outcome assessors masked? Yes, No, NR	Care provider masked? Yes, No, NR	Patient masked? Yes, No, NR	Run-in/Washout? Yes, No, NR
Giles, 2008 6 months Multinational Takeda Pharmaceuticals Fair	NR	NR	Yes	Yes	Yes	Yes	Yes
Rosenstock, 2009 CV181-011 Study 24 weeks US Bristol-Myers Squibb and Astra Zeneca Fair	NR	NR	Yes	Yes	Yes	Yes	Yes
Rosenstock, 2008 12 weeks Multinational Bristol-Myers Squibb Fair	NR	NR	Yes	Yes	Yes	Yes	Yes
DeFronzo, 2009 Saxagliptin CV181-014 Study 24 weeks Multinational Bristol-Myers Squibb & AstraZeneca Fair	Yes	NR	Yes	NR	Yes	Yes	Yes

Evidence Table 12. Key Question 2: Quality assessment of trials for Key Question 2

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Overall attrition high (>20%)? Yes, No, NR	Loss to follow-up differential high (>15%)? Yes, No, NR	Outcome measures (ascertainment) equal, valid, and reliable? Yes, No, Mixed	Intention-to-treat (ITT) analysis? Yes, No, NR, Modified ITT	Post-randomization exclusions? Yes, No, NR	Adverse events pre-specified and defined? Yes, No, NR	Ascertainment techniques adequately described? Yes, No, NR
Giles, 2008 6 months Multinational Takeda Pharmaceuticals Fair	Yes	Yes	Yes	Yes	No	Yes	Yes
Rosenstock, 2009 CV181-011 Study 24 weeks US Bristol-Myers Squibb and Astra Zeneca Fair	Yes	No	Yes	Modified ITT	Yes	No	Yes
Rosenstock, 2008 12 weeks Multinational Bristol-Myers Squibb Fair	No	No	Yes	Modified ITT	Yes	Yes	Yes
DeFronzo, 2009 Saxagliptin CV181-014 Study 24 weeks Multinational Bristol-Myers Squibb & AstraZeneca Fair	Yes	Yes	Yes	Modified ITT	Yes	Yes	Yes

Evidence Table 12. Key Question 2: Quality assessment of trials for Key Question 2

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Ascertainment techniques equal, valid, and reliable? Yes, No, Mixed	Adequate duration of follow-up? Yes, No, NR	Overall quality assessment for harms Good, Fair, Poor
Giles, 2008 6 months Multinational Takeda Pharmaceuticals Fair	Yes	Yes	Good
Rosenstock, 2009 CV181-011 Study 24 weeks US Bristol-Myers Squibb and Astra Zeneca Fair	Yes	Yes	Fair
Rosenstock, 2008 12 weeks Multinational Bristol-Myers Squibb Fair	Yes	Yes	Fair
DeFronzo, 2009 Saxagliptin CV181-014 Study 24 weeks Multinational Bristol-Myers Squibb & AstraZeneca Fair	Yes	Yes	Fair

Evidence Table 12. Key Question 2: Quality assessment of trials for Key Question 2

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Randomization adequate? Yes, No, NR	Allocation concealment adequate? Yes, No, NR	Groups similar at baseline? Yes, No, NR	Outcome assessors masked? Yes, No, NR	Care provider masked? Yes, No, NR	Patient masked? Yes, No, NR	Run-in/Washout? Yes, No, NR
Hollander, 2009 CV181-013 24 weeks US Bristol-Meyers Squibb and AstraZeneca Fair	Yes	Yes	Yes	NR	Yes	Yes	Yes
Hanefeld, 2007 Sitagliptin Study 014 12 weeks Multinational Fair	NR	NR	Yes	Yes	Yes	Yes	Yes
Nonaka, 2008 12 weeks Japan Banyu Pharmaceuticals (Merck) Good	NR	NR	Yes	Yes	Yes	Yes	Yes
Mohan, 2009 18 weeks China, India, Korea Merck Good	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Raz, 2008 30 weeks Multinational Merck Fair	Yes	Yes	No	Yes	Yes	Yes	Yes

Evidence Table 12. Key Question 2: Quality assessment of trials for Key Question 2

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Overall attrition high (>20%)? Yes, No, NR	Loss to follow-up differential high (>15%)? Yes, No, NR	Outcome measures (ascertainment) equal, valid, and reliable? Yes, No, Mixed	Intention-to-treat (ITT) analysis? Yes, No, NR, Modified ITT	Post-randomization exclusions? Yes, No, NR	Adverse events pre-specified and defined? Yes, No, NR	Ascertainment techniques adequately described? Yes, No, NR
Hollander, 2009 CV181-013 24 weeks US Bristol-Meyers Squibb and AstraZeneca Fair	Yes	No	Yes	Modified ITT	Yes	No	No
Hanefeld, 2007 Sitagliptin Study 014 12 weeks Multinational Fair	No	Yes	Yes	Modified ITT	Yes	Yes	Yes
Nonaka, 2008 12 weeks Japan Banyu Pharmaceuticals (Merck) Good	No	No	Yes	Modified ITT	Yes	Yes	Yes
Mohan, 2009 18 weeks China, India, Korea Merck Good	Yes	No	Yes	Modified ITT	No	Yes	Yes
Raz, 2008 30 weeks Multinational Merck Fair	No	No	Yes	No	Yes	Yes	Yes

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Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Ascertainment techniques equal, valid, and reliable? Yes, No, Mixed	Adequate duration of follow-up? Yes, No, NR	Overall quality assessment for harms Good, Fair, Poor
Hollander, 2009 CV181-013 24 weeks US Bristol-Meyers Squibb and AstraZeneca Fair	Yes	Yes	Fair
Hanefeld, 2007 Sitagliptin Study 014 12 weeks Multinational Fair	Yes	Yes	Fair
Nonaka, 2008 12 weeks Japan Banyu Pharmaceuticals (Merck) Good	Yes	Yes	Fair
Mohan, 2009 18 weeks China, India, Korea Merck Good	Yes	Yes	Good
Raz, 2008 30 weeks Multinational Merck Fair	Yes	Yes	Fair

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Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Randomization adequate? Yes, No, NR	Allocation concealment adequate? Yes, No, NR	Groups similar at baseline? Yes, No, NR	Outcome assessors masked? Yes, No, NR	Care provider masked? Yes, No, NR	Patient masked? Yes, No, NR	Run-in/Washout? Yes, No, NR
Williams-Herman, 2009 54 weeks Williams-Herman, 2010 104 weeks Multinational Merck Fair	NR	Yes	Yes	Yes	Yes	Yes	Yes
Chan, 2008 54 weeks Multinational Merck Fair	Yes	NR	Yes	Yes	Yes	Yes	Yes
Riddle, 2009 24 weeks US Amylin Pharmaceuticals Fair	Yes	Yes	Yes	No	No	No	No
Wysham 2008 16 weeks Amylin Phamaceuticals Fair	NR	NR	Yes	NR	Yes	Yes	Yes

Evidence Table 12. Key Question 2: Quality assessment of trials for Key Question 2

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Overall attrition high (>20%)? Yes, No, NR	Loss to follow-up differential high (>15%)? Yes, No, NR	Outcome measures (ascertainment) equal, valid, and reliable? Yes, No, Mixed	Intention-to-treat (ITT) analysis? Yes, No, NR, Modified ITT	Post-randomization exclusions? Yes, No, NR	Adverse events pre-specified and defined? Yes, No, NR	Ascertainment techniques adequately described? Yes, No, NR
Williams-Herman, 2009 54 weeks Williams-Herman, 2010 104 weeks Multinational Merck Fair	Yes	Yes	Yes	Modified ITT	No	Yes	Yes
Chan, 2008 54 weeks Multinational Merck Fair	Yes	No	Yes	Modified ITT	Yes	Yes	Yes
Riddle, 2009 24 weeks US Amylin Pharmaceuticals Fair	No	No	Yes	Modified ITT	Yes	No	Yes
Wysham 2008 16 weeks Amylin Phamaceuticals Fair	No	No	Yes	Yes	No	Yes	Yes

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Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Ascertainment techniques equal, valid, and reliable? Yes, No, Mixed	Adequate duration of follow-up? Yes, No, NR	Overall quality assessment for harms Good, Fair, Poor
Williams-Herman, 2009 54 weeks Williams-Herman, 2010 104 weeks Multinational Merck Fair	Yes	Yes	good
Chan, 2008 54 weeks Multinational Merck Fair	Yes	Yes	Good
Riddle, 2009 24 weeks US Amylin Pharmaceuticals Fair	Yes	Yes	Fair
Wysham 2008 16 weeks Amylin Phamaceuticals Fair	Yes	Yes	Fair

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Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Randomization adequate? Yes, No, NR	Allocation concealment adequate? Yes, No, NR	Groups similar at baseline? Yes, No, NR	Outcome assessors masked? Yes, No, NR	Care provider masked? Yes, No, NR	Patient masked? Yes, No, NR	Run-in/Washout? Yes, No, NR
Nauck, 2009 LEAD-2 26 weeks Multinational Novo Nordisk Fair	Yes	NR	Yes	NR	NR	Yes	Yes
Gao, 2009 16 weeks Multiple, Asia Amylin Pharmaceuticals and Eli Lilly Good	Yes	NR	Yes	NR	Yes	Yes	Yes
Kadowaki, 2009 12 weeks Japan Amylin Pharmaceuticals and Eli Lilly Fair	Yes	Yes	Yes	NR	Yes	Yes	Yes

Evidence Table 12. Key Question 2: Quality assessment of trials for Key Question 2

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Overall attrition high (>20%)? Yes, No, NR	Loss to follow-up differential high (>15%)? Yes, No, NR	Outcome measures (ascertainment) equal, valid, and reliable? Yes, No, Mixed	Intention-to-treat (ITT) analysis? Yes, No, NR, Modified ITT	Post-randomization exclusions? Yes, No, NR	Adverse events pre-specified and defined? Yes, No, NR	Ascertainment techniques adequately described? Yes, No, NR
Nauck, 2009 LEAD-2 26 weeks Multinational Novo Nordisk Fair	No	Yes	Yes	Modified ITT	No	Yes	No
Gao, 2009 16 weeks Multiple, Asia Amylin Pharmaceuticals and Eli Lilly Good	No	No	Yes	Modified ITT	Yes	Yes	Yes
Kadowaki, 2009 12 weeks Japan Amylin Pharmaceuticals and Eli Lilly Fair	No	No	Yes	No	Yes	Yes	NR

Evidence Table 12. Key Question 2: Quality assessment of trials for Key Question 2

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Ascertainment techniques equal, valid, and reliable? Yes, No, Mixed	Adequate duration of follow-up? Yes, No, NR	Overall quality assessment for harms Good, Fair, Poor
Nauck, 2009 LEAD-2 26 weeks Multinational Novo Nordisk Fair	No	Yes	Fair
Gao, 2009 16 weeks Multiple, Asia Amylin Pharmaceuticals and Eli Lilly Good	Yes	Yes	Good
Kadowaki, 2009 12 weeks Japan Amylin Pharmaceuticals and Eli Lilly Fair	Yes	Yes	Fair

Evidence Table 12. Key Question 2: Quality assessment of trials for Key Question 2

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Randomization adequate? Yes, No, NR	Allocation concealment adequate? Yes, No, NR	Groups similar at baseline? Yes, No, NR	Outcome assessors masked? Yes, No, NR	Care provider masked? Yes, No, NR	Patient masked? Yes, No, NR	Run-in/Washout? Yes, No, NR
Moretto, 2008 24 weeks United States, Puerto Rico, Romania, Russia, and India Amylin Pharamceuticals and Eli Lilly and Company Good	Yes	Yes	Yes	NR	Yes	Yes	Yes
SeiNo, 2008 14 weeks Japan Novo Nordisk Good	Yes	Yes	Yes	Yes	NR	Yes	Yes
Vilsboll, 2007 14 weeks Denmark, France, the Netherlands, Slovakia Novo Nordisk Fair	NR	NR	Yes	NR	Yes	Yes	Yes
Zinman, 2009 LEAD-4 26 weeks US and Canada Novo Nordisk Fair	Yes	NR	Yes	Yes	NR	Yes	Yes

Evidence Table 12. Key Question 2: Quality assessment of trials for Key Question 2

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Overall attrition high (>20%)? Yes, No, NR	Loss to follow-up differential high (>15%)? Yes, No, NR	Outcome measures (ascertainment) equal, valid, and reliable? Yes, No, Mixed	Intention-to-treat (ITT) analysis? Yes, No, NR, Modified ITT	Post-randomization exclusions? Yes, No, NR	Adverse events pre-specified and defined? Yes, No, NR	Ascertainment techniques adequately described? Yes, No, NR
Moretto, 2008 24 weeks United States, Puerto Rico, Romania, Russia, and India Amylin Pharamceuticals and Eli Lilly and Company Good	No	No	Yes	Modified ITT	Yes	No	Yes
SeiNo, 2008 14 weeks Japan Novo Nordisk Good	No	No	Yes	Modified ITT	No	No	No
Vilsboll, 2007 14 weeks Denmark, France, the Netherlands, Slovakia Novo Nordisk Fair	No	No	Yes	Yes	Yes	NR	Yes
Zinman, 2009 LEAD-4 26 weeks US and Canada Novo Nordisk Fair	Yes	Yes	Yes	Modified ITT	Yes	Yes	No

Evidence Table 12. Key Question 2: Quality assessment of trials for Key Question 2

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Ascertainment techniques equal, valid, and reliable? Yes, No, Mixed	Adequate duration of follow-up? Yes, No, NR	Overall quality assessment for harms Good, Fair, Poor
Moretto, 2008 24 weeks United States, Puerto Rico, Romania, Russia, and India Amylin Pharamceuticals and Eli Lilly and Company Good	Yes	Yes	Fair
SeiNo, 2008 14 weeks Japan Novo Nordisk Good	Yes	Yes	Fair
Vilsboll, 2007 14 weeks Denmark, France, the Netherlands, Slovakia Novo Nordisk Fair	Yes	Yes	Fair
Zinman, 2009 LEAD-4 26 weeks US and Canada Novo Nordisk Fair	Mixed	Yes	Fair

Evidence Table 12. Key Question 2: Quality assessment of trials for Key Question 2

