Therapeutic Class Overview
Incretin Mimetics

Therapeutic Class

- **Overview/Summary:** The glucagon-like peptide-1 (GLP-1) receptor agonists, or incretin mimetics, are one of two incretin-based therapies currently available for the management of type 2 diabetes. Specifically, exenatide (Bydureon®, Byetta®) and liraglutide (Victoza®) are Food and Drug Administration-approved as adjunct therapy to diet and exercise to improve glycemic control in adults with type 2 diabetes.[1-3] This medication class was developed to mimic the effects of endogenous GLP-1, a hormone that maintains glucose homeostasis through several different mechanisms. The incretin mimetics work by stimulating insulin secretion, inhibiting glucagon secretion, improving β cell responsiveness to glucose, delaying gastric emptying, and enhancing satiety. In addition, these agents increase insulin secretion from pancreatic β cells in the presence of elevated glucose concentrations. Therefore, due to the glucose-dependent manner in which the incretin mimetics work, the medication class is associated with a low risk of hypoglycemia compared to other antidiabetic agents.[4,5] The incretin mimetics are most commonly associated with gastrointestinal-related adverse events, and all agents are associated with the risk of developing pancreatitis. Only exenatide extended-release (ER) and liraglutide have boxed warnings regarding the risk of thyroid C-cell tumors. The incretin mimetics are available as subcutaneous injections. Exenatide (Byetta®) is administered twice-daily, liraglutide (Victoza®) is administered once-daily, and exenatide ER (Bydureon®) is administered once weekly.[1-3] There are currently no generic incretin mimetics available.

Table 1. Current Medications Available in Therapeutic Class[1-3]

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Exenatide (Bydureon®, Byetta®)	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus	Extended-release injection (Bydureon®): 2 mg/vial* Injection (Byetta®): 250 µg/mL†	-
Liraglutide (Victoza®)	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus	Injection: 6 mg/mL‡	-

*Supplied in cartons of four single-dose trays (one vial containing 2 mg exenatide [as a white to off-white powder], one pre-filled syringe [0.65 mL diluents], one vial connector, and two custom needles).
†Supplied as a 5 µg/dose pre-filled syringe (1.2 mL, 60 doses) and 10 µg/dose pre-filled syringe (2.4 mL, 60 doses).
‡Supplied as 0.6 (30 doses), 1.2 (15 doses), and 1.8 mg (10 doses) pre-filled, multi-dose pens (3 mL) available in a package of two or three pens.

Evidence-based Medicine

- In general, the incretin mimetics have been evaluated in clinical trials as add-on therapy to treatment regimens of established antidiabetic agents. Data consistently demonstrate that incretin mimetics are associated with positive effects on glycosylated hemoglobin (HbA_{1c}), fasting plasma glucose (FPG), post-prandial glucose (PPG), and body weight. In addition, glycemic goals were consistently achieved when an incretin mimetic was added to existing treatment regimens.[6-48]
- When compared to other antidiabetic agents (metformin, sulfonylureas, thiazolidinediones, dipeptidyl peptidase-4 inhibitors, insulin therapy), efficacy data are not consistent, with the incretin mimetics achieving superiority or comparable benefits in glycemic outcomes. However, in general, all incretin-based therapies, including the incretin mimetics, consistently demonstrate a beneficial effect on body weight compared to other antidiabetic agents.[6-48]
- Few head-to-head clinical trials within the class have been conducted. Compared to exenatide, exenatide extended-release (ER) significantly decreased HbA_{1c}, and achieved similar decreases in

body weight.[25,31] In a single trial, liraglutide significantly decreased HbA_{1c} compared to exenatide. Furthermore, liraglutide significantly decreased FPG while exenatide significantly decreased PPG.[39]
- Overall, safety data demonstrate that incretin mimetics are commonly associated with gastrointestinal-related adverse events.[6-48] Exenatide ER appears to be associated with less nausea and vomiting, but more constipation, diarrhea, and injection site-related adverse events compared to exenatide.[25,31]

Key Points within the Medication Class
- According to Current Clinical Guidelines:
  - Type 2 diabetes:[49-53]
    - Metformin remains the cornerstone to most antidiabetic treatment regimens.[49-53]
    - Patients with high glycosylated hemoglobin will most likely require combination or triple therapy in order to achieve glycemic goals.[49-53]
    - The incretin mimetics are recommended as a potential second-line treatment option to be added to or used in combination with metformin in patients not achieving glycemic goals.[50,52]
      - A lower rate of hypoglycemia, established efficacy and safety profile when used in combination with metformin, demonstrated effectiveness in reducing post-prandial glucose, and the potential for weight loss are noted as advantages associated with the incretin mimetics compared to other classes of antidiabetic agents.[50,52]
      - No one incretin mimetic is recommended or preferred over another.[49-53]
- Other Key Facts:
  - Exenatide (Byetta®) is administered twice-daily (60 minutes prior to food).[1]
  - Exenatide extended-release (ER) (Bydureon®) is administered once weekly (independent of meals).[2]
    - The extended effect was achieved by adding the biodegradable polymer poly D, L-lactic-co-glycolic acid to exenatide. As a result, microspheres are formed and after administered, continued infiltration of water into the microspheres causes them to swell and release exenatide in a slow predictable fashion.[54]
    - Patients who administer exenatide ER will have a palpable subcutaneous nodule at the injection site that dissipates as the medication is released.[54]
  - Liraglutide (Victoza®) is administered once-daily (independent of meals).[3]
  - No generic incretin mimetics are available.

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Therapeutic Class Review
Incretin Mimetics

Overview/Summary

A significant advancement in the management of type 2 diabetes has been the development of incretin-based therapies. This novel therapeutic approach is important as type 2 diabetics have been shown to have an impaired incretin response.[1] Currently there are two classes of incretin-based therapies available; the dipeptidyl peptidase-4 (DPP-4) inhibitors and the glucagon-like peptide-1 (GLP-1) receptor agonists, or incretin mimetics. The incretin mimetics, exenatide (Bydureon®, Byetta®) and liraglutide (Victoza®), were developed to mimic the effects of endogenous GLP-1 and are Food and Drug Administration (FDA)-approved as adjunct therapy to diet and exercise to improve glycemic control in adult type 2 diabetics.[2-4] According to a press release from the manufacturer, the FDA approved exenatide for use as an add-on therapy to insulin glargine, with or without metformin and/or a thiazolidinedione, in conjunction with diet and exercise for adults with type 2 diabetes who are not achieving adequate glycemic control on insulin glargine alone.[5] Please note, this press release did not change the language in the approved package labeling for exenatide and it is not noted as a specific indication.[2,5]

Specifically, GLP-1 is an endogenous hormone that maintains glucose homeostasis by stimulating insulin secretion, inhibiting glucagon secretion, improving β cell responsiveness to glucose, delaying gastric emptying, and enhancing satiety. The endogenous hormone also increases insulin secretion from pancreatic β cells in the presence of elevated glucose concentrations. The actions of GLP-1 mainly affect fasting and post-prandial glucose levels as the hormone works in a glucose-dependent manner. Due to the glucose-dependent manner in which the incretin mimetics work, the medication class is associated with a low risk of hypoglycemia. Furthermore, the use of incretin mimetics in the management of type 2 diabetes has also demonstrated a positive benefit on weight reduction, β cell function, glycemic control, and systolic blood pressure.[1,6]

Exenatide and liraglutide are administered by subcutaneous (SC) injection and are available as branded products. There are currently two formulations of exenatide available. The immediate-release formulation (Byetta®) is administered twice-daily and should be given within 60 minutes prior to a meal, while the extended-release (ER) formulation (Bydureon®) is administered once weekly and can be administered independent of meals.[2,3] The extended effect of exenatide ER results from the addition of a biodegradable polymer poly D, L-lactic-co-glycolic acid to exenatide, which forms microspheres. After exenatide ER is administered, continued infiltration of water into the microspheres causes them to swell and release the medication in a slow predictable fashion. Of note, patients who administer exenatide ER will have a palpable SC nodule at the injection site that dissipates as the medication is released.[7] Liraglutide is administered once-daily and can also be administered independent of meals.[4] Overall, the adverse event profiles of exenatide and liraglutide appear similar; however, exenatide ER and liraglutide have a boxed warning regarding the risk of thyroid C-cell tumors. Gastrointestinal-related adverse events are commonly reported with the use of incretin mimetics, but these generally subside with continued treatment. In addition, a risk for the development of pancreatitis is associated with the use of incretin mimetics.[2-4] The incretin mimetics have been evaluated in combination with and in comparison to a variety of antidiabetic therapies. Overall, the medication class is significantly more effective compared to placebo in reducing glycosylated hemoglobin (HbA_{1c}), fasting plasma glucose, post-prandial glucose (PPG), and body weight. Efficacy data comparing treatment to sulfonylureas, thiazolidinediones, DDP-4 inhibitors, or insulin therapy are not consistent, with the incretin mimetics achieving significantly greater or comparable benefits in glycemic outcomes. However, in general, all incretin-based therapies, including the incretin mimetics, consistently demonstrate a beneficial effect on body weight compared to other antidiabetic agents.[8-50]

According to current clinical guidelines for the management of type 2 diabetes, metformin remains the cornerstone of most antidiabetic treatment regimens. Additionally, patients with a high HbA_{1c} will likely require combination or triple therapy in order to achieve glycemic goals. The incretin mimetics are

recommended as a potential second-line treatment option to be added to or used in combination with metformin in patients not achieving glycemic goals. Clinical guidelines note a lower rate of hypoglycemia, an established efficacy and safety profile when used in combination with metformin, demonstrated effectiveness in reducing PPG, and the potential for weight loss as advantages associated with the incretin mimetics compared to other classes of antidiabetic agents. No one incretin mimetic is recommended or preferred over another.[51-55]

Medications

Table 1. Medications Included Within Class Review

Generic Name (Trade Name)	Medication Class	Generic Availability
Exenatide (Bydureon®, Byetta®)	Incretin mimetics	-
Liraglutide (Victoza®)	Incretin mimetics	-

Indications

Table 2. Food and Drug Administration-Approved Indications[2-4]

Generic Name	Adjunct to Diet and Exercise to Improve Glycemic Control in Adults with Type 2 Diabetes Mellitus
Exenatide	✔
Liraglutide	✔

It is important to note that the incretin mimetics are not a substitute for insulin, and these agents should not be used in type 1 diabetics or for the treatment of diabetic ketoacidosis. The incretin mimetics would not be effective in these situations.[2-4]

According to Food and Drug Administration-approved package labeling, extended-release exenatide and liraglutide are not recommended as first-line therapy for patients who have inadequate glycemic control on diet and exercise.[4]

Pharmacokinetics

Pharmacokinetic data for exenatide extended-release (ER) are not extensively reported. According to Food and Drug Administration-approved package labeling, following a single dose of exenatide ER, exenatide is released from microspheres over approximately 10 weeks. Two peaks of exenatide in the plasma after approximately two and six to seven weeks, respectively, are observed due to an initial period of release of surface-bound exenatide, and followed by a gradual release of exenatide from the microspheres.[3]

Table 3. Pharmacokinetics[56]

Generic Name	Bioavailability (%)	Renal Excretion (%)	Active Metabolites	Serum Half-Life (hours)
Exenatide*	65 to 76†	Not reported	Not reported	2.4
Liraglutide	55	0 to 6	Not reported	13

*Immediate-release.
†Animal data.

Clinical Trials

Clinical trials demonstrating the safety and efficacy of the incretin mimetics in the management of type 2 diabetes are outlined in Table 4.[8-50]

The efficacy of exenatide as add-on therapy to metformin, a sulfonylurea, or existing antidiabetic regimen (metformin or a sulfonylurea) was evaluated in three, placebo-controlled, 30 week, randomized-controlled trials.[8,10,11] In all trials, there were significant decreases in glycosylated hemoglobin (HbA_{1c}) with exenatide compared to placebo ($P<0.002$, $P<0.001$, and $P<0.0002$). Exenatide also resulted in significant

decreases in fasting plasma glucose (FPG), body weight, and post-prandial glucose (PPG) compared to placebo. When administered as add-on therapy to a sulfonylurea, exenatide significantly decreased fasting proinsulin concentrations compared to placebo (*P*<0.01), but no difference between exenatide and placebo was observed in the decrease in fasting insulin concentrations.[11] There were also no differences in the decreases in fasting proinsulin or insulin concentrations between exenatide and placebo when added on to metformin therapy.[8] The most common adverse events were gastrointestinal in nature, and the incidence of hypoglycemia ranged from 19.2 to 36.0% (reported in two trials).[8,10,11]

Extensions of these 30 week trials demonstrate that the benefits of exenatide are sustained for up to three years.[9,12-15] Specifically, two open-label, one year extension trials (82 weeks total treatment) demonstrated that further decreases in HbA_{1c}, FPG, and body weight are achieved with long-term exenatide treatment. In addition, after 82 weeks 59 and 44% of patients with baseline HbA_{1c} >7.0% achieved a HbA_{1c} ≤7.0% when exenatide was added to metformin or a sulfonylurea.[9,12] An interim analysis of these two one-year extension trials supported these results.[13] Two additional interim analyses of patients receiving exenatide for two and three years noted sustained significant decreases in baseline HbA_{1c}. Regarding safety data, significant reductions from baseline in alanine aminotransferase and aspartate aminotransferase occurred, and nausea was the most commonly reported adverse event.[14,15]

Exenatide as add-on therapy in type 2 diabetics receiving a thiazolidinedione has also been evaluated. After 16 weeks, exenatide significantly decreased HbA_{1c} (*P*<0.001), FPG (*P*<0.001), and body weight (*P*<0.001) compared to placebo. Gastrointestinal adverse events were more common in patients receiving exenatide.[17]

When exenatide was compared to a sulfonylurea as add-on therapy to metformin, exenatide significantly decreased body weight and body mass index (*P*<0.001 for both), whereas the sulfonylurea caused significant increases in both (*P*<0.05 for both). Both treatments significantly decreased HbA_{1c}, FPG, and PPG (exenatide; *P*<0.001 for all; glyburide; *P*<0.001 for all). Only exenatide significantly improved insulin resistance (*P*<0.01) and β cell function (*P*<0.05).[20]

Several trials have compared exenatide to insulin therapy (aspart and glargine) as add-on therapy to metformin and/or a sulfonyurea.[19,21-26] Similar improvements in HbA_{1c} between treatments were observed in three of the trials (*P* value not reported, *P*=0.55 and *P*=0.067), while mixed results were observed for decreases in FPG. Specifically, in two trials, insulin therapy was "superior" in decreasing FPG (*P* value not reported and *P*<0.0001), while in another there was no difference between the two treatments (*P*=0.689). Insulin therapy was associated with an increase in body weight compared to a decrease with exenatide.[21,24,26] Patient-reported health outcome measures demonstrated no differences between exenatide or insulin therapy; both achieved significant improvements from baseline. However, neither treatment improved Diabetes Treatment Flexibility Scores (*P*=0.93 for both).[22]

Approval of exenatide extended-release (ER) in the management of type 2 diabetes was based on the clinical evidence for safety and efficacy derived from the DURATION trials (1 through 5). Exenatide ER was added to existing antidiabetic regimens in four of the five trials (1, 2, 3, and 5). In contrast, DURATION-4 compared exenatide ER, metformin, pioglitazone, and sitagliptin all as monotherapy.[27,29,31-33] Overall, exenatide ER as add-on therapy to existing antidiabetic regimens significantly decreased HbA_{1c} compared to exenatide (*P*=0.0023), sitagliptin (*P*<0.0001), pioglitazone (*P*=0.0165), and insulin therapy (*P*=0.017), with no increased risk of hypoglycemia. Furthermore, significantly greater proportions of patients receiving exenatide ER achieved HbA_{1c} goals compared to these treatments.[27,29,31,33] In terms of decreases in body weight, exenatide ER was "superior" compared to sitagliptin (*P*=0.0002) and pioglitazone (*P*<0.0001), and similar compared to exenatide (*P*=0.89).[27,29,33] As expected, gastrointestinal-related adverse events were reported more commonly with the incretin-based therapies.[27,29,31,33] When compared to exenatide, extended ER was associated with lower incidences of nausea (26.4 vs 34.5% and 14 vs 35%) and vomiting (10.8 vs 18.6%), and higher incidences of diarrhea (13.5 vs 13.1%), constipation (10.8 vs 6.2%), and injection site-related adverse events (22.3 vs 11.7% and 13 vs 10%).[27,33] As mentioned previously, DURATION-4 evaluated the safety and efficacy of exenatide ER as monotherapy in type 2 diabetics. As monotherapy, the decreases in HbA_{1c} achieved with exenatide ER

were “superior” compared to sitagliptin (*P*<0.001), and similar compared to metformin (*P*=0.620) and pioglitazone (*P*=0.328). In this trial, exenatide ER and metformin resulted in a similar proportion of patients achieving an HbA_{1c} goal of <7.0% (*P* value not reported), with exenatide ER being superior to sitagliptin (*P*<0.001). However, significantly more patients receiving exenatide ER achieved a goal of ≤6.5% compared to metformin (*P*=0.004). Exenatide ER and metformin were also similar in terms of associated decreases in bodyweight, with exenatide ER achieving “superiority” compared to sitagliptin and pioglitazone. Overall, exenatide ER was associated with more gastrointestinal-related adverse events, with the exception of diarrhea which occurred at the highest frequency in patients receiving metformin.[32]

Approval of liraglutide in the management of type 2 diabetes was based on the clinical evidence for safety and efficacy derived from the LEAD trials (1 through 6). The LEAD trials evaluated liraglutide monotherapy (LEAD-3); add-on therapy to a sulfonylurea (LEAD-1), metformin (LEAD-2), metformin plus a thiazolidinedione (LEAD-4), metformin plus a sulfonylurea (LEAD-5); and monotherapy head-to-head with exenatide (LEAD-6).[34-36,39-40]

In LEAD-1 liraglutide was compared to placebo or rosiglitazone as add-on therapy to a sulfonylurea. After 26 weeks, liraglutide (0.6, 1.2, and 1.8 mg/day) significantly decreased HbA_{1c} compared to placebo (*P*<0.0001 for all), with only higher doses achieving “superiority” compared to rosiglitazone (*P*<0.001 for both). Similar results were observed for the proportion of patients achieving HbA_{1c}, FPG, and PPG goals, as well as improvements in β cell function. Additionally, compared to rosiglitazone, liraglutide significantly decreased body weight (*P*<0.0001). This trial did not demonstrate a difference in the decrease in systolic blood pressure between treatments.[34]

In LEAD-2 liraglutide was compared to placebo and a sulfonylurea as add-on therapy to metformin. Again, liraglutide significantly decreased HbA_{1c} compared to placebo; however, similar decreases were observed with liraglutide compared to the sulfonylurea. Liraglutide was associated with significant decreases in body weight compared to placebo (*P*<0.01) and the sulfonylurea (*P*<0.001). Other secondary outcomes, such as decreases in FPG and PPG and improvements in β cell function, were significant for liraglutide compared to placebo, and similar compared to a sulfonylurea.[35]

In LEAD-3 liraglutide was compared to a sulfonylurea as monotherapy, and liraglutide was “superior” in decreasing HbA_{1c} (*P* value not reported). In addition, increases in body weight were reported with the sulfonylurea, while liraglutide significantly decreased body weight (*P*=0.027). Other secondary outcomes that reached significance with liraglutide compared to the sulfonylurea included decreases in FPG and PPG, improvements in β cell function, and decreases in systolic blood pressure (liraglutide 1.8 mg/day only). Patients receiving liraglutide also reported improved quality of life scores (*P*=0.02 vs sulfonylurea), mainly as a result of improvements in weight image and concern (*P*<0.01).[36] In a one year extension trial, patients continuing liraglutide for a total of two years maintained significant improvements in HbA_{1c} compared to the sulfonylurea.[37] A post-hoc analysis revealed that based on the patient reported-outcomes, enhanced glycemic control and decreased body weight achieved with liraglutide improved psychological and emotional well-being, and health perceptions by reducing anxiety and worry associated with weight gain.[38]

In LEAD-4 and LEAD-5 liraglutide was compared to placebo as add-on therapy to metformin plus a sulfonylurea and to a thiazolidinedione. LEAD-5 also had an open-label arm of insulin therapy. Results achieved with liraglutide in terms of decreases in HbA_{1c}, body weight, and FPG compared to placebo were similar to those observed in the other LEAD trials.[39,40] When compared to insulin therapy, decreases in HbA_{1c} (*P*=0.0015) and body weight (*P*<0.001) and improvements in β cell function (*P*=0.0019) were significantly greater with liraglutide. It was noted that decreases in PPG were not different between the two treatments, and the likelihood of patients achieving FPG goals were also similar.[40]

Lead-6 is a head-to-head trial comparing liraglutide to exenatide as add-on therapy to existing antidiabetic treatment regimens. Liraglutide significantly decreased HbA_{1c} compared to exenatide (1.12 vs 0.79%; *P* value not reported), and a significantly greater proportion of patients receiving liraglutide achieved HbA_{1c}

goals (HbA_{1c} <7.0%, 54 vs 43%; odds ratio [OR], 2.02; 95% confidence interval [CI], 1.31 to 3.11; *P* value not reported, and HbA_{1c} ≤6.5%, 35% vs 21%; OR, 2.73; 95% CI, 1.68 to 4.43; *P* value not reported). Significant decreases in FPG were also achieved with liraglutide (*P*<0.0001); however, exenatide significantly decreased PPG after breakfast and dinner (*P*<0.0001 and *P*=0.0005). Both treatments were associated with similar decreases in body weight and systolic blood pressure.[41] A 14 week, extension trial revealed that patients who were switched from exenatide to liraglutide achieved additional glycemic control and cardiometabolic benefits.[42]

When compared to sitagliptin as add-on therapy to metformin, liraglutide significantly decreased HbA_{1c} (liraglutide 1.2 and 1.8 mg; *P*<0.0001), FPG (*P* value not reported), and body weight (*P* value not reported). Liraglutide and sitagliptin were associated with similar improvements in β cell function and blood pressure (*P* values not reported). More gastrointestinal-related adverse events were reported with liraglutide.[45]