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Randomization adequate? Yes, No, NR	Allocation concealment adequate? Yes, No, NR	Groups similar at baseline? Yes, No, NR	Outcome assessors masked? Yes, No, NR	Care provider masked? Yes, No, NR	Patient masked? Yes, No, NR	Run-in/Washout? Yes, No, NR
Chacra, 2009 CV181-040 24 weeks Multinational Bristol-Myers Squibb and AstraZeneca Fair	Yes	Yes	Yes	NR	Yes	Yes	Yes
McCluskey, 2004 20 weeks US Funding NR Fair	No	NR	No	NR	NR	Yes	Yes
Stewart, 2006 32 weeks Multinational GlaxoSmithKline Fair	NR	NR	Yes	NR	Yes	Yes	Yes
Weissman, 2005 EMPIRE 24 weeks US GlaxoSmithKline Fair	NR	NR	NR	NR	Yes	Yes	Yes
Goldstein, 2006 EMPIRE 24 weeks US GlaxoSmithKline Fair	NR	NR	No	NR	Yes	Yes	Yes

Evidence Table 12. Key Question 2: Quality assessment of trials for Key Question 2

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Overall attrition high (>20%)? Yes, No, NR	Loss to follow-up differential high (>15%)? Yes, No, NR	Outcome measures (ascertainment) equal, valid, and reliable? Yes, No, Mixed	Intention-to-treat (ITT) analysis? Yes, No, NR, Modified ITT	Post-randomization exclusions? Yes, No, NR	Adverse events pre-specified and defined? Yes, No, NR	Ascertainment techniques adequately described? Yes, No, NR
Chacra, 2009 CV181-040 24 weeks Multinational Bristol-Myers Squibb and AstraZeneca Fair	Yes	No	Yes	No	Yes	Yes	Yes
McCluskey, 2004 20 weeks US Funding NR Fair	No	No	Yes	Yes	No	NR	Yes
Stewart, 2006 32 weeks Multinational GlaxoSmithKline Fair	Yes	No	Yes	Modified ITT	Yes	Yes	Yes
Weissman, 2005 EMPIRE 24 weeks US GlaxoSmithKline Fair	Yes	No	Yes	Modified ITT	Yes	NR	No
Goldstein, 2006 EMPIRE 24 weeks US GlaxoSmithKline Fair	No	No	Yes	Yes	Yes	Yes	NR

Evidence Table 12. Key Question 2: Quality assessment of trials for Key Question 2

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Ascertainment techniques equal, valid, and reliable? Yes, No, Mixed	Adequate duration of follow-up? Yes, No, NR	Overall quality assessment for harms Good, Fair, Poor
Chacra, 2009 CV181-040 24 weeks Multinational Bristol-Myers Squibb and AstraZeneca Fair	Yes	Yes	Good
McCluskey, 2004 20 weeks US Funding NR Fair	Yes	Yes	Fair
Stewart, 2006 32 weeks Multinational GlaxoSmithKline Fair	Yes	Yes	Fair
Weissman, 2005 EMPIRE 24 weeks US GlaxoSmithKline Fair	Mixed	Yes	Fair
Goldstein, 2006 EMPIRE 24 weeks US GlaxoSmithKline Fair	Yes	Yes	Fair

Evidence Table 12. Key Question 2: Quality assessment of trials for Key Question 2

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Randomization adequate? Yes, No, NR	Allocation concealment adequate? Yes, No, NR	Groups similar at baseline? Yes, No, NR	Outcome assessors masked? Yes, No, NR	Care provider masked? Yes, No, NR	Patient masked? Yes, No, NR	Run-in/Washout? Yes, No, NR
Seck, 2010 104 weeks Multinational Merck Fair Extension of Nauck, 2007	Yes	Yes	Yes	Yes	NR	Yes	Yes
Aschner, 2010 24 weeks Multinational Merck Good	Yes	Yes	Yes	Yes	NR	Yes	Yes
Vilsboll, 2010 24 weeks Multinational Merck Fair	NR	NR	Yes	Yes	NR	Yes	Yes
Gill, 2010 12 weeks Multinational Eli Lilly Fair	NR	NR	Yes	NR	NR	NR	Yes
Pratley, 2010 26 weeks Multinational Novo Nordisk Fair	Yes	Yes	Yes	Yes	No	No	NR
Apovian, 2010 24 weeks US Eli Lilly Fair	Yes	Yes	Yes	NR	NR	NR	No

Evidence Table 12. Key Question 2: Quality assessment of trials for Key Question 2

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Overall attrition high (>20%)? Yes, No, NR	Loss to follow-up differential high (>15%)? Yes, No, NR	Outcome measures (ascertainment) equal, valid, and reliable? Yes, No, Mixed	Intention-to-treat (ITT) analysis? Yes, No, NR, Modified ITT	Post-randomization exclusions? Yes, No, NR	Adverse events pre-specified and defined? Yes, No, NR	Ascertainment techniques adequately described? Yes, No, NR
Seck, 2010 104 weeks Multinational Merck Fair Extension of Nauck, 2007	Yes	No	Yes	No	No	Yes	Yes
Aschner, 2010 24 weeks Multinational Merck Good	No	No	Yes	No	Yes	Yes	Yes
Vilsboll, 2010 24 weeks Multinational Merck Fair	No	No	Yes	Modified ITT	No	Yes	Yes
Gill, 2010 12 weeks Multinational Eli Lilly Fair	No	No	Yes	Yes	No	NR	Yes
Pratley, 2010 26 weeks Multinational Novo Nordisk Fair	No	No	Yes	Yes	Yes	Yes	Yes
Apovian, 2010 24 weeks US Eli Lilly Fair	Yes	No	Yes	Modified ITT	No	No	No

Evidence Table 12. Key Question 2: Quality assessment of trials for Key Question 2

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Ascertainment techniques equal, valid, and reliable? Yes, No, Mixed	Adequate duration of follow-up? Yes, No, NR	Overall quality assessment for harms Good, Fair, Poor
Seck, 2010 104 weeks Multinational Merck Fair Extension of Nauck, 2007	Yes	Yes	Good
Aschner, 2010 24 weeks Multinational Merck Good	Yes	Yes	Good
Vilsboll, 2010 24 weeks Multinational Merck Fair	Yes	Yes	Good
Gill, 2010 12 weeks Multinational Eli Lilly Fair	Mixed	Yes	Fair
Pratley, 2010 26 weeks Multinational Novo Nordisk Fair	Mixed	Yes	Fair
Apovian, 2010 24 weeks US Eli Lilly Fair	Mixed	Yes	Fair

Evidence Table 12. Key Question 2: Quality assessment of trials for Key Question 2

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Randomization adequate? Yes, No, NR	Allocation concealment adequate? Yes, No, NR	Groups similar at baseline? Yes, No, NR	Outcome assessors masked? Yes, No, NR	Care provider masked? Yes, No, NR	Patient masked? Yes, No, NR	Run-in/Washout? Yes, No, NR
DeFronzo, 2010 20 weeks US Eli Lilly Fair	NR	NR	Yes	No	No	No	No
Brackenridge, 2009 3 months United Kingdom Takeda Poor	NR	NR	No	NR	Yes	Yes	No
Kadoglou, 2010 14 weeks Greece European Social Fund and National Resources - PYTHAGORAS II & Alexander S Onassis Public Benefit Foundation Fair	Yes	NR	Yes	No	No	No	Yes
Kato, 2009 12 Weeks Japan NR Fair	NR	Yes	Yes	NR	NR	NR	Yes
Perez, 2009 24 Weeks Multinational Takeda Fair	NR	NR	Yes	NR	Yes	Yes	Yes

Evidence Table 12. Key Question 2: Quality assessment of trials for Key Question 2

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Overall attrition high (>20%)? Yes, No, NR	Loss to follow-up differential high (>15%)? Yes, No, NR	Outcome measures (ascertainment) equal, valid, and reliable? Yes, No, Mixed	Intention-to-treat (ITT) analysis? Yes, No, NR, Modified ITT	Post-randomization exclusions? Yes, No, NR	Adverse events pre-specified and defined? Yes, No, NR	Ascertainment techniques adequately described? Yes, No, NR
DeFronzo, 2010 20 weeks US Eli Lilly Fair	Yes	No	Mixed	Yes	No	No	No
Brackenridge, 2009 3 months United Kingdom Takeda Poor	NR	NR	Mixed	NR	NR	NR	No
Kadoglou, 2010 14 weeks Greece European Social Fund and National Resources - PYTHAGORAS II & Alexander S Onassis Public Benefit Foundation Fair	No	No	Yes	No	Yes	No	NR
Kato, 2009 12 Weeks Japan NR Fair	NR	NR	Yes	NR	No	No	Yes
Perez, 2009 24 Weeks Multinational Takeda Fair	Yes	No	Yes	Modified ITT	No	Yes	Yes

Evidence Table 12. Key Question 2: Quality assessment of trials for Key Question 2

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Ascertainment techniques equal, valid, and reliable? Yes, No, Mixed	Adequate duration of follow-up? Yes, No, NR	Overall quality assessment for harms Good, Fair, Poor
DeFronzo, 2010 20 weeks US Eli Lilly Fair	Mixed	Yes	Fair
Brackenridge, 2009 3 months United Kingdom Takeda Poor	Mixed	Yes	Poor
Kadoglou, 2010 14 weeks Greece European Social Fund and National Resources - PYTHAGORAS II & Alexander S Onassis Public Benefit Foundation Fair	Mixed	Yes	Fair
Kato, 2009 12 Weeks Japan NR Fair	Mixed	Yes	Fair
Perez, 2009 24 Weeks Multinational Takeda Fair	Mixed	Yes	Fair

Evidence Table 12. Key Question 2: Quality assessment of trials for Key Question 2

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Randomization adequate? Yes, No, NR	Allocation concealment adequate? Yes, No, NR	Groups similar at baseline? Yes, No, NR	Outcome assessors masked? Yes, No, NR	Care provider masked? Yes, No, NR	Patient masked? Yes, No, NR	Run-in/Washout? Yes, No, NR
Petrica, 2009 12 months Romania NR Poor	NR	NR	Yes	Yes	No	No	No
Gerstein, 2010 18 months Multinational GlaxoSmithKline Fair	Yes	NR	Yes	Yes	Yes	Yes	Yes
DeFronzo, 2010 20 weeks USA Eli Lilly Fair	NR	NR	NR	No	No	No	No
Rigby, 2010 16 weeks Mulitnaional Daichi Sankyo, Inc Fair	NR	NR	Yes	No	No	No	Yes

Evidence Table 12. Key Question 2: Quality assessment of trials for Key Question 2

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Overall attrition high (>20%)? Yes, No, NR	Loss to follow-up differential high (>15%)? Yes, No, NR	Outcome measures (ascertainment) equal, valid, and reliable? Yes, No, Mixed	Intention-to-treat (ITT) analysis? Yes, No, NR, Modified ITT	Post-randomization exclusions? Yes, No, NR	Adverse events pre-specified and defined? Yes, No, NR	Ascertainment techniques adequately described? Yes, No, NR
Petrica, 2009 12 months Romania NR Poor	Yes	No	Yes	No	Yes	NR	NR
Gerstein, 2010 18 months Multinational GlaxoSmithKline Fair	Yes	No	Yes	No	No	Yes	Yes
DeFronzo, 2010 20 weeks USA Eli Lilly Fair	Yes	No	Mixed	Yes	No	No	No
Rigby, 2010 16 weeks Mulitnaional Daichi Sankyo, Inc Fair	No	No	Yes	Modified ITT	Yes	Yes	Yes

Evidence Table 12. Key Question 2: Quality assessment of trials for Key Question 2

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Ascertainment techniques equal, valid, and reliable? Yes, No, Mixed	Adequate duration of follow-up? Yes, No, NR	Overall quality assessment for harms Good, Fair, Poor
Petrica, 2009 12 months Romania NR Poor	Yes	Yes	Poor
Gerstein, 2010 18 months Multinational GlaxoSmithKline Fair	Mixed	Yes	Fair
DeFronzo, 2010 20 weeks USA Eli Lilly Fair	Mixed	Yes	Fair
Rigby, 2010 16 weeks Mulitnaional Daichi Sankyo, Inc Fair	Yes	Yes	Fair

Evidence Table 13. Key Question 3: All studies

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Inclusion and Exclusion Criteria	Overall Sample Size Interventions Group Sizes	Baseline Population Characteristics Mean Age, years Race/Ethnicity % Female
Kahn, 2008 ADOPT 5 years Multinational GlaxoSmithKline Fair	Inclusion: T2DM; age 30-75; fasting plasma glucose 126-180mg/dl with lifestyle therapy and naïve to oral hypoglycemic drugs Exclusion: Clinically significant liver disease; renal impairment; history of lactic acidosis; unstable or severe angina; New York Heart Association I-IV congestive heart failure requiring pharmacologic intervention; uncontrolled hypertension; chronic diseases requiring periodic or intermittent treatment with oral or IV corticosteroids or continuous use of inhaled corticosteroids	N=4,351 treated patients (in analysis) 4, 360 randomized G1: (rosiglitazone 4mg-8mg/day) n=645 women, 811 men; 147 premenopausal; 489 postmenopausal G2: (metformin 500mg-2000mg/day) n=590 women, 864 men; 127 premenopausal; 463 postmenopausal G3: (glyburide 2.5mg-15mg/day) n=605 women, 836 men; 156 premenopausal; 449 postmenopausal;	G1: Age: females 56.1, males 56.4 Race: NR Female: 44.3% G2: Age: females 56.7, males 57.0 Race: NR Female: 40.6% G3: Age: females 56.3, males 56.6 Race: NR Female: 42.0%

Evidence Table 13. Key Question 3: All studies

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Intermediate Outcomes HbA1c Weight (kg)	Health and Utilization Outcomes Microvascular Disease Macrovascular Disease Lower Extremity Ulcers All-Cause Mortality Quality of Life Hospitalization Medical Visits (diabetes) Other	Overall Adverse Events (N) Specific Adverse Events (N)
Kahn, 2008 ADOPT 5 years Multinational GlaxoSmithKline Fair	NR	NR	Women: G1: 60 (9.3%) G2: 30 (5.1%) G3: 21 (3.5%) Hazards ratio G1 vs. G2: 1.81 (1.17-2.80) Hazards ratio G1 vs. G3: 2.13 (1.30-3.51) Men: G1: 32 (4.0%) G2: 29 (3.4%) G3: 28 (3.4%) Hazards ratios: NS Premenopausal: G1: 10 (6.8%) G2: 4 (3.2%), *P* =0.1709 G3: 3 (1.9%), *P* =0.0362 Postmenopausal: G1: 50 (10.0%) G2: 26 (5.6%), *P* =0.0111, G1 vs. G2 G3: 18 (4.0%), *P* =0.0003