Meta-analyses and Cochrane Reviews evaluating incretin-based therapies (dipeptidyl peptidase-4 inhibitors and incretin mimetics) have been conducted and demonstrate similar decreases in HbA_{1c} and significant decreases in body weight compared to other antidiabetic agents.[46-50] A recent meta-analysis revealed that incretin-based therapies are not associated with an increased risk of cardiovascular events compared to placebo or other antidiabetic agents.[47]

Table 4. Clinical Trials

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
DeFronzo et al[8] Exenatide 5 µg SC BID vs exenatide 5 µg SC BID for 4 weeks, followed by 10 µg SC BID vs placebo All patients also received existing metformin therapy.	MC, PC, PG, RCT, TB Type 2 diabetic patients 19 to 78 years of age, treated with metformin (≥1,500 mg/day) for ≥3 months before screening, FPG <240 mg/dL, BMI 27 to 45 kg/m^2, HbA_{1c} 7.1 to 11.0%, stable weight (±10%) for 3 months prior to screening, and no lab value >25% outside of normal value	N=336 30 weeks	Primary: Change in baseline HbA_{1c} Secondary: Proportion of patients achieving HbA_{1c} ≤7.0%; change in baseline FPG, weight, fasting concentrations of insulin, proinsulin, and lipids	Primary: Significantly greater decreases in HbA_{1c} were reported with exenatide 10 (-0.78%) and 5 µg (-0.40%) compared to placebo (0.08%; *P*<0.002 for pairwise comparison). Secondary: A significantly greater proportion of patients achieved HbA_{1c}≤7.0% with exenatide 5 (27%) and 10 µg (40%) compared to placebo (11%; *P*<0.01 for pairwise comparison). Significantly greater decreases in FPG were observed with exenatide 5 (-7.2 mg/dL; *P*<0.005) and 10 µg (-10.1 mg/dL; *P*<0.0001) compared to placebo (14.4 mg/dL). Significantly greater decreases in body weight were observed with exenatide 5 (-1.6 kg; *P*<0.05) and 10 µg (-2.8 kg; *P*<0.001) compared to placebo (-0.3 kg). There was no difference in fasting insulin or proinsulin concentrations between any of the treatments (*P* values not reported). No differences in lipid profiles were observed between any of the treatments (*P* value not reported). Gastrointestinal side effects were most commonly reported with exenatide and included nausea (45%), diarrhea (16%), and vomiting (12%) in exenatide 10 µg-treated patients (*P* values not reported). The incidence of hypoglycemia was similar with all treatments. Withdrawals due to adverse event(s) occurred in 7.1, 3.6, and 0.9% of patients receiving exenatide 10 µg, exenatide 5 µg, and placebo (*P* values not reported).
Ratner et al[9] Exenatide 5 µg SC BID for 4 weeks,	ES, MC, OL (DeFronzo et al[8]) Type 2 diabetic	N=150 52 weeks (82 weeks	Primary: Changes in baseline HbA_{1c}, body weight, and lipid profile of the	Primary: At week 30, the completer cohort had significant decreases in HbA_{1c} from baseline of -1.0±0.1%. At week 82, the decrease was -1.3±0.1% (95% CI, -1.5 to -1.0; *P*<0.05). For the total cohort, the decrease at week 30 was -

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
followed by 10 µg SC BID All patients also received existing metformin therapy.	patients 19 to 78 years of age, treated with metformin (≥1,500 mg/day) for ≥3 months before screening, FPG <240 mg/dL, BMI 27 to 45 kg/m^2, HbA_{1c} 7.1 to 11.0%, stable weight (±10%) for 3 months prior to screening, and no lab value >25% outside of normal value	total)	completer cohort (those patients who completed 82 weeks of exenatide) and total cohort (ITT population) Secondary: Proportion of patients in the completer cohort with baseline HbA_{1c} >7.0% who achieved an HbA_{1c} ≤7.0%, reduction of weight after stratification by baseline BMI, safety	0.7±0.1% (95% CI, -0.8 to -0.5; *P*<0.05) and at week 82 was -0.8±0.1% (95% CI, -1.0 to -0.6; *P*<0.05). At week 30, the completer cohort had significant decreases in body weight from baseline of -3.0±0.6 kg. At week 82, the decrease from baseline was -5.3±0.8 kg (95% CI, -7.0 to -3.7; *P*<0.05). For the total cohort, the decrease at week 30 was -2.3±0.4 kg and at week 82 was -4.3±0.6 kg (95% CI, -5.5 to -3.2; *P*<0.05). At week 82, the completer cohort experienced significant decreases in apo B (-5.20 mg/dL; 95% CI, -10.00 to -0.22; *P* value not reported), a reduction in TG (-73 mg/dL; 95% CI, -107 to -39; *P* value not reported) and an increase in HDL-C (4.5 mg/dL; 95% CI, 2.3 to 6.6; *P* value not reported). Secondary: At weeks 30 and 82, the proportion of patients in the completer cohort whose baseline HbA_{1c} was >7.0% and who achieved an HbA_{1c} ≤7.0% was 46 and 59% (*P* values were not reported). Patients in the completer cohort whose baseline BMI ≥30 kg/m^2 experienced a greater decrease of weight (-6.9±1.1 kg) compared to those whose baseline BMI was <30 kg/m^2 (-2.3±0.8 kg; *P* values were not reported). The following adverse events were experienced by patients in the total cohort: nausea (14 to 33%), upper respiratory tract infections (3 to 10%), diarrhea (3 to 7%), vomiting (1 to 5%), and dizziness (2 to 6%) (*P* values were not reported).
Kendall et al[10] Exenatide 5 µg SC BID vs exenatide 5 µg SC	DB, MC, PC, PG, RCT Type 2 diabetic patients 22 to 77 years of age, treated with maximally effective doses of metformin (≥1,500	N=733 30 weeks	Primary: Change in baseline HbA_{1c} Secondary: Change in baseline FPG, PPG, and body weight	Primary: Significantly greater decreases in HbA_{1c} were achieved with exenatide 5 (-0.55±0.07%) and 10 µg (-0.77±0.08%) compared to placebo (0.23±0.07%; *P*<0.001 for pairwise comparison). Secondary: Significantly greater decreases in FPG were achieved with exenatide 5 (-0.5±0.2 mmol/L) and 10 µg (-0.6±0.2 mmol/L) compared to placebo

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
BID for 4 weeks, followed by 10 µg SC BID vs placebo All patients also received existing diabetes regimens. All patients continued pre-trial metformin regimen. To standardize sulfonylurea use, patients were randomized to either maximally effective or minimum recommended sulfonylurea dose.	mg/day) and a sulfonylurea (4 mg/day glimepiride, 20 mg/day glipizide, 10 mg/day glipizide XL, 10 mg/day glyburide, 6 mg/day micronized glyburide, 350 mg/day chlorpropamide, 500 mg/day tolazamide, or 1,500 mg/day tolbutamide) for ≥3 months before screening, FPG <13.3 mmol/L, BMI 27 to 45 kg/m^2, HbA_{1c} 7.5 to 11.0%, stable weight (±10%) for 3 months prior to screening, and no lab value >25% outside of normal value			(0.8±0.2 mmol/L; *P*<0.0001 for pairwise comparison). Significantly greater decreases in PPG were achieved with exenatide 5 (*P*=0.009) and 10 µg (*P*=0.0004) compared to placebo. Significantly greater decreases in body weight were achieved with exenatide 5 (-1.6±0.2 kg) and 10 µg (-1.6±0.2 kg) compared to placebo (-0.9±0.2 kg; *P*≤0.01). Nausea was the most commonly reported adverse event and was observed in 48.5, 39.2, and 20.6% of patients receiving exenatide 10 µg, exenatide 5 µg, and placebo (*P* values not reported). A higher incidence of hypoglycemia was reported with exenatide. Hypoglycemia was reported in 27.8, 19.2, and 12.6% of patients receiving exenatide 10 µg, exenatide 5 µg, and placebo (*P* values not reported).
Buse et al[11] Exenatide 5 µg SC BID vs exenatide 5 µg SC BID for 4 weeks, followed by 10 µg SC BID	MC, PC, PG, RCT, TB Type 2 diabetic patients 22 to 76 years of age, treated with maximally effective doses of a sulfonylurea (4 mg/day glimepiride, 20 mg/day glipizide, 10 mg/day glipizide XL, 10 mg/day	N=377 30 weeks	Primary: Change in baseline HbA_{1c} Secondary: Change in baseline FPG, weight, fasting concentrations of insulin, proinsulin, and lipoproteins	Primary: Significantly greater decreases in HbA_{1c} were noted with exenatide 10 (-0.86%) and 5 µg (-0.46%) compared to placebo (0.12%; *P*<0.0002 for pairwise comparison). Secondary: A significantly greater decreases in FPG was reported with exenatide 10 µg at week 30 compared to placebo (-0.6 vs 0.4 mmol/L; *P*<0.05). There was no difference between exenatide 5 µg and placebo (*P* value not reported). A significantly greater decrease in body weight was noted with exenatide 10 µg at week 30 compared placebo (-1.6 vs -0.6 kg; *P*<0.05). There was

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs placebo All patients also received existing sulfonylurea therapy.	glyburide, 6 mg/day micronized glyburide, 350 mg/day chlorpropamide, or 500 mg/day tolazamide) for ≥3 months, FPG <240 mg/dL, BMI 27 to 45 kg/m^2, HbA_{1c} 7.1 to 11.0%, stable weight (±10%) for 3 months prior to screening, and no lab value >25% outside of normal value			no difference between exenatide 5 µg and placebo (*P* value not reported). There were no differences in fasting insulin concentrations between any of the treatments (*P* value not reported). A significantly greater decrease in fasting proinsulin concentrations was noted with exenatide 10 µg at week 30 compared to placebo (-16 mmol/L; *P*<0.01). A similar trend was reported with exenatide 5 µg compared to placebo, but no significance was reported (*P* value not reported). There was a small decrease in LDL-C and apo B (*P*<0.05 for pairwise comparisons for both values) with exenatide compared to placebo. No differences were observed in other lipid parameters evaluated (*P* values not reported). Side effects reported by patients receiving exenatide 10 µg included nausea (51%), vomiting (13%), diarrhea (9%), constipation (9%), and hypoglycemia (36%) (*P* values not reported). There were 13 (10.1%) withdrawals due to adverse event(s) with exenatide 10 µg compared to nine (7.2%) withdrawals with exenatide 5 µg and four (3.3%)withdrawals with placebo (*P* values not reported). The majority of the events reported were mild to moderate in nature. Serious adverse events were reported in 4, 3, and 8% of patients receiving exenatide 10 µg, exenatide 5 µg, and placebo. Such events included a MI in an exenatide-treated patient and one placebo-treated patient who experienced clinical manifestations of coronary artery disease.
Riddle et al[12] Exenatide 5 µg SC BID or exenatide 5 µg SC BID for 4 weeks, followed by 10 µg SC BID All patients also	ES, MC, OL (Kendall et al[10] and Buse et al[11]) Type 2 diabetic patients 19 to 78 years of age, treated with metformin (≥1,500 mg/day) or	N=401 52 weeks (82 weeks total)	Primary: Change in baseline HbA_{1c} and FPG in the completer cohort (those patients who completed 82 weeks of exenatide therapy) and total cohort (ITT population)	Primary: At week 30, the completer cohort experienced a significant decrease in HbA_{1c} of -0.8±0.1% for the original exenatide 5 µg arm and -1.0±0.1% for the original 10 µg arm. At week 82, the decrease was -1.0±0.1% (95% CI, -0.9 to -1.2; *P* value not reported). For the total cohort group, the decrease at week 82 was -0.7±0.1% (95% CI, -0.8 to -0.5; *P* value not reported). Results from week 30 week were not reported. At week 30, the completer cohort observed a decrease in FPG of -

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
received existing metformin and sulfonylurea therapies.	maximally effective doses of a sulfonylurea (4 mg/day glimepiride, 20 mg/day glipizide, 10 mg/day glipizide XL, 10 mg/day glyburide, 6 mg/day micronized glyburide, 350 mg/day chlorpropamide, or 500 mg/day tolazamide) for ≥3 months before screening, FPG <240 mg/dL, BMI of 27 to 45 kg/m^2, HbA_{1c} 7.1 to 11.0%, stable weight (±10%) for 3 months prior to screening, and no lab value >25% outside of normal value		Secondary: Change in baseline weight, change in baseline HbA_{1c} and weight stratified by baseline HbA_{1c} and BMI	0.52±0.16 mmol/L (*P* value not reported). At week 82, the decrease was -0.62±0.19 mmol/L (*P* value not reported). FPG data for the total cohort were not reported. Secondary: At week 30, the completer cohort group experienced a decrease in body weight of -1.4±0.3 kg for the original exenatide 5 µg arm and -2.1±0.3 kg for the original 10 µg arm. At week 82, the decrease was -4.0±0.3 kg (95% CI, -4.6 to -3.4). The total cohort experienced a decrease in body weight of -3.3±0.2 kg (95% CI, -2.8 to -3.7; *P* value not reported). At week 82, patients in the completer cohort who had a baseline BMI ≥30 kg/m^2 experienced a greater decrease in mean weight from baseline of -4.4±0.4 kg compared to -3.2±0.5 kg in patients with a baseline BMI <30 kg/m^2 (*P* values not reported). Of the patients in the completer cohort who had a baseline HbA_{1c} >7.0%, 44% achieved an HbA_{1c} ≤7.0% at week 82. Patients with a baseline HbA_{1c} ≥9.0% experienced a greater decrease (-1.9±0.2%) compared to those with a baseline HbA_{1c}<9.0% (-0.7±0.1%) (*P* values were not reported). The most common reasons for withdrawal were administrative (study site closure) (12%), withdrawal of consent (11%), and adverse events (7%) (*P* values were not reported). In the total cohort, nausea and hypoglycemia were reported in ranges of 14 to 27% and 8 to 15% of patients, respectively (*P* values not reported).
Blonde et al[13] Exenatide 5 µg SC BID or exenatide 5 µg SC BID for 4 weeks, followed by 10 µg SC BID All patients also received existing	IA, MC, OL (Ratner et al[9] and Riddle et al[12]) Type 2 diabetics	N=551 52 weeks (82 weeks total)	Primary: Change in baseline HbA_{1c} and safety in the completer cohort (those patients who completed 82 weeks of exenatide therapy) and total cohort (ITT population)	Primary: At week 30, the completer cohort experienced a significant decrease in HbA_{1c} of -0.9±0.1%, and this decrease was maintained at week 82, with a decrease of -1.1±0.1% (95% CI, -1.0 to -1.3; *P* value not reported). The total cohort experienced a decrease at week 82 of -0.8±0.1% (95% CI, -0.6 to -0.9; *P* value not reported). Of the 551 ITT population, 314 (57%) patients completed the ES. Reasons for withdrawal included withdrawal of consent (11%), adverse events (7%), loss of glucose control (4%), and other (21%) (*P* values were not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
metformin and sulfonylurea therapies.			Secondary: Change in baseline FPG and weight, change in baseline weight and HbA_{1c} stratified by baseline BMI and HbA_{1c}, change in lipid profile	In the total cohort, nausea and hypoglycemia were reported in ranges of 14 to 29% and 7 to 12% of patients, respectively (*P* values not reported). Secondary: At week 30, the completer cohort experienced a decrease in FPG of -0.7±0.1 mmol/L (*P* value not reported). At week 82, the decrease was -0.9±0.2 mmol/L (*P* value not reported). The total cohort FPG levels were not reported. At week 30, the completer cohort group experienced a decrease in body weight of -2.1±0.2 kg and at week 82 the decrease was -4.4±0.3 kg (95% CI, -3.8 to -5.1; *P* value not reported). At week 82, the total cohort experienced a decrease in body weight of -3.5±0.2 kg (95% CI, -3.1 to -4.0; *P* value not reported). At week 82, patients in the completer cohort who had a baseline BMI ≥40 kg/m^2 experienced a decrease of -7 kg compared to -2 kg in patients with a baseline BMI <25 kg/m^2 (*P* values not reported). In the completer cohort, of those patients whose baseline HbA_{1c} was >7.0%, 39 and 48% achieved HbA_{1c} ≤7.0% at weeks 30 and 82, respectively. At week 82, a greater decrease in HbA_{1c} was achieved in patients who had a baseline HbA_{1c} ≥9.0% (-2.0±0.2) compared to those with a baseline HbA_{1c} <9.0% (-0.8±0.1) (*P* values were not reported). In the completer cohort, of the lipid levels measured, significant benefits were observed in HDL-C (4 mg/dL; 95% CI, 3.7 to 5.4) and TG (-38.6 mg/dL; 95% CI, -55.5 to -21.6) at week 82 (*P* values not reported).
Buse et al[14] Exenatide 5 µg SC BID or exenatide 5 µg SC BID for 4 weeks, followed by 10 µg SC BID	IA, OL (Ratner et al[9], Riddle et al[12], and Blonde et al[13]) Type 2 diabetics	N=521 104 weeks (2 years total)	Primary: Change in baseline HbA_{1c}, weight, and hepatic biomarkers; safety Secondary: Not reported	Primary: At week 104, exenatide significantly decreased HbA_{1c} by -1.1% (95% CI, -1.3 to -1.0; *P*<0.001). At week 104, exenatide significantly decreased weight by -4.7 kg (95% CI, -5.4 to -4.0; *P*<0.001). At Week 104, exenatide significantly decreased ALT by -5.3 IU/L (95% CI, -

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
All patients also received existing metformin and sulfonylurea therapies.				7.1 to -3.5; *P*<0.05) and decreased AST by -2.0 IU/L (95% CI, -3.3 to -0.8; *P*<0.05). Adverse events with an overall incidence ≥10% during 104 weeks of treatment were reported with the following proportion of patients affected: nausea (8 to 39%), upper respiratory tract infections (2 to 10%), and hypoglycemia (<1 to 13%) (*P* values were not reported). Secondary: Not reported
Klonoff et al[15] Exenatide 5 µg SC BID or exenatide 5 µg SC BID for 4 weeks, followed by 10 µg SC BID All patients also received existing metformin and sulfonylurea therapies.	IA, OE, OL (Ratner et al[9], Riddle et al[12], and Blonde et al[13]) Type 2 diabetics	N=217 156 weeks (3 years total)	Primary: Change in baseline HbA_{1c}, weight, and ALT; safety Secondary: Not reported	Primary: At Week 156, exenatide significantly decreased HbA_{1c} by -1.0±0.1% (*P*<0.0001). At Week 156, exenatide significantly decreased weight by -5.3±0.4 kg (*P*<0.0001). At Week 156, exenatide significantly decreased ALT by -10.4±1.5 IU/L in patients with elevated ALT at baseline (*P*<0.0001). The most frequently reported adverse event was mild to moderate nausea. Secondary: Not reported
Viswanathan et al[16] Exenatide 5 µg SC BID vs control group (patients who discontinued exenatide therapy within 2 weeks on initiation due to	RETRO Obese type 2 diabetic patients not adequately controlled despite treatment with oral hypoglycemic agents and insulin and HbA_{1c} >7.0%	N=52 26 weeks	Primary: Change in baseline body weight, HbA_{1c}, and insulin dose Secondary: Change in baseline TC, TG, DBP, SBP, and high-sensitivity CRP; safety	Primary: Exenatide-treated patients experienced a significant decrease in body weight of -6.46±0.80 kg (*P*<0.001) compared to the patients in the control group who experienced a significant weight gain of 2.4±0.6 kg (*P*<0.001). Exenatide-treated patients experienced a decrease in HbA_{1c} (-0.60±0.21%; *P*=0.007). The patients in the control group also experienced a decrease in HbA_{1c} (-8.4±0.5%; *P* value not reported). Exenatide-treated patients experienced a significant decrease in rapid-acting insulin requirements from 50.4±6.7 to 36.6±5.1 units (*P*<0.02) and for mixed insulin from 72.9±15.6 to 28.3±14.8 units (*P*<0.02). Insulin

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
insurance-related, personal or economic reasons) The dosages of rapid-acting and mixed insulin were reduced by 10% in patients with HbA_{1c} <7.5%. Subsequent dosage adjustments were made carefully based on ambient glucose concentrations.				requirements for the control group were not reported. Secondary: Exenatide-treated patients experienced a significant decrease in TC from 163.9±8.2 to 149.8±5.9 mg/dL (*P*=0.03) compared to the patients in the control group who experienced a decrease from 168.1±16.3 to 144.33±10.39 mg/dL (*P*=0.08). Exenatide-treated patients experienced a significant decrease in TG from 202.5±28.8 to 149.9±17.3 mg/dL (*P*=0.01) compared to the patients in the control group who experienced a decrease from 182.7±23.9 to 171.1±39.2 mg/dL (*P*=0.91). Exenatide-treated patients experienced a significant decrease in SBP of -9.2±3.3 mm Hg (*P*=0.02). Data for the control group were not reported. Neither group experienced a reduction in DBP. Exenatide-treated patients experienced a significant decrease in high-sensitivity CRP of -34.0±14.3% (*P*=0.05). Data for the control group were not reported. Four patients receiving exenatide experienced severe nausea during treatment which led to discontinuation. Mild nausea was experienced by several other patients that did not interfere with therapy. Hypoglycemia (glucose <60 mg/dL) was rare and did not lead to any hospital admissions. No other adverse events were observed.
Zinman et al[17] Exenatide 5 µg SC BID for 4 weeks, followed by 10 µg SC BID vs placebo	MC, PC, RCT Type 2 diabetics 21 to 75 years of age with a stable dose of a TZD (rosiglitazone ≥4 mg/day or pioglitazone ≥30 mg/day) for ≥4 months before screening, alone or in	N=233 16 weeks	Primary: Change in baseline HbA_{1c} Secondary: FPG, body weight, self-monitored blood glucose concentrations, safety	Primary: Exenatide significantly decreased HbA_{1c} compared to placebo (-0.89±0.09 vs 0.09±0.10%; *P*<0.001). Secondary: Exenatide significantly decreased FPG compared to placebo (-1.59±0.22 vs 0.10±0.21 mmol/L; *P*<0.001). Exenatide significantly decreased weight compared to placebo (treatment difference, -1.51 kg; *P*<0.001).

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All patients also received existing TZD therapy (with or without metformin).	combination with a stable dose of metformin for 30 days, HbA_{1c} 7.1 to 10.0%, BMI 25 to 45 kg/m^2, and a history of stable body weight (≤10% variation) for ≥3 months before screening			Exenatide-treated patients achieved significantly decreased self-monitored blood glucose profiles at each measurement throughout the day at week 16 compared to baseline (*P*<0.001) and placebo treated patients (*P*<0.001). Adverse events that were reported more commonly with exenatide included nausea (39.7 vs 15.2%; 95% CI, 12.7 to 36.3), vomiting (13.2 vs 0.9%; 95% CI, 5.2 to 19.5), and dyspepsia (7.4 vs 0.9%; 95% CI, 0.7 to 12.4).
Buse et al[18] Exenatide 5 µg SC BID for 4 weeks, followed by 10 µg SC BID vs placebo All patients also received optimized insulin glargine dosing (at randomization, patients with HbA_{1c} levels >8.0% continued to receive current insulin glargine dose; those with HbA_{1c} ≤8.0% decreased their dose by 20%; these doses were maintained for 5 weeks, after which patients began to	DB, MC, PC, RCT Type 2 diabetics ≥18 years of age who had been receiving insulin glargine at a minimum of 20 units/day without any other insulin, alone or in combination with a stable dose of metformin or pioglitazone (or both agents) for ≥3 months, HbA_{1c} 7.1 to 10.5%, BMI ≤45 kg/m^2, and stable body weight over past 3 months	N=261 30 weeks	Primary: Change in baseline HbA_{1c} Secondary: Proportion of patients achieving HbA_{1c} ≤7.0 or ≤6.5%; 7-point self-monitored glucose concentrations; change in baseline body weight, waist circumference, and insulin dose; safety	Primary: Exenatide significantly decreased HbA_{1c} compared to placebo (-1.74 vs -1.04%; *P*<0.001). Secondary: A significantly greater proportion of patients receiving exenatide achieved an HbA_{1c} ≤7.0% (60 vs 35%; treatment difference, 25%; 95% CI, 12 to 39; *P*<0.001). Similar results were observed with HbA_{1c} ≤6.5% (40 vs 12%; treatment difference, 28%; 95% CI, 17 to 39; *P*<0.001). With regards to 7-point self-monitored glucose concentrations, exenatide significantly decreased concentrations during morning and evening time points compared to placebo (*P*<0.001), but no at midday (*P*=0.320). Exenatide significantly decreased body weight compared to placebo (-1.8 vs 1.0 kg; *P*<0.001), but no difference between treatments was observed in waist circumference (*P*=0.23). The number of hypoglycemic events per-participant per-year did not differ between the exenatide and placebo (*P*=0.49).

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titrate to achieve a fasting glucose level ≤100 mg/dL).				
Okerson et al[19] Exenatide 5 µg SC BID for 4 weeks, followed by 10 µg SC BID vs placebo or insulin All patients also received existing antidiabetic treatment regimens.	Post-hoc analysis (6 RCTs) Type 2 diabetics ≥18 years of age with HbA_{1c} ≥6.5 to ≤11.0%, BMI ≥25 to ≤45 kg/m^2, and stable body weight	N=2,171 24 to 52 weeks	Primary: Change in baseline BP and pulse pressure Secondary: Not reported	Primary: In the overall study population, by the end of the six month trial period, exenatide was associated with a significantly greater decrease in SBP compared to placebo (-2.2±0.56 vs 0.6±0.56 mm Hg; treatment difference, -2.8±0.75 mm Hg; *P*=0.002) and insulin (-4.5±0.60 vs -0.9±0.60 mm Hg; treatment difference, -3.7±0.85 mm Hg; *P*<0.0001). In contrast, DBP was minimally decreased and not different between exenatide and placebo (-0.7±0.33 vs -0.2±0.33 mm Hg; *P*=0.21) or insulin (-1.6±0.35 vs -0.8±0.36 mm Hg; *P*=0.16). No differences in the proportions of patients altering the number, type, or intensity of ongoing antihypertensive regimens were observed between treatments (data not reported). Patients with abnormal SBP at baseline achieved the greatest decreases with exenatide (exenatide vs placebo, -8.3 vs -4.5 mm Hg; treatment difference, -3.8 mm Hg; *P*=0.0004 and exenatide vs insulin, -8.3 vs -4.2 mm Hg; treatment difference, -4.0 mm Hg; *P*<0.0001). In patients with normal BP at baseline, no differences in the decreases in SBP or DBP were observed between any of the treatments (*P* values not reported). Pulse pressure effects trended similarly to SBP effects, with the most pronounced decrease occurring in exenatide-treated patients with baseline pulse pressures ≥40 mm Hg. In this subgroup, the reduction in pulse pressure was significantly greater with exenatide compared to placebo (-3.5 vs -0.5 mm Hg; treatment difference, -2.9 mm Hg; *P*<0.0001) and insulin (-4.0 vs -0.9 mm Hg; treatment difference, -3.0 mm Hg; *P*<0.0001). By the end of the six month treatment period, a significantly greater proportion of exenatide-treated patients with elevated baseline SBP (26%) achieved the SBP goal for type 2 diabetics compared to insulin (treatment difference, 19%; *P*=0.03); however, no treatment effect on DBP was observed. In contrast, although no significant exenatide-related shifts were observed in SBP classifications, a significantly greater proportion of exenatide-treated patients were favorably shifted from a baseline classification of “abnormal DBP” to “normal DBP” compared to placebo

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				(treatment difference, 41.4 vs 32.4%; *P*=0.02). Secondary: Not reported
Derosa et al[20] Exenatide 5 µg SC BID for 4 weeks, followed by 10 µg SC BID vs glyburide 2.5 mg TID for 4 weeks, followed by 5 mg TID All patients also received existing metformin therapy.	MC, RCT, SB Type 2 diabetic patients ≥18 years of age with an HbA_{1c} >8.0%, BMI ≥25 to ≤35 kg/m^2 who were receiving therapy with metformin (mean dosage 1,500±500 mg/day)	N=128 12 months	Primary: Treatment effect on body weight, glycemic control, β cell function, insulin resistance, and inflammatory state Secondary: Not reported	Primary: At 12 months, exenatide-treated patients achieved a significant decrease in body weight and BMI (*P*<0.001 for both), whereas there was a significant increase with glyburide (*P*<0.05 for both). Body weight and BMI values achieved with exenatide were significantly lower compared to glyburide after six (*P*<0.05 for both), nine (*P*<0.01 for both), and 12 months (*P*<0.001 for both). Significant decreases in HbA_{1c}, FPG, and PPG compared to baseline with both treatments (exenatide, *P*<0.001 for all; glyburide, *P*<0.001 for all), without any differences between the two treatments were achieved at 12 months (*P* values not reported). Fasting plasma insulin was significantly decreased with exenatide after none and 12 months (*P*<0.05 and *P*<0.01), whereas it significantly increased with glyburide (*P*<0.05 and *P*<0.01). Exenatide significantly decreased fasting plasma insulin compared to glyburide (*P*<0.05). HOMA-B significantly increased after nine and 12 months with exenatide (*P*<0.05 and *P*<0.01), whereas there were no variations with glyburide (*P* values not reported). Increases in HOMA-B with exenatide were significantly greater compared to glyburide at 12 months (*P*<0.05). A similar decrease in plasma proinsulin after nine (*P*<0.05 for both) and 12 (*P*<0.01 for both) months compared to baseline with both treatments was observed, as was a significant decrease of plasma proinsulin:fasting plasma insulin ratio with glyburide (*P*<0.05 and *P*<0.01), but not with exenatide (*P* values not reported). HOMA-IR significantly decreased after nine and 12 months with exenatide (*P*<0.05 and *P*<0.01), but not with glyburide (*P* values not reported). Decreases in HOMA-IR were significantly greater with exenatide compared to glyburide after nine (*P*<0.05) and 12 months (*P*<0.01). Resistin and

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				retinal binding protein-4 significantly decreased at six (*P*<0.05 for both), nine (*P*<0.01 for both), and 12 (*P*<0.001) months with exenatide, whereas an increase with glyburide was observed (*P* values not reported). Decreases in resistin and retinal blinding protein-4 were significantly greater with exenatide compared to glyburide at six (*P*<0.05 for both) and nine (*P*<0.01 for both) months. A significant decrease in high-sensitivity CRP was achieved after six (*P*<0.05), nine (*P*<0.01), and 12 (*P*<0.001) months with exenatide, whereas there were no variations with glyburide (*P* values not reported). High-sensitivity CRP with exenatide was significantly lower compared to glyburide at 12 months (*P*<0.05). Secondary: Not reported
Heine et al[21] Exenatide 5 µg SC BID for 4 weeks, followed by 10 µg SC BID vs insulin glargine QD at bedtime (forced insulin glargine titration to fasting blood sugar <100 mg/dL) All patients also received existing metformin and sulfonylurea therapies.	OL, RCT Type 2 diabetic patients 30 to 75 years of age not adequately controlled (HbA_{1c} 7.0 to 10.0%) with combination metformin and sulfonylurea therapy at maximally effective doses, BMI 25 to 45 kg/m^2, and a history of stable body weight (≤10% variation for ≥3 months before screening)	N=551 26 weeks	Primary: Change in baseline HbA_{1c} Secondary: FPG, proportion of patients achieving fasting glucose <100 mg/dL, body weight, safety	Primary: Similar decreases in HbA_{1c} were achieved with exenatide and insulin glargine (-1.11%; 95% CI, -0.123 to 0.157; *P* value not reported). Secondary: A significant decrease in FPG was observed with insulin glargine (-51.5 mg/dL; *P*<0.001), but not with exenatide (-25.7 mg/dL; *P* value not reported). Insulin glargine significantly decreased FPG compared to exenatide (95% CI, 20 to 34). A significantly greater proportion of insulin glargine-treated patients (21.6%) achieved fasting glucose <100 mg/dL compared to exenatide treated patients (8.6%; *P*<0.001). Exenatide significantly decreased weight compared to insulin glargine (-2.3 vs 1.8 kg; *P*<0.001). Similar rates of hypoglycemia were reported with both treatments (95% CI, -1.3 to 3.4 events/patient-year). Exenatide resulted in a higher incidence of daytime hypoglycemia (95% CI, 0.4 to 4.9 events/patient-year; *P* value not reported) and a lower rate of nocturnal hypoglycemia compared to insulin

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				glargine (95% CI, -2.3 to -0.9 events/patient-year; *P* value not reported). A significantly higher incidence of gastrointestinal side effects, including nausea (57.1 vs 8.6%; *P*<0.001), vomiting (17.4 vs 3.7%; *P*<0.001), diarrhea (8.5 vs 3.0%; *P*=0.006), upper abdominal pain (*P*=0.012), constipation (*P*=0.011), dyspepsia (*P*=0.011), decreased appetite (*P*=0.021), and anorexia (*P*=0.002) were reported with exenatide compared to insulin glargine. Withdrawals due to adverse events occurred in 9.5 and 0.7% of patients receiving exenatide and insulin glargine (*P* value not reported).
Secnik Boye et al[22] Exenatide 5 µg SC BID for 4 weeks, followed by 10 µg SC BID vs insulin glargine QD at bedtime (forced insulin glargine titration to fasting blood sugar <100 mg/dL) All patients also received existing metformin and sulfonylurea therapies.	Post-hoc analysis (Heine et al[21]) Type 2 diabetic patients 30 to 75 years of age not adequately controlled (HbA_{1c} 7.0 to 10.0%) with combination metformin and sulfonylurea therapy at maximally effective doses, BMI 25 to 45 kg/m^2, and a history of stable body weight (≤10% variation for ≥3 months before screening)	N=455 26 weeks	Primary: Patient-reported health outcome measures (DSC-R, DTSQ, EQ-5D, SF-36, and TFS) Secondary: Not reported	Primary: Both treatments were associated with significant improvements in patient-reported health outcome measures as demonstrated by DSC-R, DTSQ, EQ-5D, and SF-36 scores (*P*<0.05 for all measures). There was no difference between treatments in any of the outcomes measured (*P*>0.05 for all measures). Neither treatment was associated with a significant improvement in TFS scores (*P*=0.93 for both). Secondary: Not reported
Davies et al[23] Exenatide 5 µg SC BID for 4 weeks, followed by 10 µg SC BID vs	MC, OL, RCT Patients with type 2 diabetes, BMI >27 kg/m^2, inadequate glycemic control (HbA_{1c} 7.5 to 10.0%), despite treatment with	N=235 26 weeks	Primary: Proportion of patients achieving HbA_{1c} ≤7.4% and weight gain ≤1 kg Secondary: Change in baseline	Primary: Compared to insulin glargine, exenatide was significantly more effective in achieving the primary composite endpoint (53.4 vs 19.8%; OR, 4.71; 95% CI, 2.62 to 8.46; *P*<0.001). A post-hoc analysis using an endpoint HbA_{1c} ≤7.0% and a weight gain ≤1 kg revealed similar results (39.0 vs 18.1%; OR, 2.90; 95% CI, 1.59 to 5.28; *P*< 0.001).

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insulin glargine (titrated weekly according to a target fasting plasma glucose ≤100 mg/dL) All patients received existing antidiabetic treatment regimens.	stable doses of 2 or 3 oral antidiabetic agents (metformin, sulfonylurea, and TZD) for ≥3 months before randomization, and ≥1 cardiovascular risk factor		HbA_{1c}, weight, FPG, lipid profile, and BP	Secondary: There were no difference between exenatide and insulin glargine in the decrease in HbA_{1c} (-1.25 vs -1.26%, respectively; *P*=0.924). Insulin glargine significantly decreased FPG compared to exenatide (-3.61 vs -2.12 mmol/L; *P*<0.001). There were no differences between the two treatments in regard to changes in LDL-C, TG, or TC (*P*=0.471, *P*=0.650, and *P*=0.125, respectively). Changes in DBP were not different between the two treatments (*P*=0.158); however, SBP was significantly decreased with exenatide compared to insulin glargine (-2.9 vs 0.7 mm Hg; *P*=0.034).
Bunck et al[24] Exenatide 5 µg SC BID for 4 weeks, followed by 10 µg SC BID vs insulin glargine (titrated based on self-monitored blood glucose levels) All patients also received existing metformin therapy.	RCT Type 2 diabetic patients 30 to 75 years of age with HbA_{1c} 6.5 to 9.5%, BMI 25 to 40 kg/m^2, and on a stable dose of metformin for ≥2 months	N=69 52 weeks	Primary: Treatment effect on β cell function Secondary: Glycemic control, body weight, safety	Primary: At baseline, both glucose- and arginine-stimulated C-peptide secretion did not differ between the treatments. After 52 weeks, exenatide demonstrated a significant increase in all measures of β cell function. Accordingly, exenatide significantly increased first- and second-phase glucose-stimulated C-peptide secretion by 1.53±0.11- and 2.85±0.22-fold, respectively (*P*<0.0001) compared to insulin glargine. The C-peptide response to arginine during hyperglycemia increased 3.19±0.24-fold from pre-treatment with exenatide compared to a 1.31±0.07-fold increase with insulin glargine (between-group difference, 2.46±0.20-fold; *P*<0.0001). When treatments were stopped, measures of β cell function returned to pre-treatment values with both treatments. Secondary: Both treatments resulted in similar decreases in HbA_{1c} (-0.8±0.1 vs -0.7±0.2%, respectively; *P*=0.55), with both achieving an HbA_{1c} of 6.8% at 52 weeks. Insulin glargine achieved a significantly greater decrease in FPG compared to exenatide (-2.9±0.4 vs -1.6±0.3 mmol/L, respectively; *P*<0.0001), whereas self-monitored blood glucose concentration profiles demonstrated significantly greater decreases in PPG excursions with

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				exenatide. When the treatments were stopped, both HbA_{1c} and FPG increased in both treatment groups that were not different compared to pre-treatment values after 12 weeks of treatment. Fifty two weeks of treatment with exenatide resulted in a significantly greater lowering of body weight compared to insulin glargine (-3.6±0.6 vs 1.0±0.8 kg; between-group difference, -4.6±1.1 kg; *P*<0.0001). When treatments were stopped, body weight trended toward baseline values with both treatments (between-group difference, -2.4±11.0 kg; *P*=0.03). At baseline, insulin-mediated glucose uptake did not differ between the two treatments. Exenatide and insulin glargine improved insulin sensitivity to the same extent by 0.9±0.3 and 1.1±0.3 mg/(min/kg), respectively (*P*=0.49). The most frequently observed adverse event with exenatide was mild to moderate nausea (50%). Other gastrointestinal adverse events were reported more commonly with exenatide including vomiting, diarrhea, and abdominal distension. Hypoglycemia was observed more frequently with insulin glargine (24.2 vs 8.3%). There was no severe hypoglycemia events reported.
Bunck et al[25] Exenatide 5 µg SC BID for 4 weeks, followed by 10 µg SC BID (possible titration up to a maximum of 20 µg SC TID) vs insulin glargine (titrated based on self-monitored blood glucose levels)	Post-hoc analysis (Bunck et al[24]) Type 2 diabetic patients 30 to 75 years of age with HbA_{1c} 6.5 to 9.5%, BMI 25 to 40 kg/m^2, and on a stable dose of metformin for ≥2 months	N=60 52 weeks	Primary: Treatment effect on post-prandial lipidemia, glycemia, measures of oxidative stress Secondary: Not reported	Primary: No between-group differences in fasting lipid parameters were observed (data not reported). Treatment with exenatide significantly reduced PPG excursions, whereas treatment with insulin glargine did not, which resulted in a significant between-group difference change from pre-treatment (*P*<0.001). The observed effect was predominantly a result of the effect of exenatide on the breakfast meal. No between-group difference in glucose excursions following the lunch meal was observed (*P*=0.559). As exenatide predominantly lowers PPG excursions and insulin glargine lowers FPG, no between-group difference was observed in the total mal test glucose exposure (*P*=0.310). No correlation was found between changes in body weight and PPG excursions. Exenatide lead to significantly lower post-prandial malondialdehyde profiles

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All patients also received existing metformin therapy.				(*P*<0.001), whereas insulin glargine did not have such an effect (*P*=0.527), resulting in a significant between-treatment group difference (*P* value not reported). The post-prandial oxidative LDL:LDL-C ratio was significantly reduced with exenatide (*P*=0.019), whereas insulin glargine did not affect this oxidative stress marker (*P*=0.711). No between-group difference was observed (*P*=0.184). Secondary: Not reported
Nauck et al[26] Exenatide 5 µg SC BID for 4 weeks, followed by 10 µg SC BID vs insulin aspart BID All patients received existing metformin and sulfonylurea therapies.	MC, OL, RCT Type 2 diabetics 30 to 75 years of age who had suboptimal glycemic control despite receiving optimally effective metformin and sulfonylurea therapy for ≥3 months, HbA_{1c} ≥7.0 to ≤11.0%, BMI ≥25 to ≤40 kg/m^2, and a history of stable body weight for the last 3 months	N=501 52 weeks	Primary: Change in baseline HbA_{1c}, weight, FPG, and PPG; adverse events Secondary: Not reported	Primary: There was no difference in the decrease in HbA_{1c} between exenatide and insulin aspart (-1.04 vs -0.89%; 95% CI, -0.32 to 0.01; *P*=0.067). Exenatide significantly decreased weight compared to insulin aspart (-2.5 vs 2.9 kg; 95% CI, -5.9 to -5.0; *P*<0.001). Exenatide (-1.8 mmol/L) and insulin aspart (-1.7 mmol/L) resulted in significant (*P*<0.001 for both) decreases in FPG with no difference between the two treatments (95% CI, -0.6 to 0.4; *P*=0.689). Insulin aspart resulted in significantly decreased glucose concentrations at pre-breakfast (*P*=0.037), pre-lunch (*P*=0.004), and 0300 hour (*P*=0.002) time points. Exenatide resulted in significantly greater decreases in PPG excursions following morning (*P*<0.001), midday (*P*=0.002), and evening meals (*P*<0.001). The withdrawal rate was 21.3 and 10.1% with exenatide and insulin aspart. Adverse events that were more commonly reported with exenatide included nausea (33.2 vs 0.4%), vomiting (15.0 vs 3.2%), and diarrhea (9.5 vs 2.0%). Secondary: Not reported
Drucker et al[27] DURATION-1	AC, OL, non-inferiority, RCT	N=303 30 weeks	Primary: Change in baseline HbA_{1c}	Primary: Both treatments achieved significant decreases in HbA_{1c}, with a decrease at week 30 of -0.33±0.10% (95% CI, -0.54 to -0.12). Decreases were