Evidence Table 13. Key Question 3: All studies

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Inclusion and Exclusion Criteria	Overall Sample Size Interventions Group Sizes	Baseline Population Characteristics Mean Age, years Race/Ethnicity % Female
Raz, 2008 30 weeks Multinational Merck Fair	Inclusion: 18 - 78 years of age, currently on metformin monotherapy or any other single oral hypoglycemic agent or being treated with metformin in combination with another oral hypoglycemic agent, and HbA1c was 8.0 - <11.0%. Exclusion: Received treatment with insulin within 8 weeks prior to screening, treatment with a TZD or exenatide within 12 weeks, had type 1 diabetes, a BMI < 20 kg/m2 or > 43 kg/m2, or fasting plasma glucose during run-in that was consistently < 7.2 mmol/L or > 15.6 mmol/L.	N=190 (187 analyzed) Overall G1: (placebo) n=94 G2: (sitagliptin 100mg qd) n=96	G1: Age: 56.1 (9.5) Race: White 47%, Hispanic 25%, Black 1%, Multiracial 25%, Other 2% Female: 58.5% G2: Age: 53.6 (9.5) Race: White 42%, Hispanic 32%, Black 3%, Multiracial 22%, Other 1% Female: 39%

Evidence Table 13. Key Question 3: All studies

Study Characteristics Author, Year Trial Name (if app.) Duration Country Funding Quality	Intermediate Outcomes HbA1c Weight (kg)	Health and Utilization Outcomes Microvascular Disease Macrovascular Disease Lower Extremity Ulcers All-Cause Mortality Quality of Life Hospitalization Medical Visits (diabetes) Other	Overall Adverse Events (N) Specific Adverse Events (N)
Raz, 2008 30 weeks Multinational Merck Fair	HbA1c mean (SE) at 30 weeks: SG1 (age ≤55 years): Placebo -0.1 (0.2); sitagliptin -1.0 (0.2) SG2(age > 55years): Placebo 0.2 (0.2); sitagliptin -1.1 (0.2) SG3 (BMI ≤ 30.1 kg/m2): Placebo 0.0 (0.2); sitagliptin -1.1 (0.2) SG4 (BMI > 30.1 kg/m2): Placebo 0.2 (0.2); sitagliptin -0.9 (0.2) SG5 (female): Placebo 0.1 (0.2); sitagliptin -1.1 (0.2) SG6 (male): Placebo 0.0 (0.2); sitagliptin -0.9 (0.2) SG7 (previously on metformin monotherapy): Placebo 0.0 (0.2); sitagliptin -0.9 (0.2) SG8 (previously on metformin-based combination therapy): Placebo 0.2 (0.2); sitagliptin -1.2 (0.2) Weight: NR for subgroups	NR	NR

Evidence Table 14. Key Question 3: Quality assessment of trials for Key Question 3

Author	Randomization adequate? Yes, No, NR	Allocation concealment adequate? Yes, No, NR	Groups similar at baseline? Yes, No, NR	Outcome assessors masked? Yes, No, NR	Care provider masked? Yes, No, NR	Patient masked? Yes, No, NR
Raz, 2008 30 weeks Multinational Merck Fair	Yes	Yes	No	Yes	Yes	Yes
Kahn, 2008 ADOPT 5 years Multinational GlaxoSmithKline Fair	NR	NR	Yes	NR	Yes	Yes

Evidence Table 14. Key Question 3: Quality assessment of trials for Key Question 3

Author	Run-in/Washout? Yes, No, NR	Overall attrition high (≥20%)? Yes, No, NR	Loss to follow-up differential high (≥15%)? Yes, No, NR	Outcome measures (ascertainment) equal, valid, and reliable? Yes, No, Mixed	Intention-to-treat (ITT) analysis? Yes, No, NR, Modified ITT	Post-randomization exclusions? Yes, No, NR
Raz, 2008 30 weeks Multinational Merck Fair	Yes	No	No	Yes	No	Yes
Kahn, 2008 ADOPT 5 years Multinational GlaxoSmithKline Fair	NR	Yes	No	Yes	Yes	NR

Evidence Table 14. Key Question 3: Quality assessment of trials for Key Question 3

Author	Efficacy and Effectiveness Outcomes Quality Rating Good, Fair, Poor	Adverse events pre-specified and defined? Yes, No, NR	Ascertainment techniques adequately described? Yes, No, NR	Ascertainment techniques equal, valid, and reliable? Yes, No, Mixed	Adequate duration of follow-up? Yes, No, NR	Quality assessment for harms Good, Fair, Poor
Raz, 2008 30 weeks Multinational Merck Fair	Fair	Yes	Yes	Yes	Yes	Fair
Kahn, 2008 ADOPT 5 years Multinational GlaxoSmithKline Fair	Fair	Yes	Yes	Mixed	Yes	Fair

Evidence Table 15. Key Question 1: Systematic reviews

Study Characteristics Author, Year Quality	Aim(s) of Review	Eligibility Criteria Characterstics of Included Studies	# studies # of Patients	Characteristics of included populations	Characteristics of Interventions

Diamond, 2007
Fair
	A reanalysis of the data set of 42 trials considered by Nissen and Wolski.	Eligibility: Had to have a randomized comparator group; At least 24 weeks of drug exposure in all groups; Had to report cardiovascular events
		
		Included Studies: RCT; Phase 2, 3, or 4 trials; 38 double blind trials; 4 open-label; See Comments.
			42 Trials
			
			27,847 Patients
				NR	rosigilitazone monotheapy vs. placebo (n=10);
					
					rosigilitazone vs. placebo add-on to sulfonylurea (n = 12);
					
					rosigilitazone vs. placebo add-on to metformin (n=10);
					
					rosigilitazone vs. placebo add-on to insulin (n=5);
					
					rosigilitazone vs. placebo add-on to usual care (n=1);
					
					rosigilitazone vs. sulfonylurea or metformin (n=4)

Evidence Table 15. Key Question 1: Systematic reviews

Study Characteristics Author, Year Quality	Main efficacy and effectivenes outcomes and results	Comments
Diamond, 2007 Fair	Myocardial Infarction Excluding trials without diabetes or congestive heart failure (k=38) [k, OR, 95%CI] Fixed, Peto: k= 35, 1.37, 0.98-1.92 Fixed, MH (TAC): k= 35, 1.31, 0.96-1.79 Fixed, MH (CC): k= 35, 1.25, 0.91.70 Fixed, MH (TAC+): k= 38, 1.31, 0.96-1.78 Fixed, MH (CC+): k = 38, 1.23, 0.9-1.67 rosigilitazone monotherapy vs. placebo (k=10) [k, OR, 95%CI] Fixed, Peto: k= 9, 1.52, 0.7-2.94 Fixed, MH (TAC): k= 9, 1.44, 0.77-2.69 Fixed, MH (CC): k= 9, 1.31, 0.71-2.43 Fixed, MH (TAC+): k= 10, 1.43, 0.7-2.66 Fixed, MH (CC+): k = 10, 1.28, 0.70-2.35 rosigilitazone vs. other antidiabetic regimens (k = 32) [k, OR, 95%CI] Fixed, Peto: k= 29, 1.40, 0.96-2.04 Fixed, MH (TAC): k= 29, 1.33, 0.94-1.88 Fixed MH (CC): k= 29, 1.27, 0.90-1.79 Fixed, MH (TAC+): k= 32, 1.32, 0.94-1.87 Fixed, MH (CC+): k = 32, 1.25, 0.89-1.75	This was a reanalysis of the data set of 42 trials considered by Nissen and Wolski (Refid #5575 in Previous Report). Abbreviations for Outcomes : MH= Mantel-Haenszel, TAC = treatment arm correction for continuity, TAC+ = treatment arm correction for continuity that includes all zero-total-event studies, CC = Constant correction for continuity, CC+ = Constant correction for continuity that includes all zero-total-event studies

Evidence Table 15. Key Question 1: Systematic reviews

Study Characteristics Author, Year Quality	Main efficacy and effectivenes outcomes and results	Comments
Diamond, 2007 Fair continued	rosiglitazone plus sulfonylurea vs. sulfonylurea (k = 12) [k, OR, 95%CI] Fixed, Peto: k= 11, 1.23, 0.48-3.18 Fixed, MH (TAC): k= 11, 1.16, 0.52-2.56 Fixed, MH (CC): k= 11, 1.11, 0.50-2.44 Fixed, MH (TAC+): k= 12, 1.15, 0.53-2.51 Fixed, MH (CC+): k = 12, 1.08, 0.50-2.33 rosigiltazone plus metformin vs. metformin (k = 10) [k, OR, 95%CI] Fixed, Peto: k= 10, 1.49, 0.48-4.65 Fixed, MH (TAC): k= 10, 1.28, 0.51-3.17 Fixed MH (CC): k= 10, 1.05, 0.44-2.51 Fixed, MH (TAC+): k= 10, 1.28, 0.51-3.17 Fixed, MH (CC+): k = 10, 1.05, 0.44-2.51 rosiglitazone plus insulin vs. insulin (k=5) [k, OR, 95%CI] Fixed, Peto: k= 3, 3.49, 0.84-14.96 Fixed, MH (TAC): k= 3, 3.53, 0.65-19.26 Fixed, MH (CC): k= 3, 2.77, 0.5-13.31 Fixed, MH (TAC+): k=5, 2.68, 0.65-11.11 Fixed, MH (CC+): k = 5, 2.07, 0.55-7.76	

Evidence Table 15. Key Question 1: Systematic reviews

Study Characteristics Author, Year Quality	Main efficacy and effectivenes outcomes and results	Comments
Diamond, 2007 Fair continued	Cardiovascular Death Excluding trials without diabetes or congestive heart failure (k=38) [k, OR, 95%CI] Fixed, Peto: k= 19, 1.58, 0.91-2.74 Fixed, MH (TAC): k= 19, 1.46, 0.88-2.44 Fixed, MH (CC): k= 19, 1.34, 0.81-2.21 Fixed, MH (TAC+): k= 38, 1.34, 0.86-2.10 Fixed, MH (CC+): k = 38, 1.16, 0.75-1.79 rosigilitazone monotherapy vs. placebo (k=10) [k, OR, 95%CI] Fixed, Peto: k= 8, 1.50, 0.72-3.11 Fixed, MH (TAC): k= 8, 1.42, 0.71-2.83 Fixed, MH (CC): k= 8, 1.24, 0.64-2.44 Fixed, MH (TAC+): k= 10, 1.40, 0.71-2.74 Fixed, MH (CC+): k = 10, 1.19, 0.62-2.28 rosigilitazone vs. other antidiabetic regimens (k = 32) [k, OR, 95%CI] Fixed, Peto: k= 15, 1.79, 0.87-3.71 Fixed, MH (TAC): k= 15, 1.60, 0.82-3.11 Fixed, MH (CC): k=15, 1.42, 0.74-2.73 Fixed, MH (TAC+): k= 32, 1.38, 0.80-2.40 Fixed, MH (CC+): k = 32, 1.16, 0.68-1.98	

Evidence Table 15. Key Question 1: Systematic reviews

Study Characteristics Author, Year Quality	Main efficacy and effectivenes outcomes and results	Comments
Diamond, 2007 Fair continued	rosiglitazone plus sulfonylurea vs. sulfonylurea (k = 12) [k, OR, 95%CI] Fixed, Peto: k= 6, 2.43, 0.67-8.86 Fixed, MH (TAC): k=6, 2.00, 0.59-6.80 Fixed, MH (CC): k=6, 1.67, 0.52-5.36 Fixed, MH (TAC+): k= 12, 1.58, 0.61-4.13 Fixed, MH (CC+): k = 12, 1.38, 0.54-3.48 rosigiltazone plus metformin vs. metformin (k = 10) [k, OR, 95%CI] Fixed, Peto: k= 4, 1.75, 0.35-8.82 Fixed, MH (TAC): k= 4, 1.47, 0.37-5.82 Fixed, MH (CC): k= 4, 1.34, 0.35-5.17 Fixed, MH (TAC+): k= 10, 1.27, 0.44-3.70 Fixed, MH (CC+): k = 10, 0.96, 0.34-2.66 rosiglitazone plus insulin vs. insulin (k=5) [k, OR, 95%CI] Fixed, Peto: k=3, 5.37, 0.51-56.51 Fixed, MH (TAC): k= 3, 2.70, 0.35-20.83 Fixed, MH (CC): k= 3, 1.92, 0.30-12.23 Fixed, MH (TAC+): k=5, 2.01, 0.40-10.17 Fixed, MH (CC+): k = 5, 1.45, 0.32-6.51	

Evidence Table 15. Key Question 1: Systematic reviews

Study Characteristics Author, Year Quality	Aim(s) of Review	Eligibility Criteria Characterstics of Included Studies	# studies # of Patients	Characteristics of included populations	Characteristics of Interventions
Lago , 2007 Good	Systematic review and meta-analysis of pooled data from randomized trials of TZDs in subjects with prediabetes or type 2 diabetes to assess the risk of development of heart failure and death from cardiovascular causes in patients given TZDs	Eligibility: Randomized, double-blind, controlled trials of TZDs; Report of risk estimates, frequency data for congestive heart failure and cardiovascular death; trials with male human patients; written in English Excluded non-randomized clinical trials;No data for cardiovascular outcomes or death Included Studies: All RCTs published since 2005; Follow-up with pts btwn 12 - 48 mos (mean 29.7 mos); Trial population range: 200- 5269 participants, median 4351	7 trials; includes one trial with two control groups 20,191 Patients	Age: 59.2 Male: 66.9% BMI: 31 (5.0) Baseline HbA1c: 7.72 (1.1) Baseline Medical History: Hypertension: 50.4% Hyperlipidaemia: 47.9% Coronary artery disease: 18.6% Congestive heart failure: 20% Chronic kidney disease or neuropathy: 2.4%	Daily TZD dosage: rosiglitazone vs. placebo: 8mg rosiglitazone vs. metformin and sulfonylurea: 4 - 8mg rosiglitazone vs. placebo: 4-8mg rosiglitazone vs. metformin/rosiglitazone vs. glibeclamide: 4-8mg rosiglitazone vs. placebo: 4-8mg pioglitzaone vs. glimepiride: 15-45mg pioglitazone vs. placebo: 15-45 mg

Evidence Table 15. Key Question 1: Systematic reviews

Study Characteristics Author, Year Quality	Main efficacy and effectivenes outcomes and results	Comments
Lago , 2007 Good	Cardiovascular Death Overall Risk, RR (95% CI)) TZDs: 0.93 (0.67, 1.29) rosiglitazone: 0.91 (0.63, 1.32) pioglitazone: 1.01 (0.51, 2.01) CV Deaths: rosiglitazone: 52 pioglitazone: 15 Controls (rosiglitazone trials): 63 Controls (pioglitazone trials): 15	

Evidence Table 15. Key Question 1: Systematic reviews

Study Characteristics Author, Year Quality	Aim(s) of Review	Eligibility Criteria Characterstics of Included Studies	# studies # of Patients	Characteristics of included populations	Characteristics of Interventions
Mannucci, 2008 Fair	Meta-analysis of RCTs to assess whether pioglitzaone is also associated with increased cardiovascular risk	Eligibility: RCT; pioglitazone vs. any other drug; Duration ≥ 4 weeks; Ongoing studies excluded. Included Studies: RCT; 24 placebo; 19 insulin secretagogues; 8 metformin; 8 PPAR agonists; 1 insulin; 4 α-glucosidase inhibitors; 4 DPP-IV inhibitors	Studies: 94 - 68 on patients w/ T2DM; 26 on patents w/ different conditions Patients: 19, 803 T2DM patients (excluding PROACTIVE study) 25,041 T2DM patients (including PROACTIVE study)	Weighted mean age: 51.7 y Mean diabetes duration: 6.6 yrs Mean HbA1c: 8.1% (excluding PROACTIVE)	Some combined therapy; Some monotherapy
Monami, 2008 Poor	Identification of moderators of the effects of rsoiglitazone on the risk of MI an dsevere heart failure	Eligibility: RCTs; Efficacy of rosiglitazone on type 2 diabetes; Comparator = any other ttreatment; Duration ≥ 4 wks; Type 2 diabetic pts; MI or CHF outcomes; Exclusion of ongoing trials Included Studies: Duration range: 6-312 wks; Comparators: 52 Placebo; 8 Metformin; 15 Insulin secretagogues; 2 Pioglitazone; 3 Insulin; 12 None (?); 1 Multiple comparators	86 studies 30,003 Patients	Rosiglitazone: N = 16284 Comparators: N = 13719	NR

Evidence Table 15. Key Question 1: Systematic reviews

Study Characteristics Author, Year Quality	Main efficacy and effectivenes outcomes and results	Comments
Mannucci, 2008 Fair	All-Cause Mortality PROACTIVE: pioglitazone not associated w/ significant modification of mortality Non-diabetic patients: 1 death observed among pioglitazone treated patients. T2DM patients (excluding PROACTIVE): pioglitazone: 17 deaths comparator: 39 deaths RR 0.41 (0.23-0.72) All Trials (including PROACTIVE): No significant reduction of mortality was observed w/ pioglitazone tx CV Death: pioglitazone (n=7644): 7 CV deaths comparator (n=6106): 16 CV deaths RR 0.35 (0.14-0.85)	Not able to determine if any of the "combined" therapies included in analysis were augmentation strategies or dual therapy.
Monami, 2008 Poor	MI (No. of Cases) Rosi: 124 Comp: 111 MH-OR. 1.18; 95% CI, 0.91 to1.53 <6 mos: MH-OR, 1.10; 95% CI, 0.59 to 1.86 ≥6 mos: MH-OR, 1.07; 95% CI, 0.51 to 1.89	

Evidence Table 15. Key Question 1: Systematic reviews

Study Characteristics Author, Year Quality	Aim(s) of Review	Eligibility Criteria Characterstics of Included Studies	# studies # of Patients	Characteristics of included populations	Characteristics of Interventions
Selvin, 2008 (AHRQ) Good	To systematically review the peer-reviewed literature on cardiovascular risk associatd with oral agents for treating adults with type 2 diabetes mellitus	Eligibility: Reported original data; Adults with type 2 diabetes; Excluded combinations of three oral diabetes agents and studies of 1st generation sulfonylureas. Excluded alpha-glucosidase inhibitors; Excluded studies that did not report all-cause mortality, cardiovascular morbidity or mortality; Excluded studies < 3 months; Excluded studies with total sample size < 40 Included studies: Majority of trials conducted in U.S. or U.K. Majority of trials were < 1 yr in duration	40 studies 29,734 Patients	Mean age range: 52-69 years Mean HbA1c at baseline: 6.2% - 10.2%	Metformin vs. Any Comparator metformin vs. any Sulfonylurea combined w/ Metformin Sulfonylurea vs. any comparator Any Sulfonylurea vs. any sulfonylurea combined with metformin Rosiglitazone vs. any comparator Rosiglitazone plus metformin vs. metformin alone Pioglitazone vs. any comparator Meglitinides vs any comparator

Evidence Table 15. Key Question 1: Systematic reviews

Study Characteristics Author, Year Quality	Main efficacy and effectivenes outcomes and results	Comments
Selvin, 2008 (AHRQ) Good	Cardiovascular Morbidity Metformin vs. Placebo or Other Oral Agent Pooled OR (95%CI), Overall: 0.85 (0.69- 1.05) Pooled OR (95%CI), Excluding UKPDS 34: 1.04 (0.80- 1.37) Any sulfonylurea vs. Placebo or Other Oral Agent Pooled OR (95%CI), Overall: 0.89 (0.71-1.11) Pooled OR (95%CI), Excluding UKPDS 33: 0.72 (0.41-1.28) Rosiglitazone vs. Placebo or Other Oral Agent Pooled OR (95%CI), Overall: 1.68 (0.92-3.06)	Unable to determine if studies included were dual therapy or fixed dose combination products.

Evidence Table 15. Key Question 1: Systematic reviews

Study Characteristics Author, Year Quality	Main efficacy and effectivenes outcomes and results	Comments
Selvin, 2008 (AHRQ) Good continued	Pioglitazone vs. Placebo or Oral Agent Pooled OR (95%CI), Overall: 0.88 (0.78-1.00) Pooled OR, Excluding PROactive: 0.86 (0.57-1.31) Cardiovascular Mortality Metformin vs. Any comparator Pooled OR (95%CI): 0.74 (0.62-0.89) Any sulfonylurea vs. Placebo or Other Oral Agent Pooled OR (95%CI): 0.92 (0.68-1.26) Rosiglitazone vs. Placebo or Other Oral Agent Pooled OR (95%CI): 1.03 (0.30-3.53)	

Evidence Table 15. Key Question 1: Systematic reviews

Study Characteristics Author, Year Quality	Main efficacy and effectivenes outcomes and results	Comments
Selvin, 2008 (AHRQ) Good continued	All-Cause Mortality Metformin vs. Placebo or Other Oral Agent Pooled OR (95%CI): 0.81 (0.60-1.08) Any Sulfonylurea Placebo or Other Oral Agent Pooled OR (95%CI): 0.90 (0.70-1.15) Rosiglitazone vs. Placebo or Other Oral Agent Pooled OR (95%CI): 1.21 (0.39-3.77) Rosiglitazone + metformin vs. metformin alone Pooled OR (95%CI): 2.52 (0.51-12.52) Pioglotizone vs. Any comparator Pooled OR (95%CI): 0.96 (0.78-1.18)	

Evidence Table 15. Key Question 1: Systematic reviews

Study Characteristics Author, Year Quality	Aim(s) of Review	Eligibility Criteria Characterstics of Included Studies	# studies # of Patients	Characteristics of included populations	Characteristics of Interventions
Pinelli, 2008 Good	To provide a relative compariosn of the efficacy and safey of addint TZDs or exenatide to oral agents for the management of type 2 DM by performing meta-analyses of relevant published studies.	Eligibility: Inclusion criteria: English; prospective, RCT; Placebo/Active comparator; ≥ 24 week duration; nonpregnant adults w/ type 2 DM; full-text, peer reviewe articles examining efficacy of TZDs or exenatide in combination with other oral agents; reported HbA1c outcomes. Exclusion criteria: assessed these agents as mnotherapy or adjunctive therapy to insulin-based regimens; open-label extension trials; interim analysis of Phase 3 clinical trials. Included studies: 5 TZD open-label trials 2 exenatide open-label trials Randomized; double blind (13) and triple-blind (2) trials	22 studies 9,325 patients	Mean age range: 53-61 Years; Mean baseline HbA1c range: 7.5-9.9	8 TZD + metformin, sulfonylurea, or combined metformin/sulfonylurea vs. placebo-control trials 3 exenatide + metformin, sulfonylurea, or combined metformin/sulfonylurea vs. placebo-control trials 9 TZD vs. other glucose-lowering agents and open-label subcutaneous insulin 2 exenatide vs. other glucose-lowering agents and open-label subcutaneous insulin

Evidence Table 15. Key Question 1: Systematic reviews

Study Characteristics Author, Year Quality	Main efficacy and effectivenes outcomes and results	Comments
Pinelli, 2008 Good	HbA1c: mean change from baseline (95%CI) TZD: -0.80% (-1.10, -0.50) Exenatide: -0.60% (-1.04, -0.16) HbA1c: Achieving target goal of <7%, OR (95%CI) TZD: 2.27 (1.22, 4.24) Exenatide: 2.90 (1.28, 6.55) Subgroup Analyses: HbA1c: weighted mean difference (WMD) from baseline (95%CI) TZD vs. Placebo: n=2649, 8 studies WMD: -1.14%(-1.30, -0.98) Exenatide vs. Placebo: n=966, 3 studies WMD: -0.97% (-1.11, -0.83) TZD vs. active controls: n=3938, 9 studies WMD: -0.38% (-0.75, -0.01)	

Evidence Table 15. Key Question 1: Systematic reviews

Study Characteristics Author, Year Quality	Main efficacy and effectivenes outcomes and results	Comments
Pinelli, 2008 Good continued	Exenatide vs. insulin: n=1036, 2 studies WMD: -0.08 (-0.23, 0.07) HbA1c: Achieving target goal of <7%, OR (95%CI) Exenatide vs. placebo: n=966, 3 studies OR: 5.72 (3.87, 8.46) TZD vs. placebo: n=1131, 4 studies OR: 3.72 (2.80, 4.93) Exenatide vs. Insulin: n=999, 2 studies OR: 1.15 (0.73, 1.80) TZD vs. active controls: n=2685, 5 studies OR: 1.40 (0.71, 2.75)	

Evidence Table 15. Key Question 1: Systematic reviews

Study Characteristics Author, Year Quality	Aim(s) of Review	Eligibility Criteria Characterstics of Included Studies	# studies # of Patients	Characteristics of included populations	Characteristics of Interventions
Monami, 2009 Fair	Offer a comprehensive and updated synthesis of all available clinical data on safety and efficacy of GLP-1 receptor agonists.	Eligibility: RCTs; Cross-over of parallel series design; patients w/ type 2 DM; Duration ≥ 12 weeks; Comparing GLP-1 receptor agonists w/ placebo or active drugs; English Included studies: 16 peer-reviewed publications; 5 unpublished trials; 6 open-label trials; duration of trial range (weeks): 12-52	21 studies 8,482 patients	Mean age range: 53-61 years; Mean baseline HbA1c range: 7.0-8.9, Mean baseline BMI range: 23.9-36.0	9 Liraglutide studies; 12 exenatide studies; 12 placebo-controlled; 6 active comparator studies; 3 two comparator arms vs. placebo and active drugs;
Richter, 2008 Good	To assess the effects of dipeptydyl peptidase-4 (DPP-4) inhibitors for type 2 DM	Eligibilty: RCTs; Adults w/ type 2 DM; tx for a minimum of 12 wks w/ DPP-4 inhibitors alone or in combination; outcomes measuring HbA1c, adverse events, health-related quality of life Included studies: Duration range: 12 -52 wks; Most trials lasted 24 wks	25; 11 sitagliptin trials 6,743 patients	Most pts were inadequately controlled, either on diet, exercise or both or on metformin, glimepiride with or without metformin or pioglitazone treatment. Sex ration ws rougly balanced between intervention vs. control. Pts mostly white, obese , approx 55 yrs; duration of diabetes 3-5 yrs.	6 Sitagliptin monotherapy vs. placebo; 2 Sitagliptin monotherapy vs. hypoglycaemic agent monotherapy; sitagliptin combination vs. other combination therapies

Evidence Table 15. Key Question 1: Systematic reviews

Study Characteristics Author, Year Quality	Main efficacy and effectivenes outcomes and results	Comments
Monami, 2009 Fair	HbA1c weighted mean difference (95% CI) at endpoint: Placebo-controlled trials: Weighted Mean Difference: -0.953 (-1.109, -0.796), p <0.001 Death: Investigational drug: 2 Comparator: 3 Major Cardiovascular Event: GLP-1 receptor agonists vs. control: MH-OR 0.99 (0.52, 1.91), p = 0.98 GLP-1 receptor agonists vs. placebo: MH-OR 0.46 (0.18, 1.20), p = 0.11	
Richter, 2008 Good	Change in HbA1c Sitagliptin (11 trials, n = 6910): Mean Difference [MD], (95%CI): -0.54 (-0.58, -0.50) Sitagliptin vs. placebo (6 trials, n = 1714): MD (95%CI): -0.77 (-0.85, -0.68) Sitagliptin vs. another agent (2 trials, n = 592): MD, (95%CI): 0.33 (0.18, 0.48) Sitagliptin combination vs. another combination (6 trials, n = 2890): MD, (95%CI): -0.40 (-0.47, -0.33) Sitagliptin vs. placebo (12 weeks) (3 trials, n = 605): MD, (95%CI): -0.79 (-0.90, -0.67) Sitagliptin vs. placebo (18 – 52 wks)(3 trials, n = 1109): MD, (95%CI): -0.75 (-0.86, -0.63)	

Evidence Table 15. Key Question 1: Systematic reviews

Study Characteristics Author, Year Quality	Aim(s) of Review	Eligibility Criteria Characterstics of Included Studies	# studies # of Patients	Characteristics of included populations	Characteristics of Interventions
Phung, 2010 Good	To determine the comparative efficacy, risk of weight gain, and hypoglycemia associated with noninsuling antideiabetic drugs in patients with T2DM not controlled by metformin alone	nclusion Criteria: Parallel-design RCTs; Compared noninsulin antidiabetic drugs with either placebo or another noninsulin antidiabetic drug in addition tometformin in all treatment groups; treated patients for ≥ 12 wks but ≤ 52 wks after randomization; only patients who showed inadequate response to stable metformin monotherapy; reported outcomes of HbA1c Exclusion Criteria: evaluated the addition of more than 1 drug to metformin; participants were not considered to have inadequate response to a stable metformin monotherapy, participants were taking background threapies other than metformin; evaluated insulin. 27 RCTs; mean trial duration [range] 32 [12-52] wks;	N = 27 N = 11, 198	53-62 yrs; 23% - 75% mean; baseline HbA1c range 6.4% - 9.3%	Compares classes of drugs: Sulfonylureas, glinides, TZDs, alpha-glucosidase inhibitors; dipeptidyl peptidase 4 inhibitors; GLP-1 Agonists All studies had to have a mean metformin dose of enrolled patienta of at least 1500 mg/d during the study.