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Exenatide ER 2 mg SC once weekly vs exenatide 5 µg SC BID for 28 days, followed by 10 µg BID	Type 2 diabetics for ≥2 months prior to screening; ≥16 years of age; HbA_{1c} 7.1 to 11.0%; FPG <16 mmol/L; BMI 25 to 45 kg/m^2; and therapy with diet modification and exercise, or treatment with metformin, sulfonylurea, TZD, or any combination of 2 of these agents		Secondary: Safety and tolerability; FPG and PPG; body weight; fasting glucagon; fasting lipids; BP; proportion of patients achieving HbA_{1c} ≤7.0, ≤6.5, and ≤6.0%; exenatide antibodies	significantly greater with exenatide ER compared to exenatide (-1.9±0.1 vs -1.5±0.1%; *P*=0.0023). Significant decreases with both treatments were observed as early as week six, and the mean decrease was significantly greater with exenatide ER compared to exenatide by week 10, and the difference persisted throughout the remainder of the trial. Overall, decreases were consistent across all treatment background therapies and did not vary notably with sex or age (>65 years vs <65 years). Secondary: Adverse events reported in >10% of patients include nausea (26.4 vs 34.5%), vomiting (10.8 vs 18.6%), injection site pruritis (17.6 vs 1.4%), upper respiratory tract infection (8.1 vs 17.2%), diarrhea (13.5 vs 13.1%), constipation (10.8 vs 6.2%), injection site bruising (4.7 vs 10.3%), and urinary tract infection (10.1 vs 8.3%). Gastrointestinal complaints were the most frequently reported adverse events with exenatide. Treatment-related nausea was reported in significantly fewer patients receiving exenatide ER (*P* value not reported). Reported nausea with both treatments was predominantly mild in intensity, and no severe nausea was reported with exenatide ER. Injection site pruritis with either treatment was typically mild in intensity, and resolved with continued treatment. No episodes of major hypoglycemia were reported with either treatment, and the incidence of minor hypoglycemia was low. Withdrawals due to adverse events were 6.1 vs 4.8% (*P* value not reported). No clinically significant abnormalities in vital signs; electrocardiogram reports; or hematological, chemistry, or urinalysis values were reported. The incidence of serious adverse events was low (5.4 vs 3.4%). No cases of pancreatitis were reported with either treatment. Both treatments achieved significant decreases in FPG and PPG, with exenatide ER achieving significantly greater decreases in FPG compared to exenatide (-2.3±0.2 vs -1.4±0.2 mmol/L; 95% CI, -1.3 to -5.2; *P*<0.0001). Analysis across all background treatments revealed similar results. Similar results were observed with PPG (data reported in graphical form only). Both treatments resulted in significant improvements in 7-point self-monitored glucose concentrations profiles. Body weight decreased progressively with both treatments (-3.7±0.5 vs -

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				3.6±0.5 kg; 95% CI, -1.3 to 1.1; *P*=0.89). At week 30, the mean percentage of weight loss from baseline was -3.6 vs -3.7% with exenatide ER and exenatide (*P*>0.05). Both treatments significantly decreased FPG and PPG (*P* values not reported). Exenatide ER achieved significantly greater decreases in TC (-0.31±0.06 vs -0.10±0.06 mmol/L) and LDL-C (-0.13±0.05 vs 0.03±0.05 mmol/L) compared to exenatide (*P* values not reported). TG decreased with both treatments (-15 vs -11%; *P* value not reported). Both treatments achieved significant improvements in SBP and DBP (*P* values not reported). A significantly greater proportion of patients receiving exenatide ER achieved an HbA_{1c} ≤7.0% compared to patients receiving exenatide (77 vs 61%; *P*=0.0039). Forty nine and 25% of patients receiving exenatide ER achieved HbA_{1c} ≤6.5 and ≤6.0%. Anti-exenatide antibody levels were significantly higher with exenatide ER compared to exenatide (*P*=0.0002), but most antibodies were either not detectable or of low titer.
Buse et al[28] DURATION-1 Exenatide ER 2 mg SC once weekly (continued exenatide ER) vs exenatide ER 2 mg SC once weekly (switched to exenatide	ES (DURATION-1[27]) Type 2 diabetics for ≥2 months prior to screening; ≥16 years of age; HbA_{1c} 7.1 to 11.0%; FPG <16 mmol/L; BMI 25 to 45 kg/m^2; and therapy with diet modification and exercise, or treatment with metformin,	N=258 22 weeks (52 weeks total)	Primary: Efficacy, body weight, glucose control, lipid and BP profile, safety and tolerability Secondary: Not reported	Primary: During the 22 weeks, patients who continued exenatide ER maintained improvements in HbA_{1c}, with a decrease of -2.1% (95% CI, -2.2 to -1.9) at week 30 and -2.0% (95% CI, -2.1 to -1.8) at week 52. Patients who switched to exenatide ER (week 30 HbA_{1c} decrease, -1.8%; 95% CI, -1.9 to -1.6) exhibited further improvements in glycemic control and achieved the same reduction (-2.0%) and mean HbA_{1c} (6.6%) at week 52 compared to patients who continued exenatide ER. After 52 weeks, 71 and 54% of all patients achieved an HbA_{1c} ≤7.0 and ≤6.5% (similar between the two cohorts). In patients with a baseline HbA_{1c} <9.0%, the decrease at week 52 was -1.2 (95% CI, -1.4 to -1.1) and -1.3% (95% CI, -1.5 to -1.2%) in patients who continued exenatide ER and in those who switched to exenatide ER. Larger decreases in HbA_{1c} were observed in patients with a

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ER) Patients enrolled in DURATION-1 who were randomized to exenatide 10 µg SC BID were transitioned to exenatide ER 2 mg SC once weekly after the initial 30 week trial period.	sulfonylurea, TZD, or any combination of 2 of these agents			baseline HbA_{1c} ≥9.0% (-2.8 [95% CI, -3.1 to -2.5] vs -2.6% [95% CI, -3.0 to -2.3]). Body weight decreased similarly with both treatments. At week 52, the decreases in body weight were -4.1 (95% CI, -5.3 to -2.9) vs -4.5 kg (95% CI, -5.7 to -3.3) in patients who continued exenatide ER and those who switched to exenatide ER. In patients who continued exenatide ER, the decreases in FPG achieved at week 30 (-46 mg/dL; 95% CI, -52 to -40) were maintained throughout the 52 weeks (-47 mg/dL; 95% CI, -53 to -41). Patients who switched to exenatide ER achieved a similar decrease in FPG at week 52 (-43 mg/dL; 95% CI, -49 to -37). Subsequent to week 30, patients switched to exenatide ER experienced a transient rise in mean FPG followed by a rapid decreases within two weeks after switching treatment. Clinically significant improvements in BP were observed in patients who continued exenatide ER for 52 weeks. (SBP, -6.2 mm Hg; 95% CI, -8.5 to -3.9 and DBP, -2.8 mm Hg; 95% CI, -4.3 to -1.3) and in patients who switched to exenatide ER (SBP, -3.8 mm Hg; 95% CI, -6.1 to -1.5 and DBP, -1.8 mm Hg; 95% CI, -3.2 to -0.3). Fifty and 36% of patients in the two treatment groups who had elevated SBP at baseline achieved normal SBP at week 52. Improvements in lipid profiles were achieved in both treatment groups, with clinically significant decreased in TC (-9.6 [95% CI, -14.8 to -4.3] and -9.0 mg/dL [95% CI, -14.5 to -3.6]) and TG (-15%; 95% CI, -21 to -9). Treatment-emergent adverse events that occurred for the first time or worsened during the 22 week long second phase were similar to those observed during the initial 30 weeks of treatment. Nausea was predominantly mild, and no severe cases were reported. Twenty one patients (four vs 17) reported injection site-related adverse events. Mild to moderate injection site pruritis was observed after switching from exenatide to exenatide ER in six patients. No cases of pancreatitis were reported. Secondary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Not reported
Bergenstal et al[29] DURATION-2 Exenatide ER 2 mg SC once weekly vs sitagliptin 100 mg QD vs pioglitazone 45 mg QD All patients received existing metformin therapy.	DB, DD, MC, PG, RCT Type 2 diabetics ≥18 years of age, receiving a stable metformin therapy for ≥2 months, HbA_{1c} 7.1 to 11.0%, and BMI 25 to 45 kg/m^2	N=514 26 weeks	Primary: Change in baseline HbA_{1c} Secondary: Proportion of patients achieving an HbA_{1c} ≤6.5 or ≤7.0%, FPG, 6-point self-monitored glucose concentrations, body weight, fasting lipid profile, fasting insulin profile, BP, cardiovascular risk markers, patient-reported QOL, safety	Primary: Exenatide ER (-1.5%; 95% CI, -1.7 to -1.4) significantly decreased HbA_{1c} compared to sitagliptin (-0.9% [95% CI, -1.1 to -0.7]; treatment difference, -0.6% [95% CI, -0.9 to -0.4]; *P*<0.0001) and pioglitazone (-1.2% [95% CI, -1.4 to -1.0]; treatment difference, -0.3% [95% CI, -0.6 to -0.1]; *P*=0.0165). Secondary: A significantly greater proportion of patients receiving exenatide achieved HbA_{1c} targets of ≤6.5 (*P*<0.0001 and *P*=0.0120) or ≤7.0% (*P*<0.0001 and *P*=0.0015) compared to patients receiving sitagliptin or pioglitazone. Exenatide ER (-1.8 mmol/L; 95% CI, -2.2 to -1.3) achieved significantly greater decreases in FPG compared to sitagliptin (-0.9 mmol/L [95% CI, -1.3 to -0.5]; treatment difference, -0.9 mmol/L [95% CI, -0.3 to -1.4]; *P*=0.0038), but not pioglitazone (-1.5 mmol/L [95% CI, -1.9 to -1.1]; treatment difference, -0.2 mmol/L [95% CI, -0.8 to 0.3]; *P*=0.3729). A significantly greater proportion of patients receiving exenatide ER (60%) achieved the FPG goal of ≤7 mmol/L compared to patients receiving sitagliptin (35%; *P*<0.0001), but no difference was observed between patients receiving pioglitazone (52%; *P*=0.1024). In all measurements of the 6-point self-monitored glucose concentrations profile, decreases at week 26 were significantly greater with exenatide ER compared to sitagliptin, but not pioglitazone (*P* values not reported). Weight loss with exenatide ER (-2.3 kg; 95% CI, -2.9 to -1.7) was significantly greater compared to sitagliptin (difference, -1.5 kg; 95% CI, -2.4 to -0.7; *P*=0.0002) and pioglitazone (difference, -5.1 kg; 95% CI, -5.9 to -4.3; *P*<0.0001). Pioglitazone was the only treatment to achieve significant decreases in TG (-16%; 95% CI, -21 to -11) and increases in TC (0.16 mmol/L; 95% CI, 0.04 to 0.28), the former of which was significantly different compared to exenatide ER (-5%; 95% CI, -11 to 0).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Fasting insulin was significantly increased after 26 weeks with exenatide ER (3.6 µIU/mL; 95% CI, 1.6 to 5.6) compared to sitagliptin (0.4 µIU/mL [95% CI, -1.6 to 2.3]; treatment difference, 3.2 µIU/mL [95% CI, 0.6 to 5.8]; *P*=0.0161) and pioglitazone (-3.9 µIU/mL [95% CI, -5.9 to -2.0]; treatment difference, 7.5 µIU/mL [95% CI, 4.9 to 10.1]; *P*<0.0001). Decreases in SBP with exenatide ER were significantly greater compared to sitagliptin (treatment difference, -4 mm Hg; 95% CI, -6 to -1), but not pioglitazone (data reported in graphical form only). All treatments achieved significant improvements in high-sensitivity CRP and adiponectin. Exenatide ER was the only treatment to achieve a significant improvement in BNP and albumin:creatinine ratio, with the changes in BNP being significantly greater compared to sitagliptin and pioglitazone (*P* values not reported). All five domains of weight-related QOL and IWQOL total score were significantly improved with exenatide ER (IWQOL total score, 5.15; 95% CI, 3.11 to 7.19) and sitagliptin (4.56; 95% CI, 2.56 to 6.57), but not pioglitazone (1.20; 95% CI, -0.87 to 3.28), which improved only on self-esteem. Improvements in IWQOL with exenatide ER were significantly greater compared to sitagliptin (treatment difference, 3.94; 95% CI, 1.28 to 6.61; *P*=0.0038). All treatments achieved improvements in all domains of the PGWB and DTSQ total score, with greater improvement in overall satisfaction recorded with exenatide ER (3.96; 95% CI, 2.78 to 5.15) compared to sitagliptin (2.35 [95% CI, 1.19 to 3.51]; treatment difference, 1.61 [95% CI, 0.07 to 3.16]; *P*=0.0406). The most commonly reported adverse events with exenatide ER and sitagliptin were nausea (24 vs 10%, respectively) and diarrhea (18 vs 10%, respectively). Upper respiratory tract infection (10%) and peripheral edema (8%) were the most commonly reported adverse events with pioglitazone. No episodes of major hypoglycemia were reported.
Wyshman et al[30] DURATION-2	ES (DURATION-2[29]) Type 2 diabetics ≥18	N=319 26 weeks	Primary: Change in baseline HbA_{1c}, FPG, body	Primary: Patients who continued exenatide ER demonstrated significant 52 week improvements in HbA_{1c} (-1.6±0.1%), FPG (-1.8±0.3 mmol/L), and body

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Exenatide ER 2 mg SC once weekly (continued exenatide ER) vs exenatide ER 2 mg SC once weekly (switched to exenatide ER) Patients enrolled in DURATION-2 who were randomized to sitagliptin 100 mg QD or pioglitazone 45 mg QD were transitioned to exenatide ER 2 mg SC once weekly after the initial 26 week trial period.	years of age, receiving stable metformin therapy for ≥2 months, HbA_{1c} 7.1 to 11.0%, and BMI 25 to 45 kg/m^2	(52 weeks total)	weight, proportion of patients achieving an HbA_{1c} <7.0 or ≤6.5%, proportion of patients achieving FPG <7 mmol/L, and markers of cardiovascular risk at week 52 and from week 26 to 52; safety Secondary: Not reported	weight (-1.8±0.5 kg; *P*=0.0002 vs baseline). Patients originally receiving sitagliptin who switched to exenatide ER demonstrated significant incremental improvements in HbA_{1c} (-0.3±0.1%; *P*=0.0010), FPG (-0.7±0.2 mmol/L; *P*=0.0017), and body weight (-1.1±0.3 kg; *P*=0.0006). Patients originally receiving pioglitazone who switched to exenatide ER maintained HbA_{1c} and FPG improvements (week 52, -1.6±0.1% and -1.7±0.3 mmol/L, with significant weight loss; -3.0±0.3 kg; *P*<0.0001). No differences in the proportions of patients achieving target HbA_{1c} <7.0 or ≤6.5% were observed between weeks 26 and 52 in patients who continued exenatide ER and who switched to exenatide ER from pioglitazone. A significantly greater proportion of patients achieved both targets after switching from sitagliptin to exenatide ER (*P*<0.05 for both). Similar results were observed for the FPG target (<7 mmol/L) (*P*=0.0002). Patients who continued exenatide ER achieved greater SBP improvements at week 52 (-12.2 mm Hg; 95% CI, -16.1 to -8.3). Patients with abnormal SBP at 26 weeks who were receiving sitagliptin and pioglitazone, achieved greater SBP decreases (-11.3 [95% CI, -14.9 to -7.7] and -9.4 mm Hg [95% CI, -13.4 to -5.3], respectively) at week 52. Patients who continued exenatide ER maintained improvements in HDL-C at week 52; all other lipid variables were not different from baseline. Patients switched to exenatide ER from sitagliptin maintained HDL-C improvements and achieved a significant decrease in TC at week 52. Patients switched to exenatide ER from pioglitazone achieved significant decreases in HDL-C, LDL-C, and TC at week 52. Patients who continued exenatide ER achieved improvements in urinary albumin/creatinine ratio, BNP, and high-sensitivity CRP. The urinary albumin/creatinine ratio was significantly decreased for all treatment groups by week 52. Patients who switched to exenatide ER from sitagliptin and pioglitazone achieved significant reductions in BNP, with high-sensitivity CRP and plasminogen activator inhibitor-1 improvements observed after 26 weeks of initial treatment with pioglitazone were not maintained once switched to exenatide ER. Exenatide ER was well tolerated and adverse events were predominantly mild or moderate in intensity. Nausea was the most frequent adverse event

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				(continued exenatide ER, 5%; switched to exenatide ER from sitagliptin, 11%; switched to exenatide ER from pioglitazone, 10%). No major cases of hypoglycemia or pancreatitis were reported. Secondary: Not reported
Diamant et al[31] DURATION-3 Exenatide ER 2 mg SC once weekly vs insulin glargine SC QD All patients received existing background oral glucose-lowering regimens.	OL, PG, RCT Type 2 diabetics ≥18 years of age with suboptimum glycemic control despite maximum tolerated doses of metformin (stable dose of ≥1,500 mg ≥8 months) or combined metformin and sulfonylurea treatment ≥3 months, HbA_{1c} 7.1 to 11.0%, BMI 25 to 45 kg/m^2, and a stable body weight ≥3 months	N=456 26 weeks	Primary: Change in baseline HbA_{1c} Secondary: Proportion of patients achieving HbA_{1c} <7.0 or <6.5%, fasting serum glucose, self-monitored blood glucose concentrations, body weight, fasting lipid profile, BP, markers of cardiovascular risk, β cell function, insulin profile, patient-reported QOL, safety	Primary: Decreases in HbA_{1c} were significantly greater with exenatide ER (-1.5±0.05%) compared to insulin glargine (-1.3±0.06%; treatment difference, -0.16±0.07%; 95% CI, -0.29 to -0.03; *P*=0.017). In patients receiving exenatide ER or insulin glargine plus metformin only, HbA_{1c} was decreased by -1.5±0.06 and -1.4±0.07% (treatment difference, -1.8±0.08%; 95% CI, -0.34 to -0.02; *P*=0.031). Secondary: Significantly greater proportions of exenatide ER-treated patients achieved HbA_{1c} <7.0 (60 vs 48%; *P*=0.010) and <6.5% (35 vs 23%; *P*=0.004) compared to insulin glargine treated patients. Fasting serum glucose decreased with both treatments (-2.1±0.2 vs -2.8±0.2 mmol/L); however, insulin glargine significantly decreased values compared to exenatide ER (treatment difference, -0.6 mmol/L; 95% CI, 0.2 to 1.0; *P*=0.001). With regards to self-monitored blood glucose concentrations, both treatments significantly decreased FPG and PPG at all eight time points (*P*<0.0001 for all). Significantly lower concentrations with insulin glargine compared to exenatide ER were observed at 0300 hour (*P*=0.022) and before breakfast (*P*<0.0001), and significantly lower concentrations with exenatide ER were observed after dinner (*P*=0.004). Exenatide ER resulted in significantly greater reductions in post-prandial glucose excursions compared to insulin glargine after morning (*P*=0.001) and evening meals (*P*=0.033). Seventy nine percent of patients receiving exenatide ER experienced both a decrease in HbA_{1c} and body weight compared to 63% of patients

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				receiving insulin glargine who experienced a decrease in HbA_{1c} and increase in body weight. Only exenatide ER resulted in a significant decrease in TC (-0.12 mmol/L; *P*<0.05). There were no differences between the two treatments in the decreases in TC (treatment difference, -0.07 mmol/L; 95% CI, -0.21 to 0.06) and LDL-C (treatment difference, -0.09 mmol/L; 95% CI, -0.21 to 0.03), and the increase in HDL-C (treatment difference, -0.02; 95% CI, -0.05 to 0.02) observed. Only exenatide ER resulted in a significant decrease in SBP (-3 mm Hg; *P*<0.05). There were no differences between the two treatments in the decreases in SBP (treatment difference, -2 mm Hg; 95% CI, -4 to 1) and DBP (treatment difference, 0 mm Hg; 95% CI, -2 to 1) observed. Only exenatide ER resulted in a significant decrease in high-sensitivity CRP (-2.0 mg/dL; *P*<0.05). There were no differences between the two treatments in the decreases in high-sensitivity CRP (-1.2 mg/dL; 95% CI, -2.8 to 0.3) and urinary albumin:creatinine ratio (0.06 mg/mmoL; 95% CI, -1.70 to 1.80) observed. Both treatments resulted in improvements in IWQOL-Lite, BES, and DTSQ total scores, with only patients receiving exenatide ER achieving significant improvements on the EQ-5D index. Significant improvements with exenatide ER compared to insulin glargine were observed for one of the IWQOL-Lite domains (self-esteem) and one EQ-5D dimension (usual activities) (data not reported). Gastrointestinal events including nausea and diarrhea were among the most common reported adverse events with exenatide ER, with nasopharyngitis and headache being the most commonly reported with insulin glargine. Gastrointestinal events were all mild or moderate and no serious adverse events were reported by more than one patient, except chest pain (two patients).
Russell-Jones et al[32] DRUATION-4	DB, DD, MC, PG, RCT	N=820 26 weeks	Primary: Change in baseline HbA_{1c}	Primary: Decreases in HbA_{1c} were -1.53±0.07, -1.48±0.07, -1.63±0.08, and -1.15±0.08% with exenatide ER, metformin (*P*=0.620 vs exenatide ER),

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Exenatide ER 2 mg SC once weekly vs metformin 2,000 mg/day vs pioglitazone 45 mg/day vs sitagliptin 100 mg/day	Drug-naïve (patients excluded if treated with any antihyperglycemic drug for >7 days within 3 months of screening) adult type 2 diabetics with HbA_{1c} 7.1 to 11.0%, BMI 23 to 45 kg/m^2, and stable weight		Secondary: Proportion of patients achieving HbA_{1c} <7.0 and ≤6.5%, fasting serum glucose, 7-point self-monitored glucose concentrations, weight, lipid profile, insulin profile, safety and tolerability, patient-reported QOL	pioglitazone (*P*=0.328 vs exenatide ER), and sitagliptin (*P*<0.001 vs exenatide ER). The HbA_{1c} at trial end was 6.94±0.07, 6.99±0.07, 6.84±0.08, and 7.32±0.08% with exenatide ER, metformin, pioglitazone, and sitagliptin, respectively. Secondary: Similar proportions of patients receiving exenatide ER and metformin achieved HbA_{1c} <7.0% (63 vs 55%; *P* value not reported). A significantly greater proportion of patients receiving exenatide ER achieved HbA_{1c} <7.0% compared to patients receiving sitagliptin (63 vs 43%; *P*<0.001), and ≤6.5% compared to patients receiving metformin (49 vs 36%; *P*=0.004) and sitagliptin, respectively (49 vs 26%; *P*<0.001). Decreases in fasting serum glucose at weeks 16 and 26 were significantly greater with exenatide ER compared to sitagliptin (*P*<0.001 for both). There were no differences observed with exenatide ER compared to metformin (*P*=0.155 at week 26) and pioglitazone (*P*=0.153 at week 26). Seven-point self-monitored glucose concentrations demonstrated similar decreases with exenatide ER, metformin, and pioglitazone. Exenatide ER demonstrated greater decreases at all time points compared to sitagliptin. Mean decreases in post-meal excursions after 26 weeks were similar among all treatments. Decreases in weight were significantly greater with exenatide ER compared to pioglitazone and sitagliptin by weeks four and eight, and the effect was sustained through 26 weeks (*P*≤0.003 for all). There was no difference between exenatide ER and metformin after 26 weeks (-2.0 vs -2.0 kg; *P*=0.892). No clinically significant changes in serum lipids were observed with any treatment. Mean HOMA-B was significantly improved with exenatide ER compared to metformin, pioglitazone, and sitagliptin (*P*<0.001 for all). HOMA-S significantly improved with metformin and pioglitazone compared to