Evidence Table 15. Key Question 1: Systematic reviews

Study Characteristics Author, Year Quality	Main efficacy and effectivenes outcomes and results	Comments
Phung, 2010 Good	Baseline HbA1c < 8% (n = 9) Relative Risk (95% CI): Sulfonylurea: -0.57 (-0.75, -0.39) Glinides: -0.44 (-0.85, -0.04) TZDs: -0.62 (-0.88, -0.39) AGIs: NR DPP-4 inhibitors: -0.51 (-0.69, -0.34) GLP-1 analogs: NR Baseline HbA1c ≥ 8% (n = 16) Relative Risk (95% CI): Sulfonylurea: -0.97 (-1.35, -0.62) Glinides: -0.65 (-1.10, -0.26) TZDs: -1.02 (-1.39, -0.69) AGIs: -0.65 (-1.07, -0.24) DPP-4 inhibitors: -0.89 (-1.11, -0.68) GLP-1 analogs: -0.99 (-1.36, -0.63) Study Duration, wk 12 -24 (n = 11) Sulfonylurea: -0.53 (-0.88, -0.20) Glinides: -0.65 (-1.15, -0.24) TZDs: -0.75 (-1.14, -0.24) AGIs: NR DPP-4 inhibitors: -0.76 (-1.02, -0.53) GLP-1 analogs: NR	

Evidence Table 15. Key Question 1: Systematic reviews

Study Characteristics Author, Year Quality	Main efficacy and effectivenes outcomes and results	Comments
Phung, 2010 cont'd Good	Study Duration, wk > 24 (n = 15) Sulfonylurea: -0.99 (-1.26, -0.78) Glinides: -0.86 (-1.36, -0.452) TZDs: -0.95 (-1.27, -0.73) AGIs: -0.63 (-0.98, -0.30) DPP-4 inhibitors: -0.90 (-1.13, -0.71) GLP-1 analogs: -0.98 (-1.27, -0.42) Comparison of noninsulin antidiabetic drugs with placebo, Traditional Meta-analysis: Change in Body Weight, N = # of trials, kg Weighted Mean Difference (95% CI): DPP-4 Inhibitors: N = 4; -0.09 (-0.47, 0.30) GLP-1 Analogs: N = 2; -1.76 (-2.90, -0.62) Comparison of noninsulin antidiabetic drugs with placebo, Mixed-treatment Meta-analysis: Change in Body Weight, kg Weighted Mean Difference (95% CI): DPP-4 Inhibitors: -0.14 (-0.94, 0.63) GLP-1 Analogs: -1.74(-3.11, -0.48)	

Evidence Table 16. Key Question 1: Quality assessment of systematic reviews

Study Characteristics Author, Year Quality	Is the review based on a focused question of interest? Yes, No, NR	Did the search strategy employ a comprehensive, systematic, literature search? Yes, No, NR	Are eligibility criteria for studies clearly described? Yes, No, NR	Did at least 2 people independently review studies? Yes, No, NR	Did authors use a standard method of critical appraisal before including studies? Yes, No, NR
Lago , 2007 Good	Yes	Yes	Yes	Yes	Yes
Diamond, 2007 Fair	Yes	No	No	No	NR
Mannucci, 2008 Fair	Yes	Yes	Yes	Yes	Yes
Monami, 2008 Poor	Yes	Yes	Yes	Yes	NR
Selvin, 2008 (AHRQ) Good	Yes	Yes	Yes	Yes	Yes
Monami, 2009 Fair	Yes	Yes	Yes	NR	Yes
Pinelli, 2008 Good	Yes	Yes	Yes	Yes	Yes
Richter, 2008 Good	Yes	Yes	Yes	Yes	Yes
Phung, 2010	Yes	Yes	Yes	Yes	Yes

Evidence Table 16. Key Question 1: Quality assessment of systematic reviews

Study Characteristics Author, Year Quality	Was publication bias assessed? Yes, No, NR	Was heterogeneity assessed and addressed? Yes, No, NR	Was the approach used to synthesize information adequate and appropriate? Yes, No	Quality Rating? Good, Fair, Poor	Was a meta-analysis done? Yes, No
Lago , 2007 Good	Yes	Yes	Yes	Good	Yes
Diamond, 2007 Fair	NR	Yes	Yes	Fair	Yes
Mannucci, 2008 Fair	Yes	No	Yes	Fair	Yes
Monami, 2008 Poor	NR	No	No	Fair	Yes
Selvin, 2008 (AHRQ) Good	NR	Yes	Yes	Good	Yes
Monami, 2009 Fair	Yes	Yes	Yes	Good	Yes
Pinelli, 2008 Good	Yes	Yes	Yes	Good	Yes
Richter, 2008 Good	Yes	Yes	Yes	Good	Yes
Phung, 2010	Yes	Yes	Yes	Good	Yes

Evidence Table 17. Key Question 2: Systematic reviews

Study Characteristics Author, Year Quality	Aim(s) of Review	Eligibility Criteria Characterstics of Included Studies	Number studies Number of Patients	Characteristics of included populations
Lago , 2007 Good	Systematic review and meta-analysis of pooled data from randomized trials of TZDs in subjects with prediabetes or type 2 diabetes to assess the risk of development of heart failure and death from cardiovascular causes in patients given TZDs	Eligibility: Randomized, double-blind, controlled trials of TZDs; Report of risk estimates, frequency data for congestive heart failure and cardiovascular death; trials with male human patients; written in English Excluded non-randomized clinical trials;No data for cardiovascular outcomes or death Included Studies: All RCTs published since 2005; Follow-up with pts btwn 12 - 48 mos (mean 29.7 mos); Trial population range: 200- 5269 participants, median 4351	7 trials; includes one trial with two control groups 20,191 Patients	Age: 59.2 Male %: 66.9% BMI: 31 (5.0) Baseline HbA1c: 7.72 (1.1) Baseline Medical History Hypertension: 50.4% Hyperlipidaemia: 47.9% Coronary artery disease: 18.6% CHF: 20% Chronic kidney disease or neuropathy: 2.4%

Evidence Table 17. Key Question 2: Systematic reviews

Study Characteristics Author, Year Quality	Characteristics of Interventions	Main harms outcomes and results
Lago , 2007 Good	Daily TZD dosage: Rosiglitazone vs. Placebo: 8mg Rosiglitazone vs. Metformin and Sulf: 4 - 8mg Rosiglitazone vs. Placebo: 4-8mg Rosiglitazone vs. Metformin/Rosiglitazone vs. Glibeclamide: 4-8mg Rosiglitazone vs. Placebo: 4-8mg Pioglitzaone vs. glimepiride: 15-45mg Pioglitazone vs. placebo: 15-45 mg	CHF Overall Risk, Risk Ratio (95% CI): TZDs: 1.72 (1.21, 2.41), p=0.002 Rosi: 2.18 (1.44, 3.32) Pioglitazone: 1.32 (1.04, 1.68) CHF events Rosi: 69 Pioglitazone: 145 Controls (Rosi trials): 35 Controls (Pioglitazone trials): 111 Comparison of risk of CHF and CV death: RR (95% CI) Rosi Trials: 2.41 (1.61, 3.61) Pioglitazone Trials: 1.32 (1.04, 1.68) Total: 1.74 (0.97, 3.14) Comparison of risk of CHF for Rosi and Pioglitazone: RR (95%CI) Rosi Trials: 1.01 (0.70, 1.45) Pioglitazone Trials: 1.01 (0.49, 2.06) Total: 1.01 (0.73, 1.40)

Evidence Table 17. Key Question 2: Systematic reviews

Study Characteristics Author, Year Quality	Aim(s) of Review	Eligibility Criteria Characterstics of Included Studies	Number studies Number of Patients	Characteristics of included populations
Mannucci, 2008 Fair	Meta-analysis of RCTs to assess whether pioglitzaone is also associated with increased cardiovascular risk	Eligibility: RCT; Pioglitazone vs. any other tx; Duration ≥ 4 weeks; Ongoing studies excluded. Included Studies: RCT; 24 placebo; 19 insulin secretagogues; 8 metformin; 8 PPAR agonists; 1 insulin; 4 α-Glucosidase inhibitors; 4 DPP-IV inhibitors	Studies: 94 - 68 on pts w/ type 2 diabetes; 26 on pts w/ different conditions Patients: 19, 803 type 2 diabetes pts (excluding PROACTIVE study) 25,041 type 2 diabetes pts (including PROACTIVE study)	Weighted mean age: 51.7 years; Mean diabetes duration: 6.6 yrs; mean HbA1c 8.1% (excluding PROACTIVE)
Monami, 2008 Poor	Identification of moderators of the effects of rsoiglitazone on the risk of MI an dsevere heart failure	Eligibility: RCTs; Efficacy of rosiglitazone on type 2 diabetes; Comparator = any other ttreatment; Duration ≥ 4 wks; Type 2 diabetic pts; MI or CHF outcomes; Exclusion of ongoing trials Included Studies: Duration range: 6-312 wks; Comparators: 52 Placebo; 8 Metformin; 15 Insulin secretagogues; 2 Pioglitazone; 3 Insulin; 12 None (?); 1 Multiple comparators	86 studies 30,003 Patients	Rosiglitazone: N = 16284 Comparators: N = 13719

Evidence Table 17. Key Question 2: Systematic reviews

Study Characteristics Author, Year Quality	Characteristics of Interventions	Main harms outcomes and results
Mannucci, 2008 Fair	Some combined therapy; Some monotherapy	Non-fatal CV Events: Type 2 Diabetes pts: (k=40) Pioglitazone (n=4259): 44 events Comparator (n=3989): 50 events RR 0.82 (0.55-1.23) CHF: PROACTIVE: Pioglitazone associated with increased risk for CHF Other Trials (k=40) Pioglitazone (n = 5380): 58 cases Comparator (n= 4791): 39 cases RR 1.32 (0.88-1.98)
Monami, 2008 Poor	NR	Serious CHF (No. of Cases) Rosi: 78 Comp: 47 MH-OR 1.59 (1.11-2.28) < 6 mos: MH-OR 1.18 (0.89-1.63) ≥ 6 mos: MH-OR 1.21 (0.92-1.61)

Evidence Table 17. Key Question 2: Systematic reviews

Study Characteristics Author, Year Quality	Aim(s) of Review	Eligibility Criteria Characterstics of Included Studies	Number studies Number of Patients	Characteristics of included populations
Pinelli, 2008 Good	To provide a relative compariosn of the efficacy and safey of addint TZDs or exenatide to oral agents for the management of type 2 DM by performing meta-analyses of relevant published studies.	Eligibility: Inclusion criteria: English; prospective, RCT; Placebo/Active comparator; ≥ 24 week duration; nonpregnant adults w/ type 2 DM; full-text, peer reviewe articles examining efficacy of TZDs or exenatide in combination with other oral agents; reported HbA1c outcomes. Exclusion criteria: assessed these agents as mnotherapy or adjunctive therapy to insulin-based regimens; open-label extension trials; interim analysis of Phase 3 clinical trials. Included studies: 5 TZD open-label trials 2 exenatide open-label trials Randomized; double blind (13) and triple-blind (2) trials	22 studies 9,325 patients	Mean age range: 53-61 Years; Mean baseline HbA1c range: 7.5-9.9

Evidence Table 17. Key Question 2: Systematic reviews

Study Characteristics Author, Year Quality	Characteristics of Interventions	Main harms outcomes and results
Pinelli, 2008 Good	8 TZD + metformin, sulfonylurea, or combined metformin/sulfonylurea vs. placebo-control trials 3 exenatide + metformin, sulfonylurea, or combined metformin/sulfonylurea vs. placebo-control trials 9 TZD vs. other glucose-lowering agents and open-label subcutaneous insulin 2 exenatide vs. other glucose-lowering agents and open-label subcutaneous insulin	Adverse Events: Severe Hypoglycemia: Exenatide: 1 study TZD: 4 studies Nonsevere hypoglycemic events, TZD vs. other tx arms: OR: 1.59 (0.76, 3.32) Exenatide vs. placebo: OR: 3.53 (0.92, 13.61) Body Weight TZD vs. comparator (n=6): WMD: 1.51 kg (-0.12, 3.15) Exenatide vs. comparator (n=5): WMD: -2.74 kg (-4.85, -0.64) Exenatide vs. placebo (n=3): WMD: -1.29 kg (-2.22, -0.36) Exenatide vs. insulin comparator (n=2): WMD: -4.79 kg (-6.06, -3.52) Nausea: Exenatide: OR: 9.02 (3.66, 22.23) Vomiting: Exenatide: OR: 4.56 (3.13, 6.65) Diarrhea: Exenatide: OR: 2.96 (2.05, 4.26)

Evidence Table 17. Key Question 2: Systematic reviews

Study Characteristics Author, Year Quality	Aim(s) of Review	Eligibility Criteria Characterstics of Included Studies	Number studies Number of Patients	Characteristics of included populations
Monami, 2009 Fair	Offer a comprehensive and updated synthesis of all available clinical data on safety and efficacy of GLP-1 receptor agonists.	Eligibility: RCTs; Cross-ver of parallel series design; pts w/ type 2 DM; Duration ≥ 12 weeks; Comparing GLP-1 receptor agonists w/ placebo or active drugs; English Included studies: 16 peer-reviewed publications; 5 unpublished trials; 6 open-label trials; duration of trial range (wks): 12-52	21 studies 8,482 patients	Mean age range: 53-61 years; Mean baseline HbA1c range: 7.0-8.9, Mean baseline BMI range: 23.9-36.0

Evidence Table 17. Key Question 2: Systematic reviews

Study Characteristics Author, Year Quality	Characteristics of Interventions	Main harms outcomes and results
Monami, 2009 Fair	9 Liraglutide studies; 12 exenatide studies; 12 placebo-controlled; 6 active comparator studies; 3 two comparator arms vs. placebo and active drugs;	Hypoglycaemia (n= 15 trials): Exenatide bid: 325 patients reported Comparator: 109 patients reported MH-OR 2.92 (1.49, 5.75), p = 0.002 Exenatide +Sulfonylurea: MH-OR 4.62 (1.89, 11.21), p = 0.001 Exenatide with or without sulfonylurea: MH-OR 1.37 (0.72, 2.63), p = 0.34 Exenatide vs. insulin: MH-OR 0.61 (0.33, 1.14), p = 0.125 Liraglutide: 78 patients reported Comparator: 109 patients reported Severe Hypoglycaemia : Exenatide vs. Insulin: MH-OR 0.74 (0.23, 2.39), p = 0.61 Nausea: GLP-1 receptor agonists (17 trials): No. of cases Interventional Drug (ID): 1354 Comparator (C): 230 MH-OR 3.88 (2.79, 5.42), p <0.001 Exenatide bid (10 trials): No. of cases ID: 818 C: 133 MH-OR 8.38 (4.27, 16.48), p <0.001 Liraglutide (6trials): No. of cases ID: 522 C: 69 MH-OR 3.48 (2.29, 5.28), p <0.001

Evidence Table 17. Key Question 2: Systematic reviews

Study Characteristics Author, Year Quality	Characteristics of Interventions	Main harms outcomes and results
Monami, 2009 Fair continued		Vomiting: GLP-1 receptor agonists (14 trials): No. of cases Interventional Drug (ID): 365 Comparator (C): 56 MH-OR 4.23 (2.67, 6.13), p <0.001 Exenatide bid (9 trials): No. of cases ID: 253 C: 42 MH-OR 4.54 (3.24, 6.38), p <0.001 Liraglutide (5 trials): No. of cases ID: 108 C: 11 MH-OR 4.26 (1.01, 18.07), p = 0.049 Diarrhea: GLP-1 receptor agonists (14 trials): No. of cases Interventional Drug (ID): 396 Comparator (C): 88 MH-OR 2.36 (1.67, 3.33), p <0.001 Exenatide bid (9 trials): No. of cases ID: 192 C: 49 MH-OR 2.56 (1.85, 3.54), p <0.001 Liraglutide (5 trials): No. of cases ID: 204 C: 35 MH-OR 2.36 (1.67, 3.33), p <0.001

Evidence Table 17. Key Question 2: Systematic reviews

Study Characteristics Author, Year Quality	Aim(s) of Review	Eligibility Criteria Characterstics of Included Studies	Number studies Number of Patients	Characteristics of included populations
Richter, 2008 Good	To assess the effects of dipeptydyl peptidase-4 (DPP-4) inhibitors for type 2 DM	Eligibilty: RCTs; Adults w/ type 2 DM; tx for a minimum of 12 wks w/ DPP-4 inhibitors alone or in combination; outcomes measuring HbA1c, adverse events, health-related quality of life Included studies: Duration range: 12 -52 wks; Most trials lasted 24 wks	25; 11 sitagliptin trials 6,743 patients	Most pts were inadequately controlled, either on diet, exercise or both or on metformin, glimepiride with or without metformin or pioglitazone treatment. Sex ration ws rougly balanced between intervention vs. control. Pts mostly white, obese , approx 55 yrs; duration of diabetes 3-5 yrs.

Evidence Table 17. Key Question 2: Systematic reviews

Study Characteristics Author, Year Quality	Characteristics of Interventions	Main harms outcomes and results
Richter, 2008 Good	6 Sitagliptin monotherapy vs. placebo; 2 Sitagliptin monotherapy vs. hypoglycaemic agent monotherapy; sitagliptin combination vs. other combination therapies	Adverse Events: 11 trials, n = 12416 RR, (95%CI) 1.15 (1.02, 1.31) Discontinuation due to AEs : 11 trials, n = 4414 RR, (95%CI) 1.05 (0.77, 1.43) Serious AEs : 11 trials, n = 4413 RR, (95%CI) 0.97 (0.75, 1.27) All-cause infections : 8 trials, n = 3589 RR, (95%CI) 1.29 (1.09, 1.52) Change in body weight: 4 trials, n = 1259 Mean Difference [MD] 0.66 (0.37, 0.94) Sitagliptin vs. placebo: 3 trials, n = 1109 MD: 0.69 (0.32, 1.06) Sitagliptin vs. another agent: 1 trials, n = 150 MD: 0.6 (0.13, 1.07)

Evidence Table 17. Key Question 2: Systematic reviews

Study Characteristics Author, Year Quality	Aim(s) of Review	Eligibility Criteria Characterstics of Included Studies	Number studies Number of Patients	Characteristics of included populations
Nagajothi, 2008 Fair	Meta-analysis of RCTs comparing pioglitazone with either placebo or other oral hypoglycemic agents	Eligibility: Randomized, drug-controlled or placebo-controlled trials evaluating pioglitazone; Reports MI as primary, secondary, or adverse outcome; Published data; English Included Studies: Radomized double-blinded controlled trial; Comparators: 2 Placebo; 1 metformin or gliclazide; 1 glyburide 1 glimepiride; Duration range: 6 months - 34.5 months	5 Studies 9,755 Patients	NR

Evidence Table 17. Key Question 2: Systematic reviews

Study Characteristics Author, Year Quality	Characteristics of Interventions	Main harms outcomes and results
Nagajothi, 2008 Fair	NR	MI (no. of events/ total no. of pts) Pioglitazone: 143 /4969 Control: 168/4996 RR (95%CI): 0.86 (0.69-1.07), p = 0.17 Stroke Pioglitazone: 98/4692 Control: 126/4717 RR (95% CI): 0.79 (0.61-1.02), p = 0.07 Revascularization Pioglitazone: 200/2861 Control: 264/2889 RR(95% CI): 0.40 (0.13-1.23), p = 0.11 Mortality Pioglitazone: 185/4969 Control: 198/4996 RR (95%CI):0.94 (0.78-1.15), p =0.56 CV Mortality: Pioglitazone: 130/4969 Control: 143/4996 RR (95%CI): 0.92 (0.73-1.16), p = 0.47

Evidence Table 17. Key Question 2: Systematic reviews

Study Characteristics Author, Year Quality	Aim(s) of Review	Eligibility Criteria Characterstics of Included Studies	Number studies Number of Patients	Characteristics of included populations
Phung, 2010 Good	To determine the comparative efficacy, risk of weight gain, and hypoglycemia associated with noninsuling antideiabetic drugs in patients with T2DM not controlled by metformin alone	nclusion Criteria: Parallel-design RCTs; Compared noninsulin antidiabetic drugs with either placebo or another noninsulin antidiabetic drug in addition tometformin in all treatment groups; treated patients for ≥ 12 wks but ≤ 52 wks after randomization; only patients who showed inadequate response to stable metformin monotherapy; reported outcomes of HbA1c Exclusion Criteria: evaluated the addition of more than 1 drug to metformin; participants were not considered to have inadequate response to a stable metformin monotherapy, participants were taking background threapies other than metformin; evaluated insulin. 27 RCTs; mean trial duration [range] 32 [12-52] wks;	N = 27 N = 11, 198	53-62 yrs; 23% - 75% mean; baseline HbA1c range 6.4% - 9.3%

Evidence Table 17. Key Question 2: Systematic reviews

Study Characteristics Author, Year Quality	Characteristics of Interventions	Main harms outcomes and results
Phung, 2010 Good	Compares classes of drugs: Sulfonylureas, glinides, TZDs, alpha-glucosidase inhibitors; dipeptidyl peptidase 4 inhibitors; GLP-1 Agonists All studies had to have a mean metformin dose of enrolled patienta of at least 1500 mg/d during the study.	Comparison of noninsulin antidiabetic drugs with placebo, Traditional Meta-analysis: Change in Body Weight, Kg, N = # of Trials; Weighted Mean Difference (95% CI): All drugs: N = 12; 0.14 (-1.37, 1.65) Sulfonylurea: N = 2; 1.99 (0.86, 3.12) Glinides: N = 2; 0.91 (0.35, 1.46) TZDs: N = 1; 2.30 (1.70, 2.90) AGIs: N = 1; -1.80 (-2.83, -0.77) Comparison of noninsulin antidiabetic drugs with placebo, Mixed-treatment Meta-analysis: Change in Body Weight, Kg, Weighted Mean Difference (95% CI): Sulfonylurea: +2.06 (1.15, 2.96) Glinides: +1.77 (0.46, 3.28) TZDs: +2.08 (0.98, 3.17) AGIs: -1.80 (-3.79, 0.21)

Evidence Table 17. Key Question 2: Systematic reviews

Study Characteristics Author, Year Quality	Characteristics of Interventions	Main harms outcomes and results
Phung, 2010 Good cont'd		Comparison of noninsulin antidiabetic drugs with placebo, Traditional Meta-analysis: Overall Hypoglycemia, N = # of Trials; Relative Risk (95% CI): All drugs: N = 19; 1.43 (0.89, 2.30) Sulfonylurea: N = 3; 2.63 (0.76, 9.13) Glinides: N = 2; 7.92 (1.45, 43.21) TZDs: N = 2; 2.04 (0.50, 8.23) AGIs: N = 2; 0.60 (0.08, 4.55) DPP-4 inhibitors: N = 8; 0.67 (0.30, 1.50) GLP-1 analogs: N = 2; 0.94 (0.42, 2.12) Comparison of noninsulin antidiabetic drugs with placebo, Mixed treatmentMeta-analysis: Overall Hypoglycemia, Relative Risk (95% CI): Sulfonylurea: 4.57 (2.11, 11.45) Glinides: 7.50 (2.12, 41.52) TZDs: 0.56 (0.19, 1.69) AGIs: 0.42 (0.01, 9.00) DPP-4 inhibitors: 0.63 (0.26, 1.71) GLP-1 analogs: 0.89 (0.22, 3.96)

Evidence Table 17. Key Question 2: Systematic reviews

Study Characteristics Author, Year Quality	Aim(s) of Review	Eligibility Criteria Characterstics of Included Studies	Number studies Number of Patients	Characteristics of included populations
Loke, 2009 Good	To determine systematically the reisk of fractures associated with thiazolidinedione therapy and to evaluate the effect of the therapy on bone density	RCT; Controlled observational studies; Comparsion of risk of fracture among pts with type 2 diabetes taking TZDs and those not taking TZDs; parallel-design trial; ≥ year duration; pts had impaired glucose tolerance or type 2 DM; use of either placebo or oral therapy as active comparator; Fracture outcomes reported All trials were double blinded, Included particiapnts with impaired glucose and type 2 diabetes; duration range 1 - 4 years. Data on fractures by sex available for 5 trials.	N = 10 N = 13, 715	Pts in tx groups similar to control pts re: ethnic background, disease duration, HbA1c, BMI

Evidence Table 17. Key Question 2: Systematic reviews

Study Characteristics Author, Year Quality	Characteristics of Interventions	Main harms outcomes and results
Loke, 2009 Good	TZD or control	Fractures Overall, No of fractures: TZD: 185/6122 Control: 186/793 OR (95% CI): 1.45 (1.18-1.79), p < 0.001 Fractures in Women, No. of Fractures: TZD: 111/1903 Control: 76/2497 OR (95% CI): 2.23 (1.6-3.01), p<0.001 Fractures in men, No. of fractures: TZD: 64/3064 Control: 95/3937 OR: 1.00 (0.73-1.39), p = 0.98 Difference between male and female subgroups: χ^2 12.01, p <0.001

Evidence Table 18. Key Question 2: Quality assessment of systematic reviews

Study Characteristics Author, Year Quality	Is the review based on a focused question of interest? Yes, No, NR	Did the search strategy employ a comprehensive, systematic, literature search? Yes, No, NR	Are eligibility criteria for studies clearly described? Yes, No, NR	Did at least 2 people independently review studies? Yes, No, NR	Did authors use a standard method of critical appraisal before including studies? Yes, No, NR
Lago , 2007 Good	Yes	Yes	Yes	Yes	Yes
Mannucci, 2008 Fair	Yes	Yes	Yes	Yes	Yes
Monami, 2008 Poor	Yes	Yes	Yes	Yes	NR
Monami, 2009 Good	Yes	Yes	Yes	NR	Yes
Pinelli, 2008 Good	Yes	Yes	Yes	Yes	Yes
Richter, 2008 Good	Yes	Yes	Yes	Yes	Yes
Loke, 2009 Good	Yes	Yes	Yes	Yes	Yes
Nagajothi, 2008 Fair	Yes	Yes	Yes	Yes	Yes
Phung, 2010 Good	Yes	Yes	Yes	Yes	Yes

Evidence Table 18. Key Question 2: Quality assessment of systematic reviews

Study Characteristics Author, Year Quality	Was publication bias assessed? Yes, No, NR	Was heterogeneity assessed and addressed? Yes, No, NR	Was the approach used to synthesize information adequate and appropriate? Yes, No	Quality Rating? Good, Fair, Poor	Was a meta-analysis done? Yes, No
Lago , 2007 Good	Yes	Yes	Yes	Good	Yes
Mannucci, 2008 Fair	Yes	No	Yes	Fair	Yes
Monami, 2008 Poor	NR	No	No	Fair	Yes
Monami, 2009 Good	Yes	Yes	Yes	Good	Yes
Pinelli, 2008 Good	Yes	Yes	Yes	Good	Yes
Richter, 2008 Good	Yes	Yes	Yes	Good	Yes
Loke, 2009 Good	No	Yes	Yes	Good	Yes
Nagajothi, 2008 Fair	No	Yes	Yes	Fair	Yes
Phung, 2010 Good	Yes	Yes	Yes	Good	Yes