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				exenatide ER (*P*<0.001 for both), and the change with exenatide ER was similar to sitagliptin (*P*=0.329). Serious adverse events were reported in 1.6, 5.3, 5.5, and 1.8% of patients receiving exenatide ER, metformin, pioglitazone, and sitagliptin, respectively. No serious adverse event was reported by more than one patient. Treatment-emergent adverse events reported by at least five percent of patients in any group included headache (highest with metformin), diarrhea (highest with metformin), injection site nodule (highest with exenatide ER), nasopharyngitis (highest with sitagliptin), nausea (highest with exenatide ER), dyspepsia (highest with exenatide ER), constipation (highest with exenatide ER), back pain (highest with metformin), arthralgia (highest with exenatide ER), hypertension (highest with pioglitazone), and peripheral edema (highest with pioglitazone). No major hypoglycemia was reported. One patient receiving sitagliptin with elevated lipase at screening experienced moderate chronic pancreatitis after eight days and discontinued from study treatment. All treatments resulted in improvements in perceived treatment satisfaction, weight-related QOL, and binge eating behavior. All treatments, except pioglitazone, resulted in significant improvements in health status. Significant improvements in weight-related QOL, binge eating behavior, and health status were reported with exenatide ER compared to pioglitazone (*P* values not reported).
Blevins et al[33] DURATION-5 Exenatide ER 2 mg SC once weekly vs exenatide 5 µg SC BID for 4 weeks, followed by 10 µg SC BID	AC, MC, OL, RCT Type 2 diabetics ≥18 years of age treated for ≥2 months with diet and exercise alone or with a stable, maximally effective regimen of metformin, sulfonylurea, TZD, or a combination of these medications; HbA_{1c}	N=252 24 weeks	Primary: Change in baseline HbA_{1c} Secondary: Proportion of patients achieving HbA_{1c} <7.0 and <6.5% and FPG ≤126 mg/dL, body weight, FPG, BP, lipid profile, safety and tolerability	Primary: Decreases in HbA_{1c} were significantly greater with exenatide ER compared to exenatide (-1.6±0.1 vs -0.9±0.1%, treatment difference, -0.7%; 95% CI, -0.9 to -0.4). At week 24, HbA_{1c} was 7.1±0.1 and 7.7±0.1% with exenatide ER and exenatide. Secondary: A significantly greater proportion of patients receiving exenatide ER achieved HbA_{1c} <7.0 (58.1 vs 30.1%; *P*<0.0001) and <6.5% (41.1 vs 16.3%; *P*<0.0001) compared to exenatide. Similar results were achieved for FPG ≤126 mg/dL (50.4 vs 30.9%; *P*=0.0008).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	7.1 to 11.0%; FPG <280 mg/dL; and BMI 25 to 45 kg/m^2			Both treatments resulted in progressive decreases in body weight through 24 weeks (between group difference, -0.95 kg; 95% CI, -1.9 to 0.01). By week 24, 77 and 63% of patients receiving exenatide ER and exenatide experienced weight loss, whereas 71 and 51% of patients experienced both weight loss and a decrease in HbA_{1c}. Decreases in FPG were significantly greater with exenatide ER compared to exenatide (-35±5 vs -12±5 mg/dL; *P*=0.0008). Decreases in SBP were significant with exenatide ER (-2.9±1.1 mm Hg; 95% CI, -5.2 to -0.7), but not with exenatide. No significant decreases in DBP were observed with either treatment. Decreases in TC (-15.4±2.6 mg/dL; 95% CI, -20.5 to -10.2) and LDL-C (-6.4±2.1 mg/dL; 95% CI, -10.7 to -2.2) were significant with exenatide ER, and no significant changes were observed with exenatide. Nausea, the adverse event most commonly reported with both treatments (14 vs 35%), occurred at a lower incidence in patients receiving exenatide ER. Injection site-related adverse events were more common with exenatide ER (13 vs 10%), with one patient receiving exenatide ER withdrawing from treatment due to mild injection site pruritis. There were no major hypoglycemic episodes. The incidence of serious adverse events as low (2 vs 4%). During the course of treatment there was substantial variability in pancreatic-amylase and lipase concentrations. The incidence of adverse events, including gastrointestinal symptoms was similar between patients with normal and abnormal post-baseline amylase and lipase measured at any post-baseline time point.
Marre et al[34] LEAD-1 Liraglutide 0.6, 1.2, and 1.8 mg SC QD plus glimepiride 2 to 4 mg/day and placebo	AC, DB, DD, MC, PG, RCT Type 2 diabetic patients 18 to 80 years of age treated with an oral glucose-lowering agent for ≥3	N=1,041 26 weeks	Primary: Change in baseline HbA_{1c} Secondary: Proportion of patients reaching HbA_{1c} (<7.0 and ≤6.5%), FPG (5.0 to	Primary: After 26 weeks, HbA_{1c} decreased by -1.1% with both liraglutide 1.2 and 1.8 mg, respectively, compared to placebo (0.2%) and rosiglitazone (-0.4%). Estimated treatment differences compared to placebo were: liraglutide 1.8 mg, -1.4% (95% CI, 1.6 to -1.1; *P*<0.0001); liraglutide 1.2 mg, -1.3% (95% CI, 1.5 to -1.1; *P*<0.0001); liraglutide 0.6 mg, -0.8% (95% CI, -1.1 to -0.6; *P*<0.0001); and rosiglitazone, -0.7% (95% CI, -0.9 to -0.4; *P*<0.0001). Additionally, the two higher doses of liraglutide (1.2 and 1.8 mg) were

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs placebo plus glimepiride 2 to 4 mg/day vs placebo plus glimepiride 2 to 4 mg/day and rosiglitazone 4 mg/day	months, HbA_{1c} 7.0 to 11.0% (previously on oral glucose lowering agent monotherapy) or 7.0 to 10.0% (previously on oral glucose lowering agent combination therapy), and BMI ≤45 kg/m^2		≤7.2 mmol/L), and PPG (10.0 mmol/L) targets; change in baseline body weight, FPG, mean PPG, β cell function, and BP	"superior" compared to treatment with rosiglitazone (*P*<0.0001 for both measures). Decreases in HbA_{1c} were greater in patients previously on an oral glucose lowering agent monotherapy. Secondary: The proportion of patients reaching HbA_{1c} targets with liraglutide was dose-dependent. At week 26, 42, and 21% of patients receiving liraglutide 1.8 mg reached HbA_{1c} <7.0 and ≤6.5% compared to 8 and 4% of patients receiving placebo. Estimated proportions of patients receiving liraglutide 1.2 and 1.8 mg reaching HbA_{1c} targets were greater compared to patients receiving placebo (*P*<0.0001) and rosiglitazone (*P*<0.0003), respectively. More patients reached <7.0% with liraglutide 1.8 mg compared to 1.2 mg (*P*=0.018). The proportions of patients achieving FPG targets were significantly greater with liraglutide 0.6 mg (19%; *P*=0.002), 1.2 mg (37%; *P*<0.001), and 1.8 mg (38%; *P*=0.002) compared to placebo (7%). Compared to patients receiving rosiglitazone (26%), significantly more patients receiving liraglutide 1.2 and 1.8 mg achieved FPG targets (*P*=0.007 and *P*=0.01, respectively). The proportion of patients with one, two, or three PPG target measurements were significantly greater for all doses of liraglutide compared to placebo (*P*<0.05), but not rosiglitazone (*P* value not reported). Mean decreases in weight were -0.2 kg with liraglutide 1.8 mg and -0.1 kg with placebo. Mean increases in weight were 0.7 kg with liraglutide 0.6 mg, 0.3 kg with liraglutide 1.2 mg, and 2.1 kg with rosiglitazone. Differences between rosiglitazone and liraglutide were significant (*P*<0.0001), although there were no differences compared to placebo (*P* value not reported). Decreases in the proinsulin:insulin ratio were significantly greater with liraglutide 1.2 and 1.8 mg compared to rosiglitazone and placebo (*P*≤0.02). HOMA-B increased with liraglutide 1.2 and 1.8 mg compared to rosiglitazone (*P*<0.05), and increases were only significant compared to placebo with liraglutide 1.2 mg (*P*=0.01). No differences between treatments were observed for changes in HOMA-IR.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Decreases in SBP with liraglutide 1.2 and 1.8 mg (-2.6 to -2.8 mm Hg) were not different compared to placebo or rosiglitazone (-0.9 to -2.3 mm Hg; *P* values not reported).
Nauck et al[35] LEAD-2 Liraglutide 0.6, 1.2, and 1.8 mg SC QD vs placebo vs glimepiride 4 mg/day All patients also received metformin 1,500 to 2,000 mg/day.	AC, DB, DD, MC, PG, RCT Type 2 diabetic patients 18 to 80 years of age with HbA_{1c} 7.0 to 11.0% (pre-trial oral glucose lowering agent monotherapy ≥3 months) or 7.0 to 10.0% (pre-trial oral glucose lowering agent combination therapy ≥3 months), and BMI ≤40 kg/m^2	N=1,091 26 weeks	Primary: Change in baseline HbA_{1c} Secondary: Changes in baseline body weight, FPG, 7-point self-monitored glucose concentrations, and β cell function	Primary: HbA_{1c} decreased by -0.7±0.1% with liraglutide 0.6 mg, -1.0±0.1% with liraglutide 1.2 and 1.8 mg, and increased by 0.1±0.1% with glimepiride and placebo. Based on the estimated treatment differences, liraglutide had "superior" glycemic control compared to placebo (liraglutide 0.6 mg vs placebo, -0.8%; 95% CI, -1.0 to -0.6 and liraglutide 1.2 and 1.8 mg vs placebo, -1.1%; 95% CI, -1.3 to -0.9; *P* values not reported). Analysis of the estimated treatment difference in HbA_{1c} between liraglutide and glimepiride demonstrated that liraglutide 1.2 and 1.8 mg were noninferior to treatment with glimepiride. Secondary: Weight loss was dose-dependent with liraglutide (liraglutide 0.6 mg, -1.8±0.2 kg; liraglutide 1.2 mg, -2.6±0.2 kg; liraglutide 1.8 mg, -2.8±0.2 kg). Reductions in weight with liraglutide were significantly different compared to glimepiride (-1.0±0.2 kg; *P*<0.001). Weight loss with liraglutide 1.2 and 1.8 mg was significantly greater compared to placebo (1.5±0.3 kg; *P*≤0.01). Decreases in FPG with liraglutide (-1.1, -1.6, and -1.7 mmol/L with liraglutide 0.6, 1.2, and 1.8 mg) were significantly greater compared to the increase with placebo (0.4 mmol/L; *P*<0.0001). Decreases with liraglutide were similar to glimepiride (-1.3 mmol/L; *P* value not reported). Mean baseline PPG values decreased with all liraglutide doses and glimepiride (liraglutide 0.6 mg, -1.7 mmol/L; liraglutide 1.2 mg, -2.3 mmol/L; liraglutide 1.8 mg, -2.6 mmol/L; glimepiride, -2.5 mmol/L; placebo, -0.6 mmol/L; *P*<0.001 for comparisons of all liraglutide doses vs placebo). The decreases observed with liraglutide 1.2 and 1.8 mg were comparable to glimepiride (*P* values not reported). No differences in the fasting C-peptide values were observed between liraglutide and glimepiride or placebo (*P* values not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Decreases in the proinsulin: insulin ratio with all three liraglutide doses (-0.1) were comparable to glimepiride (*P* value not reported), and were significantly greater compared to placebo (0.1; *P*<0.0001). Liraglutide 0.6, 1.2, and 1.8 mg had improvements in HOMA-B of 63, 70, and 71%. Glimepiride had similar improvements, and there were no improvements with placebo. No differences were observed between any of the treatments (*P* values not reported).
Garber et al[36] LEAD-3 Liraglutide 1.2 and 1.8 mg SC QD vs glimepiride 8 mg/day	AC, DB, DD, MC, PG, RCT Type 2 diabetic patients 18 to 80 years of age treated previously with diet and exercise or up to half the highest dose of an oral glucose lowering agent monotherapy including sulfonylureas, meglitinides, amino acid derivatives, biguanides, α-glucosidase inhibitors, and TZDs for ≥2 months; and HbA_{1c} 7.0 to 11.0% (previous diet and exercise) or 7.0 to 10.0% (previous oral glucose lowering agent monotherapy)	N=746 52 weeks	Primary: Change in baseline HbA_{1c} Secondary: Change in baseline body weight, FPG, 8-point self-measured glucose concentrations, BP, β cell function, fasting glucagon, and patient-reported QOL	Primary: Decreases in HbA_{1c} were -0.84±1.23% with liraglutide 1.2 mg, -1.14±1.24% with liraglutide 1.8 mg, and -0.51±1.20% with glimepiride. Decreases with liraglutide were significantly greater compared to glimepiride. Differences between glimepiride and liraglutide 1.2 mg were -0.62% (95% CI, -0.83 to -0.42; *P*<0.0001) and liraglutide 1.8 mg were -0.33% (95% CI, -0.53 to -0.13; *P*=0.0014). Additionally, decreases with liraglutide 1.8 mg were significantly greater compared to liraglutide 1.2 mg (-0.29%; 95% CI, -0.50 to -0.09; *P*=0.0046). Secondary: Liraglutide-treated patients lost body weight and those receiving glimepiride gained weight (*P* values not reported). The weight loss with liraglutide after 16 weeks was sustained throughout the 52 weeks. Decreases in FPG with liraglutide (1.2 mg, -0.84 mmol/L; *P*=0.027 and 1.8 mg, -1.42 mmol/L; *P*=0.0001) were significantly greater compared to glimepiride (-0.29 mmol/L). Decreases in PPG occurred with all three treatments (liraglutide 1.2 mg vs glimepiride; *P*=0.1616, liraglutide 1.8 mg vs glimepiride; *P*=0.0038, and liraglutide 1.8 mg vs liraglutide 1.2 mg; *P*=0.1319). Decreases in SBP were -0.7 mm Hg with glimepiride compared to -0.1 mm Hg with liraglutide 1.2 mg (*P*=0.2912) and -3.6 mm Hg with liraglutide 1.8 mg (*P*<0.0118). Mean DBP decreased but not significantly with any treatment.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				HOMA-IR and fasting glucagon significantly decreased with liraglutide, but increased with glimepiride. HOMA-IR was decreased by -0.65% with liraglutide 1.2 mg and by -1.35% with liraglutide 1.8 mg, and increased by 0.85% with glimepiride (*P*=0.0249 and *P*=0.0011 for liraglutide 1.2 and 1.8 mg vs glimepiride). Patients receiving liraglutide 1.8 mg reported improved QOL scoring for physical and emotional domains compared to glimepiride (*P*=0.02). Improvements were largely as a result of improvements in weight image and weight concern (*P*<0.01).
Garber et al[37] LEAD-3 Liraglutide 1.2 mg and 1.8 mg SC QD vs glimepiride 8 mg/day	ES (LEAD-3[36]) Type 2 diabetic patients 18 to 80 years of age treated previously with diet and exercise or up to half the highest dose of an oral glucose lowering agent monotherapy including sulfonylureas, meglitinides, amino acid derivatives, biguanides, α-glucosidase inhibitors, and TZDs for ≥2 months; and HbA_{1c} 7.0 to 11.0% (previous diet and exercise) or 7.0 to 10.0% (previous oral glucose lowering agent monotherapy)	N=440 52 weeks	Primary: Change in baseline HbA_{1c} Secondary: Change in baseline body weight, FPG, β cell function, fasting glucagon, and BP	Primary: The decrease in HbA_{1c} was significantly greater with liraglutide 1.2 mg (-0.9 vs -0.6%; *P*=0.0376) and 1.8 mg (-1.1 vs -0.6%; *P*=0.0016) compared to glimepiride over two years of treatment. Secondary: Over two years, patients receiving liraglutide 1.2 or 1.8 mg experienced weight loss compared to weight gain with patients receiving glimepiride (-2.3 and -2.8 vs 1.0 kg, respectively; *P*<0.001 for both comparisons). Compared to glimepiride (-1.8 mmol/L), both liraglutide 1.2 (-1.9 mmol/L) and 1.8 mg (-2.6 mmol/L) were significantly more effective at decreasing FPG over the course of the extension period (*P*=0.0015 and *P*=0.0001, respectively). In patients who completed two years of treatment, baseline HOMA-IR decreased by -1.1% with liraglutide 1.2 mg and -0.8% with liraglutide 1.8 mg, and increased by 0.8% with glimepiride (*P*=0.0451 for liraglutide 1.2 mg vs glimepiride). The proinsulin:insulin ratio increased slightly with all treatments, by 0.108 with liraglutide 1.2 mg, 0.018 with liraglutide 1.8 mg, and 0.141 with glimepiride (*P* values not reported). After two years, all three treatments had increases in HOMA-B, fasting

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				insulin, and fasting C-peptide; and had decreases in fasting glucagon, but there were no differences between treatments (*P* values not reported). No differences between treatments in change in pulse, DBP, and SBP were observed in any patient completing two years of treatment.
Bode et al[38] LEAD-3 Liraglutide 1.2 and 1.8 mg SC QD vs glimepiride 8 mg/day	Post-hoc analysis (LEAD-3[36]) Type 2 diabetic patients 18 to 80 years of age treated previously with diet and exercise or up to half the highest dose of oral glucose lowering agent monotherapy including sulfonylureas, meglitinides, amino acid derivatives, biguanides, α-glucosidase inhibitors, and TZDs for ≥2 months and HbA_{1c} 7.0 to 11.0% (previous diet and exercise) or 7.0 to 10.0% (previous oral glucose lowering agent monotherapy)	N=746 52 weeks	Primary: Impact of treatment on patient-reported perceptions of body image, weight, and weight concern; psychological well-being and distress, cognitive functioning and health Secondary: Not reported	Primary: Both measures of weight perception (weight assessment and weight concern) were more favorable with liraglutide compared to glimepiride. Baseline-adjusted mean weight assessment compared to the reference point "my weight is just right" was significantly more favorable (i.e., shifted from more overweight to less overweight) with liraglutide 1.8 mg (*P*=0.002). Furthermore, weight concern decreased markedly with liraglutide, with mean scores significantly less compared to glimepiride (liraglutide 1.2 mg; *P*<0.0001 and liraglutide 1.8 mg; *P*<0.001). Logistic regression estimates indicated that patients receiving liraglutide 1.8 mg were 52% less likely to report feeling either "somewhat" or "very overweight" vs "just right", "somewhat underweight," or "very overweight" during treatment compared to patients receiving glimepiride (OR, 0.480; 95% CI, 0.331 to 0.696; *P* value not reported). Also, liraglutide 1.8 mg-treated patients were 39% less likely to report being "somewhat worried", "very worried," or "extremely worried" vs "a little concerned" or "not concerned at all" about their weight during treatment compared to glimepiride treated patients (OR, 0.608; 95% CI, 0.440 to 0.850; *P* value not reported). There were no differences between liraglutide and glimepiride for the body image scales (body size evaluation and body appearance distress) or for any of the cognitive functioning and performance scales during treatment (*P* values not reported). The health-related QOL composite score significantly improved more favorably with liraglutide 1.8 mg compared to glimepiride (*P*=0.004). Favorable improvements were seen in the composite scales of mental and emotional healthy, psychological well-being, psychological distress, and general perceived health (*P*<0.05 for all). The higher scores with liraglutide

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				1.8 mg for mental and emotional health reflected greater improvement in both domains of psychological well-being and psychological distress compared to glimepiride. There were no differences for these scales between liraglutide 1.2 mg and glimepiride (*P* values not reported). However, there was a significant difference between liraglutide 1.2 mg and glimepiride in general health status favoring liraglutide (*P*=0.006). Correlation analyses using data pooled from all treatments confirmed that decreases in BMI were correlated with improvements in both weight assessment and weight concern (*P*<0.0001 for both), indicating that patients' reports were valid representations of actual weight losses. Decreases in HbA_{1c} corresponded to improvements in general perceived health (*P*<0.0001), cognitive functioning composite score (*P*=0.006), and cognitive performance (*P*=0.004). Correlations of change in HbA_{1c} within treatment groups with change in patient-reported measures were strongest with liraglutide 1.8 mg. Secondary: Not reported
Zinman et al[39] LEAD-4 Liraglutide 1.2 and 1.8 mg SC QD vs placebo All patients also received metformin 2,000 mg/day and rosiglitazone 8 mg/day.	DB, MC, PC, PG, RCT Type 2 diabetic patients 18 to 80 years of age with HbA_{1c} 7.0 to 11.0% (pre-trial oral glucose lowering agent monotherapy ≥3 months) or 7.0 to 10.0% (pre-trial oral glucose lowering agent combination therapy for ≥3 months), and BMI ≤45 kg/m^2	N=533 26 weeks	Primary: Change in baseline HbA_{1c} Secondary: Change in baseline body weight, FPG, 7-point self-monitored glucose concentrations, β cell function, and lipids	Primary: The mean baseline HbA_{1c} for the overall population decreased by -1.5±0.1% with liraglutide 1.2 (95% CI, -1.1 to -0.8; *P* value not reported) and 1.8 mg (95% CI, -1.1 to -0.8; *P* value not reported) compared to -0.5±0.1% with placebo. Secondary: Weight loss with liraglutide was significantly greater compared to placebo (liraglutide 1.2 mg, -1.0±0.3 kg and liraglutide 1.8 mg, -2.0±0.3 kg; *P*<0.0001 for both). Decreases in FPG with liraglutide (liraglutide 1.2 mg, -2.2 mmol/L and liraglutide 1.8 mg, -2.4 mmol/L) were significantly greater compared to placebo (-0.4 mmol/L; *P*<0.0001 for both). Decreases in mean PPG were significantly greater with liraglutide