Evidence Table 19. Key Question 1: Observational studies

Study Characteristics Author, year Country Funding Design Duration	Aim(s) of study	Setting	Inclusion and Exclusion Criteria	Overall Sample Size Comparisons Group Sizes	Baseline Population Characteristics: Age (Mean), Race/Ethnicity (%), Sex (% Female)	Outcomes Microvascular disease Macrovascular disease Lower Extremity Ulcers All-cause mortality Quality of Life Hospitalization Medical Visits
Balkrishnan, 2007 US GlaxoSmithKline Cohort 30 months of follow up	Compare healthcare utilization	Retrospective analysis of North Carolina Medicaid	Inclusion: 18 yrs or more with T2DM and received treatment of interest; Patients that had data one year before and 30 months after start of treatment for T2DM Exclusion: Combination therapy, age > 65 yrs; Medicare beneficiaries; those getting both Medicare and Medicaid	N=1705 G1: Rosiglitizone N=660 G2: Pioglitizone N=1045	Mean age G1: 49.0 G2: 49.1 Race/Ethnicity Black G1: 47 G2: 51 White G1: 34 G2: 36 Other G1: 19 G2: 13 % Female G1: 75 G2: 74	**Hospitalization:** Likelihood of hospitalization after Rx start (unadjusted) G1: 55% G2: 57%

Evidence Table 20. Key Question 1: Quality assessment of observational studies

Study Characteristics Author, year Country Funding Design Duration	Were comparison groups selected from the same source population? Yes, No, NR	Were subjects recruited over the same time period? Yes, No, NR	Were measurements equal, valid, and reliable? Yes, No, Mixed	Were outcome assessors masked? Yes, No, NR	Were outcomes presepecified and defined? Yes, No, NR	Was time of follow-up equal for all groups? Yes, No, NR
Balkrishnan, 2007 US GlaxoSmithKline Cohort 30 months of follow up	Yes	Yes	Yes	NR	Yes	Yes

Evidence Table 20. Key Question 1: Quality assessment of observational studies

Study Characteristics Author, year Country Funding Design Duration	Overall attrition high? (≥20%) Yes, No, NR	Was differential attrition high? (≥15%) Yes, No, NR	Did the study design and/or statistical analyses account for confounding? Yes, No, NR	Was the length of follow-up adequate? Yes, No, NR	Overall Quality Rating Good, Fair, Poor
Balkrishnan, 2007 US GlaxoSmithKline Cohort 30 months of follow up			Yes	Yes	Fair

Evidence Table 21. Key Question 2: Observational studies

Study Characteristics Author, year Country Funding Design Duration Quality	Aim(s) of study	Setting	Inclusion and Exclusion Criteria	Overall Sample Size Comparisons Group Sizes	Baseline Population Characteristics: Age (Mean), Race/Ethnicity (%), Sex (% Female)
Fabunmi, 2009 US Amylin Inc, Eli Lilly Cohort 1 year Fair	Exenatide vs. insulin glargine hypoglycemia events and costs	Administrative claims database	Inclusion: Diagnosis for diabetes mellitus between May 1, 2004 and June 30, 2007 were initially identified from a review of pharmacy and medical claims; initial pharmacy claim (the index date) for exenatide or insulin glargine between May 1, 2005 and June 30, 2007 were identified; 18 years of age, have a pre-index diagnosis of type 2 diabetes and a minimum 6 months pre- and 12 months post-index health plan eligibility. Exclusion: Insulin in the exenatide group or exenatide in the insulin group	N=6,300 G1: Exenatide N= 3262 G2: Insulin Glargine N = 3038 Background therapy with oral antidiabetic drugs: Metformin (MET) % (n) G1: 77.2 (2519) G2: 68.6 (2085) P < 0.001 Sulfonylureas (SFU) % (n) G1: 47.0 (1534) G2: 64.6 (1961) P < 0.001 Thiazolidinediones (TZD) % (n) G1: 49.7 (1622) G2: 48.5 (1473) P = 0.326 MET+SFU % (n) G1: 15.2 (496) G2: 20.5 (9623) P <0.001 MET+TZD % (n) G1: 15.2 (497) G2: 8.3 (252) P < 0.001 SFU+TZD % (n) G1: 4.2 (136) G2: 6.0 (182) P = 0.001 MET+TZD+SFU % (n) G1: 21.5 (702) G2: 25.6 (779) P = 0.001	Mean age G1: 53 G2: 56 Race / Ethnicity NR % Female G1: 54 G2: 41

Evidence Table 21. Key Question 2: Observational studies

Study Characteristics Author, year Country Funding Design Duration Quality	Adverse events Overall (N) Specific Adverse Events (N)	Congestive Heart Failure (N)	Adverse Changes in Lipid Concentrations	Weight Gain	Fractures (N)
Fabunmi, 2009 US Amylin Inc, Eli Lilly Cohort 1 year Fair	Overall - NR Patients w/ hypoglycemic events G1: 138 (4.2%) G2: 212 (7.0%) 1 yr adjusted annualized hypoglycemia event rate G1: 0.065 (0.011) G2: 0.117 (0.007) G1 vs. G2 P < 0.001	NR	NR	NR	NR

Evidence Table 21. Key Question 2: Observational studies

Study Characteristics Author, year Country Funding Design Duration Quality	Aim(s) of study	Setting	Inclusion and Exclusion Criteria	Overall Sample Size Comparisons Group Sizes	Baseline Population Characteristics: Age (Mean), Race/Ethnicity (%), Sex (% Female)
Grossman, 2009 Canada Eli Lilly 2 years Poor	Long term tolerability of pioglitazone in T2DM	Multicenter (176 sites)	Inclusion: diagnosis of type 2 DM Exclusion: TZD or PPAR oral antidiabetes medication other than pioglitazone	N=1871 G1: Pioglitazone N=1527 G2: Comparator N=291	Mean age 59.9 White 78.5% East/Southeast Asian 13.0% Native American 4.1% Black 1,8% Western Asian 1.1% Hispanic 0.4% Other 1.0% Female 41.6%
Habib, 2009 US Private and Government funding Cohort ≥ 6 months of follow up Good	To investigate the association of the TZDs on the risk of cardiovascular outcomes and all-cause mortality, using time-updated propensity score adjusted analysis	Vertically integrated HMO system (hospitals and clinics)	Inclusion: members of the HMO; receive care from a specific medical group; prescription coverage; age > 18; at least one clinical encounter with a coded diagnosis of diabetes between 1/1/2000 and 12/1/2006; at least one prescription of an oral diabetic medication during this time period; 12 months of enrollment in HMO prior to index date; 6 months of follow-up after index date Exclusion: NR	N= 19,171 G1: All patients receiving any medication N=19,171 G2: patients receiving rosiglitazone alone N=1,056 G3: patients receiving pioglitazone alone N=3,217 G4: patients receiving both rosiglitazone and pioglitazone N=307	G1: Age 58.3; White 52.0%, Black 41.7%, Other 6.3%; Female 50.5% G2: Age 59.0; White 45.2%, Black 48.2%, Other 6.6%; Female 51.6% G3: Age 57.0; White 52.5%, Black 41.6%, Other 5.9%; Female 48.2% G4: Age 57.3; White 57.3%; Black 37.5%, Other 5.2%; Female 56.7%

Evidence Table 21. Key Question 2: Observational studies

Study Characteristics Author, year Country Funding Design Duration Quality	Adverse events Overall (N) Specific Adverse Events (N)	Congestive Heart Failure (N)	Adverse Changes in Lipid Concentrations	Weight Gain	Fractures (N)
Grossman, 2009 Canada Eli Lilly 2 years Poor	NR	Heart failure G1: 37 (2.4) G2: 4 (1.4)	NR	Weight gain G1: 757 (49.6) G2: 107 (36.8)	NR
Habib, 2009 US Private and Government funding Cohort ≥ 6 months of follow up Good	NR	CHF hospitalization: G1: N=2,725 other N's not reported Any TZD use: hazard ratio: 1.25 (1.08-1.43) adjusted hazard ratio: 1.33 (1.15-1.54) adjusted hazard ratio with propensity adjustment: 1.24 (1.07-1.44) G2: hazard ratio: 1.66 (1.26-2.19) adjusted hazard ratio: 1.73 (1.31-2.29) adjusted hazard ratio with propensity adjustment: 1.65 (1.25-2.19)	NR	NR	NR

Evidence Table 21. Key Question 2: Observational studies

Study Characteristics Author, year Country Funding Design Duration Quality	Adverse events Overall (N) Specific Adverse Events (N)	Congestive Heart Failure (N)	Adverse Changes in Lipid Concentrations	Weight Gain	Fractures (N)
Habib, 2009 US Private and Government funding Cohort > 6 months of follow up Good continued		CHF hospitalization: G3: hazard ratio: 1.12 (0.9501.34) adjusted hazard ratio: 1.25 (1.05-1.50) adjusted hazard ratio with propensity adjustment: 1.14 (0.96-1.37) p<0.013, comparing hazards for G2 vs. G3 (as they compared to others)			

Evidence Table 21. Key Question 2: Observational studies

Study Characteristics Author, year Country Funding Design Duration Quality	Aim(s) of study	Setting	Inclusion and Exclusion Criteria	Overall Sample Size Comparisons Group Sizes	Baseline Population Characteristics: Age (Mean), Race/Ethnicity (%), Sex (% Female)
Shaya, 2009 US Funding NR Cohort 5 years Poor	To investigate whether there was a difference in the risk of acute MI and hemorrhagic and non-hemorrhagic stroke between TZDs and other oral antidiabetic agents.	Maryland Medicaid prescription database	Inclusion: patients with type-2 diabetes first prescribed a TZD or another OAD during the study period; both medical and pharmacy claims during the study period Exclusion: patients who had submitted their first TZD or OAD claim during the first three months of the study; those treated with insulin alone during the entire study period; patients dually eligible for both Medicaid and Medicare	N= 14,623 G1 (any anti-diabetic agent) N=8,911 G2 (TZD) N=5,712	G1: Mean Age NR White 31%, Black 60.8%, other 7.5% Female 67.5% G2: Mean Age NR White 37%, Black 54%, other 9%

Evidence Table 21. Key Question 2: Observational studies

Study Characteristics Author, year Country Funding Design Duration Quality	Adverse events Overall (N) Specific Adverse Events (N)	Congestive Heart Failure (N)	Adverse Changes in Lipid Concentrations	Weight Gain	Fractures (N)
Shaya, 2009 US Funding NR Cohort 5 years Poor	Cardiovascular Event (stroke or MI): # events not reported TZD use: OR 1.009 (CI 0.909-1.121) Pioglitazone use: OR, 1.021 (0.902-1.179) Rosiglitazone use: OR, 1.124 (1.010-1.250)	NR	NR	NR	NR

Evidence Table 21. Key Question 2: Observational studies

Study Characteristics Author, year Country Funding Design Duration Quality	Aim(s) of study	Setting	Inclusion and Exclusion Criteria	Overall Sample Size Comparisons Group Sizes	Baseline Population Characteristics: Age (Mean), Race/Ethnicity (%), Sex (% Female)
Asche, 2008 US Novartis Cohort 395 days Fair	To evaluate and compare the risk of adverse events associated with the use of metformin, sulfonylureas and thiazolidinediones among geriatric patients in a usual care setting	Primary care and specialty clinics. A variety of practice types including solo practitioner, community practitioners, community clinics, academic medical centers and large integrated delivery networks.	Inclusion: Type 2 diabetes, age >= 65 years, oral antihyperglycemic drug naïve at the beginning of the study, then treated with metformin, sulfonylurea, or thiazolidinedione Exclusion: Patients were required to have continued diabetes care, measured by having at least two HbA1c levels recorded 90 days prior to or 30 days post-index date. Patients receiving combination oral antihyperglycemic therapy or combination with injectable incretin mimetic. Prior or concurrent insulin use was allowed.	N=5,438 G1: Sulfonylurea N = 2223 G2: Metformin N = 2326 G3: Thiazolidinedione N = 889	Overall: Age, 73.2; Race/Ethnicity NR; Female 56.1% Age: G1: 74.3 G2: 72.2 G3: 73.1 p <0.001; t-test relative to G2 Race/Ethnicity: NR Sex (% Female): G1: 54.9 G2: 58.0 G3: 54.1 p = 0.046

Evidence Table 21. Key Question 2: Observational studies

Study Characteristics Author, year Country Funding Design Duration Quality	Adverse events Overall (N) Specific Adverse Events (N)	Congestive Heart Failure (N)	Adverse Changes in Lipid Concentrations	Weight Gain	Fractures (N)
Asche, 2008 US Novartis Cohort 395 days Fair	Overall: N = 680 G1: 13.9% G2: 8.3% G3: 19.8% p < 0.001, G2 vs. G1 and G3 Hypoglycemia G1: N = 58 (2.6%) G2: NR G3: N = 20 (2.2%) Liver function test abnormalities G1: NR G2: NR G3: 4 (0.4%) Diarrhea, N: G1: NR G2: 35 G3: NR Nausea/vomiting, N: G1: NR G2: 30 G3: NR	G1: NR G2: NR G3: 19 (2.1%)	NR	Weight gain >= 4.5kg G1: 196 (8.8%) G2: NR G3: 120 (13.5%)	NR

Evidence Table 21. Key Question 2: Observational studies

Study Characteristics Author, year Country Funding Design Duration Quality	Adverse events Overall (N) Specific Adverse Events (N)	Congestive Heart Failure (N)	Adverse Changes in Lipid Concentrations	Weight Gain	Fractures (N)
Asche, 2008 continued	Abdominal pain: G1: NR G2: 82 G3: NR Dyspepsia: G1: NR G2: 63 G3: NR Dizziness G1: 52 (2.3%) G2: NR G3: NR Headache G1: 16 (0.7%) G2: NR G3: NR Lactic acidosis G1: NR G2: 6 (0.3%) G3: NR Edema G1: NR G2: NR G3: 39 (4.4%)				

Evidence Table 21. Key Question 2: Observational studies

Study Characteristics Author, year Country Funding Design Duration Quality	Aim(s) of study	Setting	Inclusion and Exclusion Criteria	Overall Sample Size Comparisons Group Sizes	Baseline Population Characteristics: Age (Mean), Race/Ethnicity (%), Sex (% Female)
Vlckova, 2009 England Funding source NR Cohort 9 months Poor	to quantify the incidence of hypoglycemic events and to describe the pattern of these incident events over time, in the incept cohorts of diabetic patients who were prescribed rosiglitazone, pioglitazone, nateglinide, or repaglinide in general practice in England	Prescription-event monitoring studies; General practitioners	Inclusion: patients with prescriptions dispensed for 1 of the 4 drugs identified from national health service prescriptions issued by GP's Exclusion: Patients whose first prescription was > 2 mos prior to launch date of the study drugs	N Identified: 37478 N included in analysis: 37417 Number identified: G1: Rosiglitazone N=14418 G2: Pioglitazone N=12772 G3: Nateglinide N=4557 G4: Repaglinide N=5731 Number included in analysis: G1: Rosiglitazone N=14373 G2: Pioglitazone N=12768 G3: Nateglinide N=4549 G4: Repaglinide N= 5727	G1: Age 61.6 SD 12.1 Female 47.6% G2: Age 60.9 SD 12.6 Female 45.7% G3: Age 59.4 SD 12.4 Female 45.9% G4: Age 59.1 SD 12.4 Female 49.7% Race NR

Evidence Table 21. Key Question 2: Observational studies

Study Characteristics Author, year Country Funding Design Duration Quality	Adverse events Overall (N) Specific Adverse Events (N)	Congestive Heart Failure (N)	Adverse Changes in Lipid Concentrations	Weight Gain	Fractures (N)
Vlckova, 2009 England Funding source NR Cohort 9 months Poor	No. of pts who stopped tx overall: G1: 4555 G2: 3690 G3: 1631 G4: 1772 Overall hypoglycemic event, N = 276 Incidence Rate G1: 9.94 (8.03, 12.03); G2: 9.64 (7.70, 12.04); G3: 15.71 (11.64, 21.17); G4: 20.32 (16.10, 25.66) No. of pts who stopped tx due to hypoglycemia: G1: 41; G2: 25; G3: 27; G4: 45	NR	NR	NR	NR

Evidence Table 21. Key Question 2: Observational studies

Study Characteristics Author, year Country Funding Design Duration Quality	Aim(s) of study	Setting	Inclusion and Exclusion Criteria	Overall Sample Size Comparisons Group Sizes	Baseline Population Characteristics: Age (Mean), Race/Ethnicity (%), Sex (% Female)
Miyazaki, 2008 US Funding NR Cohort 3 months Poor	To identify clinical, laboratory and metabolic parameters in rosiglitazone-and pioglitazone-treated T2D patients who could explain the difference in atherosclerotic cardiovascular disease outcomes with these two TZDs	Clinical research center	Inclusion: previously participated in metabolic studies performed by authors; age 30-70; BMI < 37; stable body weight for 3 months; fasting plasma glucose = 126-260mg/dl Exclusion: previously treated with insulin, metformin or another TZD; evidence of cardiac, hepatic, renal or other chronic diseases, heavy exercise, medications (other than sulfonylureas) that affect glucose metabolism	N=56 G1: rosiglitazone 8mg/day N=35 G2: pioglitazone 45 mg/day N=21	G1: Age: 55; White 28.6%, Black 2.9%, Mexican American 68.6%; Female 48.6% G2: Age: 52; White 38.1%, Black 9.5%, Mexican American 52.4%; Female 19.0%

Evidence Table 21. Key Question 2: Observational studies

Study Characteristics Author, year Country Funding Design Duration Quality	Adverse events Overall (N) Specific Adverse Events (N)	Congestive Heart Failure (N)	Adverse Changes in Lipid Concentrations	Weight Gain	Fractures (N)
Miyazaki, 2008 US Funding NR Cohort 3 months Poor	NR	NR	mean change in total cholesterol at 3 months NR mean change in LDL: G1: +15mg/dl (SD 5) G2: +1 mg/dl (SD 4) p=0.06, G1 vs. G2 mean change in HDL: G1: +4 mg/dl (SD 1) G2: +2 mg/dl (SD 1) NS, G1 vs. G2 mean change in TGs: G1: -8mg/dl (SD 8) G2: -47 mg/dl (SD 7) p<0.01, G1 vs. G2	NR	NR

Evidence Table 21. Key Question 2: Observational studies

Study Characteristics Author, year Country Funding Design Duration Quality	Aim(s) of study	Setting	Inclusion and Exclusion Criteria	Overall Sample Size Comparisons Group Sizes	Baseline Population Characteristics: Age (Mean), Race/Ethnicity (%), Sex (% Female)
Lewis, 2008 US NIH, Takeda, GlaxoSmithKline, Eli Lilly Nested Case Control ≥ 1year of exposure Fair	To examine the association between PPAR-gamma-targeted therapies and the risk of colonic neoplasia in patients with diabetes	Kaiser Permanente of Northern California	Inclusion: source population criteria: part of Kaiser Permanente system; completed a survey from 1994-1996 and be identified as having T2D. Study 1 (G1 and G2): undergone colonoscopy between 1999-2005, 50 years old at time of index colonoscopy. Cases were patients with one or more adenomatous lesions at the index colonoscopy. Controls were those without lesions.	Study 1 (G1/G2): 4,248 Study 2 (G3/G4): 9,813 Study 3 (G5/G6): 1,825 Study 1: G1: any adenoma on colonoscopy N=1,296 G2: no adenoma N=2,952 Study 2: G3: distal adenoma on sigmoidoscopy N=951 G4: no distal adenoma Study 3: G5: distal adenoma on second lower endoscopy N=159 G6: no distal adenoma N=1,666	G1: Age: 71; White 60%, Black 14%, Hispanic 12%, Asian 10%, Other 2%; Female 41% G2: Age: 71; White 59%, Black 12%, Hispanic 12%, Asian 11%, Other 3%; Female 49% G3: Age: 67; White 57%, Black 12%, Hispanic 12%, Asian 14%, Other 2%; Female 37% G4: Age: 66; White 52%, Black 16%, Hispanic 13%, Asian 14%, Other 3%; Female 46% G5: Age: 71; White 62%, Black 11%, Hispanic 13%, Asian 10%, Other 1%; Female 46% G6: Age: 71; White 55%, Black 16%, Hispanic 13%, Asian 12%, Other 2%; Female 47%

Evidence Table 21. Key Question 2: Observational studies

Study Characteristics Author, year Country Funding Design Duration Quality	Aim(s) of study	Setting	Inclusion and Exclusion Criteria	Overall Sample Size Comparisons Group Sizes	Baseline Population Characteristics: Age (Mean), Race/Ethnicity (%), Sex (% Female)
Lewis, 2008 continued			Inclusion: Study 2 (G3 and G4): undergone sigmoidoscopy between 1999-2005, 50 years old at the time of index colonoscopy. Cases were patients with one or more adenomatous lesions in the distal colon on either sigmoidoscopy or follow-up colonoscopy.		

Evidence Table 21. Key Question 2: Observational studies

Study Characteristics Author, year Country Funding Design Duration Quality	Aim(s) of study	Setting	Inclusion and Exclusion Criteria	Overall Sample Size Comparisons Group Sizes	Baseline Population Characteristics: Age (Mean), Race/Ethnicity (%), Sex (% Female)
Lewis, 2008 continued			Inclusion: Controls were those without lesions. Study 3 (G5 and G6): undergone two lower endoscopies between 1999-2005 with the second being at least a year after the first. The second was considered the index colonoscopy. Cases were those with adenomatous lesions at the second lower endoscopy. Controls were those without lesions. Exclusion: History of inflammatory bowel disease; familial adenomatous polyposis syndrome; hereditary non-polyposis colon cancer syndrome		

Evidence Table 21. Key Question 2: Observational studies

Study Characteristics Author, year Country Funding Design Duration Quality	Adverse events Overall (N) Specific Adverse Events (N)	Congestive Heart Failure (N)	Adverse Changes in Lipid Concentrations	Weight Gain	Fractures (N)
Lewis, 2008 US NIH, Takeda, GlaxoSmithKline, Eli Lilly Nested Case Control ≥ 1year of exposure Fair	Study 1: G1: 104, 8% of cases used TZDs G2: 318, 11% of controls used TZDs OR (95% CI) of any adenoma on first colonoscopy, TZDs vs. no TZDs unadjusted OR: 0.72 (0.57-0.91 adjusted OR: 0.73 (0.57-0.92)	NR	NR	NR	NR

Evidence Table 21. Key Question 2: Observational studies

Study Characteristics Author, year Country Funding Design Duration Quality	Adverse events Overall (N) Specific Adverse Events (N)	Congestive Heart Failure (N)	Adverse Changes in Lipid Concentrations	Weight Gain	Fractures (N)
Lewis, 2008 continued	Study 2: G3: 60, 6% of cases used TZDs G4: 656, 7% of controls used TZDs OR (95% CI) of any adenoma in distal colon on first sigmoidoscopy, TZDs vs. no TZDs unadjusted OR: NR adjusted OR: 0.86 (0.65-1.14)				

Evidence Table 21. Key Question 2: Observational studies

Study Characteristics Author, year Country Funding Design Duration Quality	Adverse events Overall (N) Specific Adverse Events (N)	Congestive Heart Failure (N)	Adverse Changes in Lipid Concentrations	Weight Gain	Fractures (N)
Lewis, 2008 continued	Study 3: G5: 11% of cases used TZDs G6: 14% of controls used TZDs OR (95% CI) of new/missed adenoma in distal colon on second lower endoscopy, TZDs vs. no TZDs unadjusted OR: NR adjusted OR: 0.75 (0.44-1.28)				

Evidence Table 22. Key Question 2: Quality assessment of observational studies

Study Characteristics Author, year Country Funding Design Duration Quality	Were comparison groups selected from the same source population? Yes, No, NR	Were subjects recruited over the same time period? Yes, No, NR	Were measurements equal, valid, and reliable? Yes, No, Mixed	Were outcome assessors masked? Yes, No, NR	Were outcomes presepecified and defined? Yes, No, NR
Fabunmi, 2009 US Amylin Inc, Eli Lilly Cohort 1 year Fair	Yes	Yes	Yes	NR	Yes
Habib, 2009 US Private and Government funding Cohort > 6 months of follow up Good	Yes	Yes	Yes	Yes	Yes
Shaya, 2009 US Funding NR Cohort 5 years Poor	Yes	Yes	Mixed	No	Yes
Asche, 2008 US Novartis Cohort 395 days Fair	Yes	Yes	Yes	No	Yes

Evidence Table 22. Key Question 2: Quality assessment of observational studies

Study Characteristics Author, year Country Funding Design Duration Quality	Was time of follow-up equal for all groups? Yes, No, NR	Overall attrition high? (≥20%) Yes, No, NR	Was differential attrition high? (≥15%) Yes, No, NR	Did the study design and/or statistical analyses account for confounding? Yes, No, NR	Was the length of folloup adequate? Yes, No, NR
Fabunmi, 2009 US Amylin Inc, Eli Lilly Cohort 1 year Fair	Yes			Yes	Yes
Habib, 2009 US Private and Government funding Cohort > 6 months of follow up Good	Yes	No	No	Yes	Yes
Shaya, 2009 US Funding NR Cohort 5 years Poor	Yes	NR	NR	Yes	Yes
Asche, 2008 US Novartis Cohort 395 days Fair	Yes	No	No	Yes	Yes

Evidence Table 22. Key Question 2: Quality assessment of observational studies

Study Characteristics Author, year Country Funding Design Duration Quality	Methods of harms assessment	Overall Quality Rating for Safety Outcomes Good, Fair, Poor
Fabunmi, 2009 US Amylin Inc, Eli Lilly Cohort 1 year Fair	Yes	Fair
Habib, 2009 US Private and Government funding Cohort > 6 months of follow up Good	Blinded outcomes assessment from electronic claims data, inpatient codes, mortality from the Division of Vital Records and Health Statistics from enrollment through 5/31/2007	Good
Shaya, 2009 US Funding NR Cohort 5 years Poor	ICD-9 claims	Poor
Asche, 2008 US Novartis Cohort 395 days Fair	Chief complaints and ICD-9 codes describing an adverse event or its symptoms and out of range laboratory values were used to identify adverse event occurrence based on clinic visits from an electronic medical record. A 4.5kg cut-off was used for weight gain.	Fair

Evidence Table 22. Key Question 2: Quality assessment of observational studies

Study Characteristics Author, year Country Funding Design Duration Quality	Were comparison groups selected from the same source population? Yes, No, NR	Were subjects recruited over the same time period? Yes, No, NR	Were measurements equal, valid, and reliable? Yes, No, Mixed	Were outcome assessors masked? Yes, No, NR	Were outcomes presepecified and defined? Yes, No, NR
Vlckova, 2009 England Funding source NR Cohort 9 months Poor	Yes	No	No	NR	Yes
Miyazaki, 2008 US Funding NR Cohort 3 months Poor	Yes	Yes	Yes	NR	Yes
Grossman, 2009 Canada Eli Lilly 2 years Poor	Yes	Yes	Mixed	No	Yes
Lewis, 2008 US NIH, Takeda, GlaxoSmithKline, Eli Lilly Nested Case Control > 1year of exposure Fair	Yes	Yes	Yes	NR	Yes

Evidence Table 22. Key Question 2: Quality assessment of observational studies

Study Characteristics Author, year Country Funding Design Duration Quality	Was time of follow-up equal for all groups? Yes, No, NR	Overall attrition high? (≥20%) Yes, No, NR	Was differential attrition high? (≥15%) Yes, No, NR	Did the study design and/or statistical analyses account for confounding? Yes, No, NR	Was the length of folloup adequate? Yes, No, NR
Vlckova, 2009 England Funding source NR Cohort 9 months Poor	Yes	NR	NR	No	Yes
Miyazaki, 2008 US Funding NR Cohort 3 months Poor	Yes	No	No	No	Yes
Grossman, 2009 Canada Eli Lilly 2 years Poor	Yes	Yes	No	No	Yes
Lewis, 2008 US NIH, Takeda, GlaxoSmithKline, Eli Lilly Nested Case Control > 1year of exposure Fair	Yes	Yes	No	Yes	Yes

Evidence Table 22. Key Question 2: Quality assessment of observational studies

Study Characteristics Author, year Country Funding Design Duration Quality	Methods of harms assessment	Overall Quality Rating for Safety Outcomes Good, Fair, Poor
Vlckova, 2009 England Funding source NR Cohort 9 months Poor	Surveys sent to physician 6 months after initial prescription	Poor
Miyazaki, 2008 US Funding NR Cohort 3 months Poor	Body weight measurements and blood draw at 3 months	Poor
Grossman, 2009 Canada Eli Lilly 2 years Poor	Yes	Poor
Lewis, 2008 US NIH, Takeda, GlaxoSmithKline, Eli Lilly Nested Case Control > 1year of exposure Fair	Kaiser Permanente Northern California Records	Fair