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				compared to placebo (liraglutide 1.2 mg, -2.6 mmol/L; liraglutide 1.8 mg, -2.7 mmol/L; and placebo, -0.8 mmol/L; *P*<0.001 for both). The decrease in proinsulin:insulin ratio with liraglutide was significantly greater compared to placebo (liraglutide 1.2 mg, -0.029±0.026; liraglutide 1.8 mg -0.085±0.260; placebo, 0.036±0.029; *P*<0.05 for both). The increase in C-peptide was significantly greater with liraglutide compared to placebo (liraglutide 1.2 mg, 131±32; liraglutide 1.8 mg, 144±31; placebo, 51±34 pmol/L; *P*<0.05 for both). Increases in HOMA-B with liraglutide were significantly greater compared to placebo (*P*<0.05), but decreases with HOMA-IR were not different between treatments (*P* values not reported). Decreases in FFA were significantly greater with liraglutide 1.2 mg (-0.03±0.02 mmol/L; *P*<0.05) and liraglutide 1.8 mg (-0.05±0.02 mmol/L; *P*<0.05) compared to placebo (0.02±0.02). Other significant decreases in lipid profiles with liraglutide compared to placebo were LDL-C (liraglutide 1.2 mg, -0.28±0.07 vs -0.10±0.07 mmol/L; *P*<0.05) and TG (liraglutide 1.2 mg, -0.38±0.10 vs -0.13±0.11 mmol/L; *P*<0.05).
Russell-Jones et al[40] LEAD-5 Liraglutide 1.8 mg SC QD vs placebo vs insulin glargine (OL)	PC, PG, RCT Type 2 diabetic patients 18 to 80 years of age with oral glucose lowering agents ≥3 months before screening, HbA_{1c} 7.5 to 10.0% (previous oral glucose lowering agent monotherapy) or 7.0 to 10.0% (previous oral glucose lowering agent combination	N=581 26 weeks	Primary: Change in baseline in HbA_{1c} Secondary: Change in baseline body weight, waist circumference, FPG, 8-point self-monitored glucose concentrations, β cell function, and BP	Primary: Decreases in HbA_{1c} were -1.33, -0.24, and -1.09% with liraglutide, placebo, and insulin. Decreases achieved with liraglutide were significantly greater compared to placebo and insulin (differences for liraglutide vs placebo, -1.09%; 95% CI, -1.28 to -0.90; *P*<0.0001 and differences for liraglutide vs glargine, -0.24%; 95% CI, -0.39 to -0.08; *P*=0.0015). Secondary: The decrease in body weight with liraglutide (-1.8 kg) was significantly greater compared to placebo (0.42 kg; treatment difference, -1.39 kg; 95% CI, -2.10 to -0.69; *P*=0.0001). Additionally, patients gained weight with insulin (1.6 kg; treatment difference, -3.43 kg; 95% CI, -4.00 to -2.86; *P*<0.0001). The decrease in waist circumference with liraglutide (-1.50 cm) was

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
All patients also received metformin 2,000 mg/day and glimepiride 4 mg/day.	therapy), and BMI ≤45 kg/m^2			significantly greater compared to insulin (0.89 cm; treatment difference, -2.40 cm; 95% CI, -3.14 to -1.65; *P*<0.0001), but not compared to placebo (-0.62 cm; treatment difference, -0.88 cm; 95% CI, -1.81 to 0.04; *P*=0.0608). Final decreases in FPG were -1.55, -1.79, and -0.53 mmol/L with liraglutide, insulin, and placebo. The decrease with liraglutide, and the likelihood of achieving American Diabetes Association targets (FPG 5.0 to 7.2 mmol/L) was significantly greater compared to placebo (treatment difference, -2.08 mmol/L; 95% CI, 2.53 to -1.64; *P*<0.0001; OR, 4.99; 95% CI, 2.65 to 9.39), but not compared to insulin (data not reported). Decreases in PPG were achieved with liraglutide (-1.81 mmol/L) and insulin (-1.61 mmol/L), with liraglutide being significantly greater compared to placebo (0.03 mmol/L; treatment difference, -1.84 mmol/L; 95% CI, -2.63 to -1.33; *P*<0.0001), but not compared to insulin (data not reported). Significant improvements in β cell function as demonstrated by the proinsulin:C-peptide ratio compared to insulin (treatment difference, -0.00366; 95% CI, -0.00597 to -0.00136; *P*=0.0019) and placebo (treatment difference, -0.00671; 95% CI, -0.00964 to -0.00377; *P*<0.0001) were achieved with liraglutide. A significant decrease in SBP was achieved with liraglutide (-4.00 mm Hg) compared to insulin (-0.54 mm Hg; treatment difference, -4.51 mm Hg; 95% CI, -6.82 to -2.20; *P*=0.001), but not compared to placebo (-1.4 mm Hg; treatment difference, -2.53 mm Hg; 95% CI, -5.36 to 0.29; *P*=0.0791). No significant decreases in DBP were achieved with liraglutide relative to either placebo or insulin.
Buse et al[41] LEAD-6 Liraglutide 1.8 mg SC QD vs	AC, MC, OL, PG, RCT Type 2 diabetic patients 18 to 80 years of age with HbA_{1c} 7.0 to 11.0%; BMI ≤45 kg/m^2; and stable on treatment	N=464 26 weeks	Primary: Change in baseline HbA_{1c} Secondary: Proportion of patients reaching HbA_{1c} targets (<7.0 and ≤6.5%);	Primary: Decreases in HbA_{1c} with liraglutide were “superior” compared to exenatide (- 1.12 vs -0.79%; treatment difference, -0.33; 95% CI, -0.47 to -0.18; *P* value not reported). Data in the ITT population demonstrated similar decreases with liraglutide and exenatide (-1.16 vs -0.87%; estimated treatment difference, -0.29%; 95% CI, -0.45 to -0.13; *P*<0.0001). Secondary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
exenatide 10 µg SC BID Background oral glucose-lowering agents were maintained at pre-trial doses unless unacceptable hypoglycemia occurred, in which case sulfonylurea doses could be reduced to no less than 50% of the starting dose.	with maximally tolerated doses of metformin, sulfonylurea, or both for ≥3 months		change in baseline FPG, 7-point self-monitored glucose concentrations, body weight, β cell function, glucagon, BP, and lipid profiles	The proportion of patients achieving target HbA_{1c} was significantly greater with liraglutide compared to exenatide (HbA_{1c} <7.0%, 54 vs 43%; OR, 2.02; 95% CI, 1.31 to 3.11; *P* value not reported and HbA_{1c} ≤6.5%, 35 vs 21%; OR, 2.73; 95% CI, 1.68 to 4.43; *P* value not reported). Significant decreases in FPG were achieved with liraglutide compared to exenatide (-1.61 vs -0.60 mmol/L; treatment difference, -1.01 mmol/L; 95% CI, -1.37 to -0.65; *P*<0.0001). In contrast, exenatide decreased PPG significantly more compared to liraglutide after breakfast (treatment difference, -1.33 mmol/L; 95% CI, 0.80 to 1.86; *P*<0.0001) and dinner (treatment difference, -1.01 mmol/L; 95% CI, 0.44 to 1.57; *P*=0.0005). After lunch differences between the two treatments were not significant (data not reported). Both treatments were associated with decreases in body weight (-3.24 vs -2.87 kg; treatment difference, -0.37 kg; 95% CI, -0.99 to 0.23; *P*=0.2235). Increases in HOMA-B were significant with liraglutide compared to exenatide (32.12 vs 2.74%; treatment difference, 29.38%; 95% CI, 16.81 to 41.93; *P*<0.0001). Decreases in fasting glucagon were not different between the two treatments (-19.44 vs -12.33 ng/L; treatment difference, -7.11 ng/L; 95% CI, -16.66 to 2.43; *P*=0.1436). No differences were observed between the two treatments in terms of decreases in SBP (*P*=0.6409) or DBP (*P*=0.1610). In terms of lipid profiles, significant changes favoring liraglutide were observed only for VLDL-C (*P*=0.0277), TG (*P*=0.0485), and FFA (*P*=0.0014). All other lipid parameters were similar between the two treatments.
Buse et al[42] Liraglutide 1.8 mg SC	ES (LEAD-6[41]) Type 2 diabetic	N=376 14 weeks	Primary: Change in baseline HbA_{1c}, FPG, body	Primary: HbA_{1c} decreased further from 7.2% at week 26 to 6.9±0.32% at week 40 (*P*<0.0001) after switching from exenatide to liraglutide, but remained

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
QD (continued liraglutide) vs liraglutide 1.8 mg SC QD (switched to liraglutide) Patients enrolled in LEAD-6 who were randomized to exenatide 10 µg SC BID were transitioned to liraglutide 1.8 mg SC QD after the initial 26 week trial period.	patients 18 to 80 years of age with HbA_{1c} 7.0 to 11.0%; BMI ≤45 kg/m^2; and stable on treatment with maximally tolerated doses of metformin, sulfonylurea, or both for ≥3 months	(40 weeks total)	weight, and SBP; adverse events Secondary: Not reported	similar with continued liraglutide treatment (7.0 to 6.9±-0.06%; *P*=0.1222). Additional patients reached HbA_{1c} targets after switching from exenatide to liraglutide. After switching from exenatide to liraglutide, further decreases in FPG (-0.9±0.16 mmol/L; *P*<0.0001), body weight (-0.9±0.15 kg; *P*<0.0001), and SBP (-3.8±0.84 mmHg; *P*<0.0001) occurred, while HOMA-B increased (14.5±4.4%; *P*=0.001), consistent with FPG reductions. With continued liraglutide treatment, reductions in FPG (-0.2±0.11 mmol/L; *P*=0.0973), body weight (-0.4±0.15 kg; *P*=0.0089), and SBP (-2.2±0.88 mmHg; *P*=0.0128) occurred. No significant changes in PPG occurred in either treatment group (*P* value not reported). Similar numbers of patients reported one or more adverse events during the ES (37.6 vs 37.4%; *P* value not reported). Most adverse events were mild in severity. Nausea and diarrhea occurred in 1.5% of patients who continued liraglutide and 3.2% of patients who switched from exenatide to liraglutide, whereas vomiting occurred in 2.0% of patients who continued liraglutide and 0.5% of patients who switched from exenatide to liraglutide. One major hypoglycemic episode occurred in a patient continuing liraglutide. Four patients who switched from exenatide to liraglutide had seven severe adverse events (cardiac failure, MI, cataract, chest discomfort, COPD, and dyspnea). Five patients continuing liraglutide had eight severe adverse events (cerebral infarction, cerebrovascular accident, TIA, acute coronary syndrome, coronary artery occlusion, portal vein thrombosis, rectal cancer, and depression). Calcitonin levels remained at the lower level of the normal range (<1 pg/mL) and did not differ between treatment groups. No medullary thyroid carcinoma or pancreatitis cases were reported. Secondary: Not reported

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Kaku et al[43] Liraglutide 0.6 and 0.9 mg SC QD vs placebo All patients received existing sulfonylurea therapy.	DB, MC, PG, RCT Japanese type 2 diabetics ≥20 years of age currently treated with a sulfonylurea for ≥8 weeks, HbA_{1c} 7.0 to <10.0%, and BMI <35 kg/m^2	N=264 52 weeks (initial 24 week DB period, followed by 28 week OL period to assess the long-term safety and efficacy of liraglutide)	Primary: Change in baseline HbA_{1c} at 24 weeks Secondary: 7-point self-monitored glucose concentrations, body weight, FPG, PPG, lipid profile, biomarkers for cardiovascular effects, proportion of patients reaching an HbA_{1c} <7.0 or <6.5% (post-hoc analysis)	Primary: Liraglutide significantly decreased and sustained HbA_{1c} compared to placebo. The decrease at week 24 was greater with liraglutide 0.9 mg (-1.56±0.84%) compared to the other treatments (liraglutide 0.6 mg, -1.46±0.95% and placebo, -0.40±0.93%). HbA_{1c} at week 24 were significantly lower with liraglutide compared to placebo (7.02 and 6.75% with liraglutide 0.6 and 0.9 mg compared to 8.02% with placebo) with the treatment differences of -1.00% (95% CI, -1.24 to -0.75) with liraglutide 0.6 mg and -1.27% (95% CI, -1.51 to -1.02) with liraglutide 0.9 mg. Secondary: Improvements in metabolic controls were apparent in the 7-point self monitored glucose concentration profiles at week 24, with significant reductions in glucose. Plasma glucose was significantly lower with liraglutide compared to placebo (*P*<0.0001). Body weight did not change with liraglutide (0.6 mg, 0.06 kg and 0.9 mg, -0.37 kg) despite the improvements seen in glycemic control (*P* values not reported). Weight decreased with placebo (-1.12 kg). Full impact on FPG levels was achieved at the first two visits at week four, and levels were significantly lower with liraglutide at week 24 compared to placebo. FPG with liraglutide 0.6 and 0.9 mg was significantly lower compared to placebo (7.34±0.19, 7.01±0.19, and 8.81±0.19 mmol/L, respectively; *P*<0.0001). The estimated means of PPG at week 24 at all time points with liraglutide were lower compared to placebo, with much lower mean values occurring with liraglutide 0.9 mg (*P* values not reported). The means of $AUC_{0\text{-}3hr}$ at week 24 were also significantly lower with liraglutide compared to placebo (*P*<0.0001). No significant treatment effects were observed in any of the parameters of the lipid profile. The cardiovascular biomarker BNP was significantly lower with liraglutide compared to placebo (liraglutide 0.6 mg vs placebo; *P*=0.0018 and liraglutide 0.9 mg vs placebo; *P*=0.0157). High-sensitivity CRP was significantly lower with liraglutide 0.6 mg compared to placebo (*P*=0.0218), but no difference was observed between liraglutide 0.9 mg and

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				placebo (*P*=0.8143). No treatment effect was seen in the estimated mean of PAI-1 at week 24 (*P* values not reported). A significantly greater proportion of patients receiving liraglutide achieved HbA_{1c} values <7.0 and <6.5% compared to placebo (*P* values not reported).
Seino et al[44] Liraglutide 0.9 mg SC QD vs glyburide 2.5 mg QD or BID	DB, DD, MC, PG, RCT Japanese type 2 diabetics ≥20 years of age treated with diet or without oral glucose lowering agent monotherapy for no less than 8 weeks, with an HbA_{1c} ≥7.0 and <10%, and BMI <35 kg/m^2	N=411 52 weeks (initial 24 week DB period, followed by 28 week OL period to assess the long-term safety and efficacy of liraglutide)	Primary: Change in baseline HbA_{1c} at 24 weeks Secondary: FPG, 7-point self-monitored glucose concentrations, PPG, body weight, lipid profile, biomarkers for cardiovascular effects, adverse events, proportion of patients reaching HbA_{1c} targets <7.0% or <6.5% (post-hoc analysis)	Primary: Liraglutide 0.9 mg significantly decreased HbA_{1c} compared to glyburide. HbA_{1c} at week 24 was 6.99±0.07% with liraglutide (decrease of -1.88±0.07%) and 7.50±0.09% with glyburide (decrease of -1.38±0.09%). The non-inferiority and "superiority" of liraglutide was demonstrated (treatment difference, -0.50%; 95% CI, -0.70 to -0.30; *P*<0.0001). Secondary: At 24 weeks, FPG was significantly lower with liraglutide (7.6 mmol/L) compared to glyburide (8.3 mmol/L), with a treatment difference of -0.70 mmol/L (95% CI, -1.0 to -0.4; *P*<0.0001). Improvement in glycemic control with liraglutide was also apparent in the 7-point self-monitored glucose concentration profiles at week 24, with significant decreases in plasma glucose and PPG with liraglutide compared to glyburide (*P*<0.0001). PPG at week 24 at all time points measured with liraglutide was lower compared to glyburide. The $AUC_{0\text{-}3hr}$ was significantly lower with liraglutide (32.1±0.5 vs 37.3±0.7 mmol/Lhr), with a treatment difference of -5.2 mmol/L (95% CI, -6.6 to -3.7; *P*<0.0001). Over 24 weeks, body weight decreased with liraglutide (-0.92±2.15 kg) compared to an increase with glyburide (0.99±1.84 kg). Body weight was significantly lower with liraglutide (treatment difference, -1.91 kg; 95% CI, -2.34 to -1.48; *P*<0.0001). No difference was seen in other lipid profile parameters (TC, LDL-C, VLDL-C, HDL-C, TG, and apo B) between the two treatments. At 24 weeks, the FFA with liraglutide (0.59±0.015 mEq/L) was significantly lower compared to glyburide (0.64±0.020 mEq/L), with a treatment difference of -0.050 mEq/L (95% CI, -0.093 to -0.006; *P*=0.0252).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				At week 24, the cardiovascular risk biomarkers BNP and high-sensitivity CRP were significantly lower with liraglutide compared to glyburide (*P*<0.0001 and *P*=0.0475, respectively). No differences in PAI-1 at 24 weeks were observed between the two treatments (*P* value not reported). A similar proportion of treatment-emergent adverse events were reported with both treatments (73.1 vs 74.2%). The most common with both treatments were nasopharyngitis, diarrhea, constipation, and upper respiratory tract infection. More patients reported gastrointestinal treatment-emergent adverse events with liraglutide (6.3 vs 3.8%; *P* value not reported). More patients receiving liraglutide achieved an HbA_{1c} <7.0% compared to patients receiving glyburide (49.0 vs 30.8%; *P*<0.0001). An HbA_{1c} <6.5% was achieved by a significantly greater proportion of liraglutide-treated patients (27.8 vs 10.8%; *P*<0.0001). A greater proportion of patients previously treated without oral glucose-lowering agent achieved an HbA_{1c} <7.0 and <6.5% compared to those previously treated with oral glucose-lowering agent monotherapy.
Pratley et al[45] Liraglutide 1.2 and 1.8 mg SC QD vs sitagliptin 100 mg QD All patients received existing metformin therapy.	MC, OL, PG, RCT Type 2 diabetic patients 18 to 80 years of age with an HbA_{1c} 7.5 to 10.0%, BMI ≤45 kg/m^2, and had been treated with metformin (≥1,500 mg/day) for ≥3 months	N=665 26 weeks	Primary: Change in baseline HbA_{1c} Secondary: Proportion of patients reaching HbA_{1c} targets <7.0 or ≤6.5%; FPG; PPG; body weight; β cell function; fasting lipid profile; cardiovascular risk markers; BP; heart rate; physical measures; treatment satisfaction; adverse events; composite endpoint of	Primary: In the "superiority" comparison, significantly greater lowering of HbA_{1c} (8.5% at baseline) was achieved with liraglutide 1.8 mg (-1.50%; 95% CI, -1.63 to -1.37) and 1.2 mg (-1.24%; 95% CI, -1.37 to -1.11) compared to sitagliptin (-0.90%; 95% CI, -1.03 to -0.77). Treatment differences for liraglutide 1.8 mg vs sitagliptin were -0.60% (95% CI, -0.77 to -0.43; *P*<0.0001) and -0.34% (95% CI, -0.51 to -0.16; *P*<0.0001) for liraglutide 1.2 mg vs sitagliptin. Secondary: Significantly more patients achieved HbA_{1c} targets (<7.0 and ≤6.5%) with liraglutide compared to sitagliptin (<7.0%: liraglutide 1.8 mg: OR, 4.50; 95% CI, 2.90 to 6.71; liraglutide 1.2 mg: OR, 2.75; 95% CI, 1.78 to 4.25; and ≤6.5%: liraglutide 1.8 mg: OR, 4.25; 95% CI, 2.55 to 7.08; liraglutide 1.2 mg: OR, 2.11; 95% CI, 1.24 to 3.59; *P* values not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			proportion of patients with a HbA_{1c} <7.0%, no hypoglycemia, and weight change of ≤0 kg	After 26 weeks, decreases in FPG were significantly greater with liraglutide compared to sitagliptin (liraglutide 1.8 mg, -2.14 mmol/L [95% CI, -2.43 to -1.84], liraglutide 1.2 mg, -1.87 [95% CI, -2.16 to -1.57], and sitagliptin, -0.83 [95% CI, -1.13 to -0.54]; *P* values not reported). Treatment differences were -1.31 mmol/L (95% CI, -1.70 to -0.91; *P* value not reported) for liraglutide 1.8 mg compared sitagliptin and -1.04 mmol/L (95% CI, -1.43 to -0.64; *P* value not reported) for liraglutide 1.2 mg compared to sitagliptin. Mean reductions in the AUC for PPG is not reported because data were difficult to interpret. The decrease in body weight after 26 weeks was significantly greater with liraglutide compared to sitagliptin (liraglutide 1.8 mg, -3.38 kg [95% CI, -3.70 to -2.84], liraglutide 1.2 mg, -2.86 kg [95% CI, -1.50 to -0.42], and sitagliptin, -0.96 kg [95% CI, -1.50 to -0.42]; *P* values not reported). Treatment differences were -2.42 kg (95% CI, -3.14 to -1.70; *P* value not reported) for liraglutide 1.8 mg compared to sitagliptin and -1.90 kg (95% CI, -2.61 to -1.18; *P* value not reported) for liraglutide 1.2 mg compared to sitagliptin. Liraglutide was associated with significant improvements in HOMA-B, C-peptide concentration, and proinsulin:insulin ratio compared to sitagliptin, but no treatment-related differences were observed for HOMA-IR or fasting insulin concentration. Changes in the lipid profile between liraglutide and sitagliptin were not different, apart from the decrease in TC which was significantly greater with liraglutide 1.8 mg compared to sitagliptin (*P* value not reported). Data on cardiovascular markers were not reported. Both liraglutide and sitagliptin had a small effect on SBP and DBP; lowering of DBP with sitagliptin seemed to be significant compared to liraglutide 1.8 mg, but not compared to liraglutide 1.2 mg (*P* values not reported). Heart rate increased with liraglutide, and decreased slightly with sitagliptin;

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				differences were small but significant with both doses of liraglutide compared to sitagliptin (*P* values not reported). Liraglutide was associated with significantly greater reductions in waist circumference compared to sitagliptin, but no treatment-related differences of waist:hip ratio were observed (*P* values not reported). Improvements were observed in all DTSQ items for all treatments. The increase in patients' treatment satisfaction from baseline was significantly greater with liraglutide 1.8 mg compared to sitagliptin (treatment difference, 1.39; 95% CI, 0.13 to 2.64; *P* value not reported), but the increase with liraglutide 1.2 mg compared to sitagliptin was not significant (*P* value not reported). Most treatment-emergent adverse events were reported with liraglutide. Two deaths occurred, neither of which was judged as likely to be related to the study drug. The most common adverse events were gastrointestinal symptoms, especially with liraglutide, and infections and infestations, which occurred with similar frequency with all treatments. Forty six, 37, and 14% of liraglutide 1.8 mg-, liraglutide 1.2 mg-, and sitagliptin-treated patients achieved the composite secondary endpoint. Measurements scheduled to be taken after baseline were missing for some patients. The ORs vs sitagliptin were 5.46 (95% CI, 3.37 to 8.85; *P*<0.0001) for liraglutide 1.8 mg and 3.45 (95% CI, 2.12 to 5.61; *P*<0.0001) for liraglutide 1.2 mg.
Fakhoury et al[46] Incretin-based therapies (exenatide, liraglutide, vildagliptin,* and sitagliptin) vs	MA (38 RCTs: 8, exenatide; 7, liraglutide; 12, sitagliptin; 11, vildagliptin) Type 2 diabetics ≥18 years of age	N=Not reported Duration varied (4 to 52 weeks	Primary: Change in baseline HbA_{1c} and weight, hypoglycemia Secondary: Not reported	Primary: Sitagliptin (WMD, -0.79; 95% CI, -0.93 to -0.65; *P*<0.001) significantly decrease HbA_{1c} compared to placebo. Exenatide (WMD, -0.75; 95% CI, -0.83 to -0.67; *P*<0.001) and liraglutide (WMD, -1.03; 95% CI, -1.16 to -0.90; *P*<0.0010) significantly decreased baseline HbA_{1c}. In the adjusted analyses for exenatide, controlling for whether exenatide was given as monotherapy or in combination with another treatment provided the most variability, but even this estimate fell within the boundaries of the unadjusted model CI (WMD, -0.84; 95% CI, -

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
placebo				0.95 to -0.73; *P*<0.001). In the adjusted analyses for liraglutide, no covariates were found to be significant. There was significant weight gain with sitagliptin (WMD, 0.60; 95% CI, 0.33 to 0.87; *P*<0.001) compared to placebo. Exenatide (WMD, -1.10; 95% CI, -1.32 to -0.88; *P*<0.001) and liraglutide (WMD, -0.82; 95% CI, -1.92 to -0.27; *P*=0.142) both exhibited reduction in weight. The most remarkable result is the average weight reduction of 1.10 kg observed with exenatide. Sitagliptin-treated patients were 156% more likely to experience some hypoglycemia compared to placebo treated patients (RR, 2.56; 95% CI, 1.23 to 5.33; *P*=0.01). When adjusted for covariates, age was the only variable found to be significant (RR, 1.84; 95% CI, 1.02 to 3.34; *P*=0.044). Exenatide-treated patients were 140% more likely to experience some hypoglycemia compared to placebo treated patients (RR, 2.40; 95% CI, 1.39 to 4.11; *P*=0.002). Liraglutide-treated patients were 69% more likely to experience some hypoglycemia compared to placebo treated patients (RR, 1.69; 95% CI, 1.00 to 2.86; *P*=0.050). Secondary: Not reported
Monami et al[47] GLP-1 receptor agonist based therapies (albiglutide*, exenatide, liraglutide, lixisenatide*, semaglutide*, and taspoglutide*) vs other classes of antidiabetic medications or	MA Type 2 diabetics	N=10,485 Up to 52 weeks	Primary: Major cardiovascular events Secondary: Not reported	Primary: GLP-1 receptor agonists are not associated with an increased risk of cardiovascular events (OR, 0.74; 95% CI, 0.50 to 1.08; *P*=0.12). Exenatide is not associated with an increased risk of cardiovascular events (OR, 0.85; 95% CI, 0.50 to 1.45; *P*=0.55). Liraglutide is not associated with an increased risk of cardiovascular events (OR, 0.69; 95% CI, 0.40 to 1.22; *P*=0.20). In PC trials, GLP-1 receptor agonists reduced the risk of cardiovascular events (OR, 0.46; 95% CI, 0.25 to 0.83; *P*=0.009). In AC trials, there was no difference between treatments in the risk of cardiovascular events (OR, 1.05; 95% CI 0.63 to 1.76; *P*=0.84).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
placebo				Secondary: Not reported
Amori et al[48] Incretin-based therapies (exenatide, liraglutide, sitagliptin, and vildagliptin*) vs non-incretin-based therapy (placebo or hypoglycemic agent)	MA (29 RCTs) Type 2 diabetics	N=12,996 Duration varied (12 to 52 weeks)	Primary: Change in baseline HbA_{1c} Secondary: FPG, proportion of patients achieving an HbA_{1c} <7.0%	Primary: Pooled analysis of trials comparing GLP-1 analogues to placebo demonstrated a significant difference in the decrease in HbA_{1c} favoring GLP-1 analogues (WMD, -0.97; 95% CI, -1.13 to -0.81). Specifically, no difference in the HbA_{1c} was found in OL non-inferiority trials between exenatide and insulin glargine or biphasic aspart (WMD, -0.06; 95% CI, -0.22 to 0.10). Liraglutide demonstrated similar HbA_{1c} efficacy compared to OL glimepiride titrated to glycemic goals or DB maximum dose metformin (data not reported). Secondary: Compared to placebo, FPG was significantly decreased with GLP-1 analogues (WMD, -27 mg/dL; 95% CI, -33 to -21). Exenatide-treated patients were more likely to achieve an HbA_{1c} <7.0% compared to placebo treated patients (45 vs 10%, respectively; RR, 4.2; 95% CI, 3.2 to 5.5), while no difference in the proportions of patients achieving this goal was observed between exenatide and insulin therapy in non-inferiority trials (39 vs 35%, respectively; RR, 1.1; 95% CI, 0.8 to 1.5). Data with liraglutide were not reported.
Pinelli et al[49] GLP-1 receptor agonist, long-acting formulations at maximum doses (liraglutide, exenatide ER, albiglutide*, and lixisenatide*) vs	MA, SR (5 RCTs) Adult type 2 diabetics	N=not reported Duration varied (not reported)	Primary: Change in baseline HbA_{1c}, FPG, PPG, weight , BP, and lipid profile; safety Secondary: Not reported	Primary: Pooled analysis demonstrates modest decreases in HbA_{1c} favoring long-acting GLP-1 receptor agonists over exenatide (WMD, -0.47%; 95% CI, -0.69 to -0.25) and sitagliptin (WMD, -0.60%; 95% CI, -0.75 to -0.45). Long-acting GLP-1 receptor agonists were significantly more likely to achieve HbA_{1c} <7.0% compared to exenatide (OR, 2.14; 95% CI, 1.38 to 3.34) and sitagliptin (OR, 3.84; 95% CI, 2.78 to 5.31). Pooled analysis demonstrates significant decreases in FPG favored long-acting GLP-1 receptor agonists compared to exenatide (WMD, -18.39 mg/dL; 95% CI, -24.67 to -12.10) and sitagliptin (WMD, -20.96; 95% CI, -27.88 to -14.04).

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exenatide and sitagliptin				In one trial, exenatide achieved significantly greater decreases in PPG compared to exenatide ER (-124 vs -95 mg/dL; *P*=0.01). In another trial, exenatide achieved significantly greater decreases in PPG after breakfast (treatment difference, -24 mg/dL; *P*<0.0001) and dinner (-18 mg/dL; *P*=0.0005) compared to liraglutide. There was no difference between treatments after lunch. In a third trial, exenatide ER significantly decreased PPG after each meal compared to sitagliptin (*P*<0.05). Pooled analysis demonstrates significant decreases in weight with long-acting GLP-1 receptor agonists compared to sitagliptin (WMD, -1.99 kg; 95% CI, -2.69 to -1.09), but not exenatide (WMD, -0.48 kg; 95% CI, -1.11 to 0.44). In one trial, exenatide ER significantly decreased SBP compared to sitagliptin (treatment difference, -4 mm Hg; *P*=0.006), but results were not significant in the three other trials (*P* values not reported). One trial demonstrated sitagliptin significantly decreased DBP compared to liraglutide (-1.78 vs 0.07 mm Hg; *P*=0.02). Between-group differences were not significant in the other three trials (*P* values not reported). Long-acting GLP-1 receptor agonists significantly improved TC compared to other incretin-based therapy in two of four trials. Exenatide ER significantly decreased TC (-12.0 vs -3.9 mg/dL; *P* value not reported) and LDL-C (-5.0 vs 1.2 mg/dL) compared to exenatide. Liraglutide significantly decreased TC compared to sitagliptin (-6.60 vs -0.77 mg/dL; *P*=0.03). In one trial, long-acting GLP-1 receptor agonists significantly improved TG compared to incretin-based therapy (-36 with liraglutide vs -20 mg/dL with exenatide ER; *P*=0.05). No episodes of severe hypoglycemia were reported in four of the trials. In another trial, two patients receiving exenatide experienced severe hypoglycemia. Non-severe hypoglycemia occurred infrequently and in similar amounts among the treatments. The most commonly reported adverse events with long-acting GLP-1 receptor agonists were gastrointestinal-related. Compared to exenatide, the incidence of vomiting

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				was significantly decreased with long-acting GLP-1 receptor agonists (OR, 0.55; 95% CI, 0.34 to 0.89), there was a trend towards decreased nausea (OR, 0.58; 95% CI, 0.32 to 1.06), and no difference in diarrhea (OR, 1.03; 95% CI, 0.67 to 1.58). Nausea (OR, 4.70; 95% CI, 1.81 to 12.24), vomiting (OR, 3.22; 95% CI, 1.63 to 6.36), and diarrhea (OR, 2.32; 95% CI, 1.42 to 3.81) with long-acting GLP-1 receptor agonists were increased compared to sitagliptin. Compared to exenatide, exenatide ER caused more injection site pruritis in two trials (17.6 vs 1.4%), in another trial exenatide had a similar rate of injection site reactions compared to placebo injection (10 vs 7%). Acute pancreatitis was not reported in any trial. One patient receiving liraglutide experienced mild pancreatitis after 88 days of treatment. Secondary: Not reported
Shyangdan et al[50] GLP-1 receptor agonist based therapies (albiglutide*, exenatide ER, liraglutide, lixisenatide*, semaglutide*, and taspoglutide*) vs non-GLP-1 receptor based therapies (placebo, TZDs, DPP-4 inhibitors, insulin glargine, and sulfonylureas)	MA (RCTs) Type 2 diabetics ≥18 years of age	N=not reported 8 to 26 weeks	Primary: Change in baseline HbA_{1c}, incidence of hypoglycemia, weight change Secondary: Health-related QOL, safety, mortality, morbidity, BP, FPG, PPG, lipid profile, β cell function	Primary: *Change in baseline HbA_{1c}* Exenatide ER significantly decreased HbA_{1c} compared to TZDs (-1.5 vs -1.2%; *P*=0.02), DPP-4 inhibitors (-1.5 vs -0.9%; *P*<0.0001), and insulin glargine (-1.5 vs -1.3%; treatment difference, -0.2%; 95% CI, -0.35 to -0.05; *P*=0.03). There was no difference in the proportion of patients achieving an HbA_{1c} <7.0% between exenatide ER and TZDs (60 vs 52%; *P*=0.15). A significantly greater proportion of patients receiving exenatide ER achieved an HbA_{1c} <7.0% compared to DPP-4 inhibitors (60 vs 35%; *P*<0.0001) and insulin glargine (60 vs 48%; *P*=0.03). Compared to placebo, treatment with liraglutide 1.2 mg significantly decreased HbA_{1c} (-1.15%; 95% CI, -1.33 to -0.96; *P*<0.00001). Patients receiving liraglutide 1.2 mg were more likely to achieve an HbA_{1c} <7.0% compared to patients receiving placebo (OR, 2.91; 95% CI, 1.74 to 4.87; *P*<0.05). Liraglutide 1.2 mg decreased HbA_{1c} to a greater extent compared to TZDs (-0.64%; 95% CI -0.83 to -0.45; *P* value not reported). The likelihood of achieving an HbA_{1c} <7.0% was greater with liraglutide 1.2 mg compared to TZDs (OR, 1.60; 95% CI, 1.18 to 2.15; *P* value not reported). Liraglutide 1.2 mg decreased HbA_{1c} to a greater extent compared to DPP-4 inhibitors (-0.34%; 95% CI -0.53 to -0.15; *P* value not reported). The likelihood of achieving an HbA_{1c} <7.0% was greater with liraglutide 1.2 mg

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				compared to DPP-4 inhibitors (OR, 2.56; 95% CI, 1.94 to 3.37; *P* value not reported). Liraglutide 1.2 mg was not associated with a decrease in HbA_{1c} compared to sulfonylureas (-0.01%; 95% CI -0.27 to 0.29; *P* value not reported). The likelihood of achieving an HbA_{1c} <7.0% was not greater with liraglutide 1.2 mg compared to sulfonylureas (OR, 0.98; 95% CI, 0.84 to 1.14; *P*=0.78). Compared to placebo, liraglutide 1.8 mg significantly decreased an HbA_{1c} (-1.15%; 95% CI, -1.31 to -0.99; *P*<0.05). Patients receiving liraglutide 1.8 mg were more likely to achieve HbA_{1c} <7.0% compared to placebo (OR, 3.25; 95% CI, 1.97 to 5.36; *P*<0.05). Liraglutide 1.8 mg decreased HbA_{1c} to a greater extent compared to TZDs (-0.69%; 95% CI -0.88 to -0.50%; *P* value not reported). The likelihood of achieving an HbA_{1c} <7.0% was greater with liraglutide 1.8 mg compared to TZDs (OR, 1.91; 95% CI, 1.43 to 2.53; *P* value not reported). Liraglutide 1.8 mg decreased HbA_{1c} to a greater extent compared to DPP-4 inhibitors (-0.60%; 95% CI -0.78 to -0.42; *P* value not reported). The likelihood of achieving HbA_{1c} <7.0% was greater with liraglutide 1.8 compared to DPP-4 inhibitors (OR, 1.99; 95% CI, 1.48 to 2.66; *P* value not reported). Liraglutide 1.8 mg was not associated with a reduction in HbA_{1c} compared to sulfonylureas (-0.02%; 95% CI -0.30 to 0.26; *P* value not reported). The likelihood of achieving an HbA_{1c} <7.0% was not greater with liraglutide 1.8 mg compared to sulfonylureas (OR, 1.09; 95% CI, 0.94 to 1.26; *P*=0.27). Liraglutide decreased HbA_{1c} to a greater extent compared to insulin glargine (-0.24%; 95% CI, -0.49 to 0.01; *P* value not reported). The likelihood of achieving an HbA_{1c} <7.0% was not different between insulin glargine and liraglutide (OR, 1.16; 95% CI, 0.96 to 1.40; *P* value not reported). Liraglutide 1.2 mg was associated with a non-significant increase in HbA_{1c} compared to 1.8 mg (0.10%; 95% CI, -0.03 to 0.23; *P*=0.13). Patients receiving liraglutide 1.2 mg were not more likely to achieve an HbA_{1c} <7.0% compared to the 1.8 mg dose (*P*=0.92). *Incidence of hypoglycemia*

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				The incidence of minor hypoglycemia was similar between exenatide ER and TZDs. The incidence of minor hypoglycemia was higher with DPP-4 inhibitors (five vs two patients) and insulin glargine (26 vs 8%) compared to exenatide ER. The incidence of major hypoglycemia was higher with insulin glargine compared to exenatide ER (two vs one patients). Overall, there was no difference in the incidence of minor hypoglycemia between liraglutide 1.2 mg and placebo (*P*=0.42), and there was significantly more hypoglycemia with liraglutide 1.8 mg (OR, 1.66; 95% CI, 1.15 to 2.40; *P*=0.007). The incidence of minor hypoglycemia was higher with insulin glargine compared to liraglutide (29 vs 27%). Liraglutide was associated with a significantly higher rate of minor hypoglycemia compared to TZDs (*P*=0.048), and similar rates compared to DPP-4 inhibitors (*P* values not reported). Liraglutide was associated with a significantly lower incidence of hypoglycemia compared to sulfonylureas (*P*<0.00001). *Weight loss* Exenatide ER significantly decreased weight compared to TZDs (-2.3 vs 2.8 kg; *P*<0.00001), DPP-4 inhibitors (-2.3 vs -0.8 kg; *P*=0.0009), and insulin glargine (-2.6 vs 1.4 kg; *P*<0.00001). Patients receiving liraglutide 1.2 mg experienced an average weight loss of -0.75 kg (95% CI, -1.95 to 0.45; *P*=0.22). Liraglutide 1.2 mg was associated with a greater decrease in weight compared to insulin glargine (-3.40 kg; 95% CI, -4.31 to -2.49; *P* value not reported), TZDs (-3.40 kg; 95% CI, -4.31 to -2.49; *P* value not reported), DPP-4 inhibitors (-1.90 kg; 95% CI, -2.65 to -1.15; *P* value not reported), and sulfonylureas (-3.60 kg; 95% CI, -4.15 to -3.05; *P* value not reported). Patients receiving liraglutide 1.8 mg experienced a significant weight loss compared to placebo (-1.33 kg; 95% CI, -2.38 to 0.27; *P*=0.0014). Liraglutide 1.8 mg was associated with a greater decrease in weight compared to TZDs (-2.30 kg; 95% CI, -2.85 to -1.75; *P* value not reported), DPP-4 inhibitors (-2.42 kg; 95% CI, -3.17 to -1.67; *P* value not reported), and (-3.80 kg; 95% CI, -4.35 to -3.25; *P* value not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Patients were more likely to experience weight gain with liraglutide 1.2 mg compared to 1.8 mg (0.48 kg; 95% CI, 0.16 to 0.80; *P* value not reported). Secondary: Data on mortality and morbidity were not reported for any treatment. *Quality of life* Exenatide ER significantly improved weight-related QOL and IWQOL total scores compared to TZDs (IWQOL treatment difference, 3.94; 95% CI, 1.28 to 6.61; *P*=0.0038). Both exenatide ER (IWQOL total score, 5.15; 95% CI, 3.11 to 7.19) and DPP-4 inhibitors (4.56; 95% CI, 2.56 to 6.57) resulted in significant improvements in weight-related QOL and IWQOL total scores. Treatment satisfaction was significantly greater with exenatide ER compared to DPP-4 inhibitors (treatment difference, 1.61; 95% CI, 0.07 to 3.16; *P*=0.0406). Exenatide ER significantly improved the self-esteem IWQOL domain and one EQ-5D dimensions compared to insulin glargine. Data for liraglutide were not reported. *Safety* Withdrawals due to adverse events were greater with exenatide ER compared to TZDs (6.9 vs 3.6%), DPP-4 inhibitors (6.9 vs 3.0%), and insulin glargine (4.7 vs 0.9%). More serious adverse events occurred with TZDs (6 vs 3%) compared to exenatide ER. The incidence of serious adverse events was similar between exenatide ER and DPP-4 inhibitors (3 vs 3%) and insulin glargine (5 vs 4%). Compared to placebo, withdrawals due to adverse events were between 5 and 10% with liraglutide 1.2 mg and between 4 and 15% with liraglutide 1.8 mg. Withdrawals were also higher with liraglutide compared to sulfonylureas (9.4 to 12.9 vs 1.3 to 3.0%). Liraglutide was associated with more gastrointestinal adverse events (nausea, vomiting, and diarrhea) compared to insulin glargine, TZDs, DPP-4 inhibitors, and sulfonylureas. *BP* There was no difference in the decreases in SBP and DBP between

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				exenatide ER and TZDs. Exenatide ER significantly decreased SBP compared to DPP-4 inhibitors (treatment difference, -4 mm Hg; 95% CI, -6 to -1; *P*=0.0055). There was no difference in the decrease in DBP between treatments. Data comparing exenatide ER and insulin glargine were not reported. Liraglutide 1.2 mg did not significantly decrease SBP (*P*=0.15) compared to placebo (*P*=0.15) and DPP-4 inhibitors (*P*=0.76). Liraglutide 1.8 mg significantly decreased SBP (*P*=0.05) compared to placebo, but not DPP-4 inhibitors (*P*=0.86). Liraglutide also significantly decreased SBP compared to insulin glargine (*P*=0.0001) and sulfonylureas (*P* value not reported). No difference in SBP was observed between liraglutide and DPP-4 inhibitors. There was no difference between liraglutide in the decrease in DBP compared to placebo, insulin glargine, or sulfonylureas. DPP-4 inhibitors significantly decreased DBP compared to liraglutide 1.8 mg (*P* value not reported). Data comparing liraglutide and TZDs were not reported. *FPG* There was no difference in the decrease in FPG between exenatide ER and TZDs (-1.8 vs -1.5 mmol/L; *P*=0.33). Exenatide ER significantly decreased FPG compared to DPP-4 inhibitors (-0.90 mmol/L; 95% CI, -1.50 to -0.30; *P*=0.0038), and insulin glargine significantly decreased FPG compared to exenatide ER (-0.70 mmol/L; 95% CI, 0.14 to 1.26; *P*=0.01). Liraglutide significantly decreased FPG compared to placebo (1.2 mg; *P*<0.0001 and 1.8 mg; *P*<0.00001), TZDs (*P*≤0.006), and DPP-4 inhibitors (*P*<0.00001). There was no difference between liraglutide and insulin glargine or sulfonylureas in decreases in FPG (*P* value not reported). *PPG* There was no difference in the decrease in PPG between exenatide ER and TZDs. Exenatide ER significantly decreased PPG at all measurements on a 6-point self-monitored glucose concentrations profile compared to DPP-4 inhibitors (*P*<0.05). Both exenatide ER and insulin glargine decreased PPG at all eight time points, with significant difference in favor of exenatide ER after dinner (*P*=0.004) and insulin glargine at 03000 hr

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				(*P*=0.022) and before breakfast (*P*<0.0001). Liraglutide significantly decreased PPG compared to placebo (*P* value not reported), TZDs (*P*<0.05), and sulfonylureas (liraglutide 1.8 mg; *P*<0.0001). There was no difference between liraglutide and insulin glargine in decreases in PPG (*P* value not reported). It was reported that PPG recorded in trials comparing liraglutide and DPP-4 inhibitors was highly variable. *Lipid profile* TZDs significantly decreased TG compared to exenatide ER. Exenatide ER decreased TC and LDL-C, while TZDs and DPP-4 inhibitors increased these measures. All treatments increased HDL-C. Data comparing exenatide ER and insulin glargine were not reported. Compared to placebo, liraglutide 1.2 decreased TG (*P*<0.05) and LDL-C (*P*<0.05), and no difference was observed with liraglutide 1.8 mg. Data comparing liraglutide to insulin glargine, TZDs, DPP-4 inhibitors, and sulfonylureas were not reported. *β cell function* Data for exenatide ER are not reported. Liraglutide significantly improved HOMA-B compared to placebo (P value not reported), TZDs (*P*<0.05), and DPP-4 inhibitors (*P* value not reported); and proinsulin:insulin ratio compared to placebo (*P* value not reported), insulin glargine (*P*=0.0019), and TZDs (*P*≤0.02). There was no difference between liraglutide and sulfonylureas in the improvements in HOMA-B and proinsulin:insulin ratio.

*Agent is not available in the United States.
Drug regimen abbreviations: BID=twice-daily, ER=extended-release, QD=once-daily, SC=subcutaneous, TID=three times daily, XL=extended-release
Study abbreviations: AC=active-comparator, CI=confidence interval, DB=double-blind, DD=double-dummy, ES=extension study, IA=interim analysis, ITT=intention-to-treat, MC=multicenter, OE=open-ended, OL=open-label, OR=odds ratio, PC=placebo-controlled, PG=parallel-group, RCT=randomized-controlled trial, RETRO=retrospective, RR=relative risk, SB=single-blind, SR=systematic review, TB=triple-blind, WMD=weighted mean difference
Miscellaneous abbreviations: ALT=alanine aminotransferase, apo B=apolipoprotein B, AST=aspartate aminotransferase, AUC=area under the curve, BES=binge eating scale, BMI=body mass index, BNP=brain natriuretic peptide, BP=blood pressure, COPD=chronic obstructive pulmonary disease, CRP=C-reactive protein, DBP=diastolic blood pressure, DPP-4 inhibitor=dipeptidyl peptidase-4 inhibitor, DSC-R=Diabetes Symptom Checklist-revised, DTSQ=Diabetes Treatment Satisfaction Questionnaire, EQ-5D=EuroQol Quality of Life, FFA=free fatty acid, FPG=fasting plasma glucose, GLP-1=glucagon-like peptide 1, HbA_{1c}=glycosylated hemoglobin, HDL-C=high density lipoprotein cholesterol, HOMA-B=homeostasis model assessment-beta, HOMA-IR=homeostasis model assessment-insulin resistance, HOMA-S=homeostasis model assessment-insulin sensitivity, IWQOL=Impact of Weight on Quality of life Questionnaire, LDL-C=low density lipoprotein cholesterol, MI=myocardial infarction, PAI-1=plasminogen activator inhibitor-1, PGWP=Psychological General Well-being index, PPG=post-prandial glucose, SBP=systolic blood pressure, SF-36=Medical

Outcomes Study 36-Item Short-Form Health Survey, TC=total cholesterol, TFS=Diabetes Treatment Flexibility Score, TG=triglycerides, TIA=transient ischemic attack, TZD=thiazolidinedione, VLDL-C=very low density lipoprotein cholesterol

Special Populations

Table 5. Special Populations[2-4]

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
Exenatide	No dosage adjustment required in the elderly, but dose should be based on renal function. Safety and efficacy in children have not been established.	Not recommended with end-stage renal disease or severe renal dysfunction (creatinine clearance <30 mL/minute). Use with caution in patients with renal transplantation. No dosage adjustment required with moderate renal dysfunction.	Not studied with hepatic dysfunction.	C	Unknown; use with caution.
Liraglutide	No dosage adjustment required in the elderly, but dose should be based on renal function. Safety and efficacy in children have not been established.	Use with caution.*	Not studied with hepatic dysfunction.	C	Unknown; use with caution.

*There is limited experience in patients with mild, moderate, and severe renal impairment, including end-stage renal disease.

Adverse Drug Events

Table 6. Adverse Drug Events* (%)[2-4]

Adverse Event	Exenatide/Exenatide ER	Liraglutide
Anorexia	-	9
Asthenia	4	-
Back pain	-	5
Constipation	-/6.3 to 10.1	5.1 to 9.9
Decreased appetite	1 to 2/5	9.3
Diarrhea	1 to 13/9.3 to 20.0	7.2 to 17.1
Dizziness	1 to 9	5.2
Dyspepsia	3 to 7/5.0 to 7.4	5.2 to 6.5
Fatigue	-/5.6 to 6.1	5.1
Feeling jittery	9	-
Gastroenteritis viral	-/8.8	-
Gastroesophageal reflux disease	3/7.4	-
Headache	9/6.1 to 9.9	8.2 to 9.6
Hyperhidrosis	3	-
Hypertension	-	3
Hypoglycemia	3.8 to 35.7/0 to 20	0.1 to 27.4
Influenza	-	7.4

Adverse Event	Exenatide/Exenatide ER	Liraglutide
Injection site erythema	-/5.4 to 7.4	-
Injection site hematoma	-/5.4	-
Injection site nodule	-/6.0 to 10.5	-
Injection site pruritis	-/5.0 to 18.2	-
Nasopharyngitis	-	5.2
Nausea	8 to 44/11.3 to 27.0	7.5 to 34.6
Sinusitis	-	5.6
Upper respiratory tract infection	-	9.5
Urinary tract infection	-	6
Vomiting	4 to 13/10.8 to 11.3	6.5 to 12.4

ER=extended-release
*Corresponds to monotherapy or combination therapy with other antidiabetic therapies.
-Event not reported.

Contraindications/Precautions

Exenatide, exenatide extended-release (ER), and liraglutide are contraindicated with a known hypersensitivity to any component of the preparations.[2-4] Exenatide ER and liraglutide is contraindicated with a personal or family history of medullary thyroid carcinoma or in patients with multiple endocrine neoplasia syndrome type 2.[3,4]

Exenatide ER and liraglutide cause dose-dependent and treatment-duration-dependent thyroid C-cell tumors at clinically relevant exposures in both genders of rats and mice, and malignant thyroid C-cell carcinomas were detected in rats and mice. It is unknown whether exenatide ER and liraglutide will cause thyroid C-cell tumors, including medullary thyroid carcinoma, in humans, as the human relevance of exenatide ER- and liraglutide-induced rodent thyroid C-cells tumors could not be determined by clinical or non-clinical trials.[3,4]

Based on post-marketing data, exenatide use has been associated with acute pancreatitis, which includes fatal and non-fatal hemorrhagic or necrotizing pancreatitis. Patients should be monitored for signs and symptoms of pancreatitis after initiation of exenatide or after a dosage increase. Exenatide should be promptly discontinued if pancreatitis is suspected and appropriate management should be initiated. Exenatide should not be restarted in patients in which pancreatitis was confirmed and other antidiabetic therapies other than exenatide should be considered in patients with a history of pancreatitis.[2,3] Pancreatitis has been also been observed in clinical trials evaluating liraglutide; however, there are no conclusive data establishing a risk of pancreatitis with liraglutide. The same monitoring criteria and actions that are recommended with exenatide should be followed with liraglutide. The recommendation to consider antidiabetic therapies other than liraglutide in patients with a history of pancreatitis is not clearly stated. Instead it is stated that liraglutide should be used with caution in these patients.[4]

When exenatide, exenatide ER, or liraglutide is used combination with a sulfonylurea the risk of hypoglycemia is increased, therefore, a reduction in the dosage of the sulfonylurea may be required. It is also possible that when these agents are used with other glucose-independent insulin secretagogues (e.g., meglitinides) the risk of hypoglycemia is increased.[2-4] Furthermore, when exenatide is used in combination with insulin, the dose of insulin should be evaluated.[2,3]

Due to the fact that exenatide has not been evaluated in patients with severe gastrointestinal disease, and since gastrointestinal adverse reactions are commonly associated with exenatide, treatment is not recommended in patients with severe gastrointestinal disease.[2,3]

Patients may develop antibodies to exenatide following treatment initiation. If glycemic control worsens or if target glycemic control is not achieved, alternative antidiabetic therapy should be considered.[2,3]

These contraindications/precautions have resulted in the assignment by the Food and Drug Administration of the Black Box Warnings outlined below.

Black Box Warning for Bydureon® (exenatide extended-release)[57]

WARNING
Exenatide extended-release (ER) causes an increased incidence in thyroid C-cell tumors at clinically relevant exposures in rats compared to controls. It is unknown whether exenatide causes thyroid C-cell tumors, including medullary thyroid carcinoma, in humans, because human relevance could not be determined by clinical or nonclinical studies. Exenatide ER is contraindicated in patients with a personal or family history of medullary thyroid carcinoma and in patients with multiple endocrine neoplasia syndrome type 2. Routine serum calcitonin or thyroid ultrasound monitoring is of uncertain value in patients treated with exenatide ER. Counsel patients regarding the risk and symptoms of thyroid tumors.

Black Box Warning for Victoza® (liraglutide)[57]

WARNING
Liraglutide causes dose-dependent and treatment-duration-dependent thyroid C-cell tumors at clinically relevant exposures in both genders of rats and mice. It is unknown whether liraglutide causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans, as human relevance could not be ruled out by clinical or nonclinical studies. Liraglutide is contraindicated in patients with a personal or family history of MTC and in patients with Multiple Endocrine Neoplasia syndrome type 2. Based on the findings in rodents, monitoring with serum calcitonin or thyroid ultrasound was performed during clinical trials, but this may have increased the number of unnecessary thyroid surgeries. It is unknown whether monitoring with serum calcitonin or thyroid ultrasound will mitigate human risk of thyroid C-cell tumors. Patients should be counseled regarding the risk and symptoms of thyroid tumors.

Drug Interactions

No clinical significant drug interactions have been reported for either exenatide or liraglutide.[2-4,57]

Dosing and Administration

The incretin mimetics are administered as a subcutaneous injection in the abdomen, thigh, or upper arm. Exenatide is administered twice-daily (60 minutes before meals), liraglutide is administered once-daily (independent of meals), and exenatide extended-release is administered once weekly (independent of meals).[2-4]

Table 7. Dosing and Administration[2-4]

Generic Name	Usual Adult Dose	Usual Pediatric Dose	Availability
Exenatide	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus: Extended-release injection: initial, 2 mg SC once weekly Injection: initial, 5 µg SC BID; maintenance, 10 µg SC BID after one month of therapy	Safety and efficacy in children have not been established.	Extended-release injection (Bydureon®): 2 mg/vial* Injection (Byetta®): 250 µg/mL†
Liraglutide	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus: Injection: initial, 0.6 mg SC QD for one week; maintenance, 1.2 to 1.8 mg SC QD	Safety and efficacy in children have not been established.	Injection: 6 mg/mL‡

BID=twice-daily, QD=once-daily, SC=subcutaneous
*Supplied in cartons of four single-dose trays (one vial containing 2 mg exenatide [as a white to off-white powder], one pre-filled syringe [0.65 mL diluents], one vial connector, and two custom needles).
†Supplied as a 5 µg/dose pre-filled syringe (1.2 mL, 60 doses) and 10 µg/dose pre-filled syringe (2.4 mL, 60 doses).
‡Supplied as 0.6 (30 doses), 1.2 (15 doses), and 1.8 mg (10 doses) pre-filled, multi-dose pens (3 mL) available in a package of two or three pens.

Clinical Guidelines

Current clinical guidelines are summarized in Table 8. Please note that guidelines addressing the treatment of type 2 diabetes are presented globally, addressing the role of various medication classes.

Table 8. Clinical Guidelines

Clinical Guideline	Recommendations
American Diabetes Association: **Standards of Medical Care in Diabetes (2011)**[51]	Current criteria for the diagnosis of diabetes • The following are the criteria for a diagnosis of diabetes: glycosylated hemoglobin (HbA_{1c}) ≥6.5%, or a fasting plasma glucose (FPG) ≥126 mg/dL, or a two-hour plasma glucose ≥200 mg/dL during an oral glucose tolerance test or patients with classic symptoms of hyperglycemia or hyperglycemic crisis with a random plasma glucose ≥200 mg/dL. Prevention/delay of type 2 diabetes • An ongoing support program for weight loss of 7% of body weight and an increase in physical activity to ≥150 minutes/week of moderate activity, should be encouraged in patients with impaired glucose tolerance, impaired fasting glucose, or an HbA_{1c} 5.7 to 6.4%. • Metformin therapy for prevention of type 2 diabetes may be considered in patients at the highest risk for developing diabetes, such as those with multiple risk factors, especially if they demonstrate progression of hyperglycemia (e.g., HbA_{1c} ≥6.0%) despite lifestyle interventions. Glycemic goals in adults • A reasonable HbA_{1c} goal for many nonpregnant adults is <7.0%. • Based on data from randomized trials, it may be reasonable for providers to suggest more stringent HbA_{1c} goals for selected patients, if this can be achieved without significant hypoglycemia or other adverse effects of treatment. Such patients may include those with short duration of diabetes, long life expectancy, and no significant cardiovascular disease. • Conversely, less stringent HbA_{1c} goals may be appropriate for patients with a history of severe hypoglycemia, limited life expectancy, advanced microvascular or macrovascular complications, extensive comorbid conditions, and those with longstanding diabetes in whom the general goal is difficult to attain. Pharmacologic and overall approaches to treatment-type 2 diabetes • The treatment algorithm outlined below from the American Diabetes Association/European Association for the Study of Diabetes is recommended.[52] • Highlights of the algorithm include the following: o Intervention at the time of diagnosis with metformin in combination with lifestyle changes. o Continuing timely augmentation of therapy with additional agents (including early initiation of insulin therapy) as a means of achieving and maintaining recommended glycemic goals. o As glycemic goals are not achieved, treatment intensification is based on the addition of another agent from a different class. o The overall objective is to achieve and maintain glycemic control and to change interventions when therapeutic goals

Clinical Guideline	Recommendations
	are not being met. o The precise drugs used and their exact sequence may not be as important as achieving and maintaining glycemic targets safely. o Medications not included in the algorithm still may be appropriate choices in individual patients to achieve glycemic goals. o Initiation of insulin at the time of diagnosis is recommended for patients presenting with weight loss or other severe hyperglycemia symptoms or signs.
American Diabetes Association/European Association for the Study of Diabetes: **Management of Hyperglycemia in Type 2 Diabetes: A Consensus Algorithm for the Initiation and Adjustment of Therapy (2009)**[52]	• The goal of the recommended algorithm is to achieve and maintain HbA_{1c} levels <7.0% and to change interventions at as rapid a pace as titration of medications allows when target glycemic goals are not being achieved. • The α-glucosidase inhibitors, amylin agonists, dipeptidyl peptidase-4 (DPP-4) inhibitors, and glinides are not included in the two tiers of preferred agents in the algorithm due to their lower or equivalent overall glucose-lowering effectiveness compared to the first- and second-tier agents, and/or due to limited clinical data or relative expense. These agents may be appropriate choices in selected patients. <u>Tier 1: well-validated core therapies</u> • These interventions represent the best established and most effective and cost-effective therapeutic strategies for achieving target glycemic goals, and are the preferred route of therapy for most type 2 diabetic patients. • Step 1: Lifestyle interventions and metformin should be initiated concurrently at diagnosis of type 2 diabetes. • Step 2: If lifestyle interventions and the maximal tolerated dose of metformin fail to achieve or sustain glycemic goals after two to three months, insulin or a sulfonylurea should be added. The choice between insulin or a sulfonylurea will be based on the HbA_{1c} levels, with consideration given to insulin (the more effective glycemia-lowering agent) for patients with an HbA_{1c} >8.5%. However, many newly diagnosed type 2 diabetic patients will usually respond to oral medications. • Step 3: If lifestyle interventions, metformin and basal insulin or a sulfonylurea do not achieve glycemic goals, insulin therapy should be initiated or intensified. <u>Tier 2: less well-validated therapies</u> • In selected clinical settings, the tier 2 algorithm may be considered. • Specifically, when hypoglycemia is particularly undesirable, the addition of exenatide or pioglitazone may be considered. Rosiglitazone is not recommended. • Additionally, if a major consideration is weight loss and the HbA_{1c} level is close to target (<8.0%), then exenatide may be an option (at the time of publication only exenatide had Food and Drug Administration [FDA] approval). • If these interventions do not effectively achieve glycemic goals or if they are not tolerated, the addition of a sulfonylurea could be considered or the tier 2 interventions should be discontinued and basal

Clinical Guideline	Recommendations
	insulin should be initiated. Rationale for selecting specific combinations • Over time the majority of patients will require more than one medication. • When selecting combination therapy, in general, antihyperglycemic drugs with different mechanisms of action will have the greatest synergy. • Combination insulin and metformin therapy is a particularly effective means of lowering glycemia with limited weight gain. Special considerations/patients • In the setting of severely uncontrolled diabetes with catabolism, combination insulin and lifestyle intervention therapy is the treatment of choice.
American College of Physicians: **Oral Pharmacologic Treatment of Type 2 Diabetes Mellitus (2012)**[53]	• Oral pharmacologic therapy in patients with type 2 diabetes should be added when lifestyle modifications, including diet, exercise, and weight loss, have failed to adequately improve hyperglycemia. • Monotherapy with metformin for initial pharmacologic therapy is recommended to treat most patients with type 2 diabetes. • It is recommended that a second agent be added to metformin to patients with persistent hyperglycemia when lifestyle modifications and monotherapy with metformin fail to control hyperglycemia.
American Association of Clinical Endocrinologists/ American College of Endocrinology: **Statement by an American Association of Clinical Endocrinologists/ American College of Endocrinology Consensus Panel on Type 2 Diabetes Mellitus: An Algorithm for Glycemic Control (2009)**[54]	Principles underlying the algorithm • Lifestyle (dietary and exercise) modifications are essential for all patients with diabetes. • Achieving an HbA_{1c} 6.5% is recommended as the primary goal; however, the goal must be customized for individual patients. • If glycemic goals are not achieved, dosages of medications can be titrated, regimens can be changed (add or discontinue medications), or, in certain instances, glycemic goals can be reconsidered and revised. • When using combination therapy it is important to have medications that have complementary mechanisms of action. • Effectiveness of therapy must be re-evaluated frequently, typically every two to three months. Stratification by current HbA_{1c} • Patients with an HbA_{1c} ≤7.5% may be able to achieve a goal of 6.5% with monotherapy; however, if monotherapy fails to achieve this goal, the usual progression is to combination therapy, and then to triple therapy. Insulin therapy, with or without additional agents, should be initiated if goals still fail to be achieved. • Patients with an HbA_{1c} 7.6 to 9.0% should be initiated on combination therapy as monotherapy in these patients is likely not to achieve glycemic goals. If combination therapy fails, triple therapy and then insulin therapy, with or without additional oral agents, should be administered. • Patients with an HbA_{1c} >9.0% have a small possibility of achieving glycemic goals, even with combination therapy. In these patients, if they are asymptomatic triple therapy based on a combination of metformin and an incretin mimetic or a DPP-4 inhibitor combined with either a sulfonylurea or a thiazolidinedione (TZD) should be initiated. If

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	patients are symptomatic or if they have failed therapy with similar agents, insulin therapy with or without additional oral agents should be initiated. Management of patients with a HbA_{1c} 6.5 to 7.5% • In these patients monotherapy with metformin, an α-glucosidase inhibitor, a DPP-4 inhibitor, or a TZD are recommended. Because of the established safety and efficacy of metformin, it is the cornerstone of monotherapy and is usually the most appropriate initial choice for monotherapy. • If monotherapy, even after appropriate dosage titration, is unsuccessful in achieving glycemic goals combination therapy should be initiated. • Because of the established safety and efficacy of metformin, it is considered the cornerstone of combination therapy for most patients. When contraindicated, a TZD may be used as the foundation for combination therapy options. • Due to the mechanism of action (insulin sensitizer) of metformin and TZDs, it is recommended that the second agent in combination therapy be an incretin mimetic, DPP-4 inhibitor, or a secretagogue (glinide or sulfonylurea). • The glucagon-like-peptide-1 (GLP-1) receptor agonists (incretin mimetics) and DPP-4 inhibitors are associated with less hypoglycemia compared to the secretagogues. • Despite the gastrointestinal side effects, dosing frequency and injection-based therapy, the GLP-1 agonists are preferred due to its greater effectiveness in reducing post-prandial glucose excursions (relative to the DPP-4 inhibitors) and the potential for weight loss. • Combination metformin and TZD therapy is efficacious but carries risks of adverse events associated with both agents. The combination is recommended with a higher priority than a secretagogue because of a lower risk of hypoglycemia and greater flexibility in timing of administration. • The combination therapies of metformin and an α-glucosidase inhibitor and metformin and colesevelam are also included in the algorithm because of their safety and the ability of colesevelam to lower lipid profiles. • If combination therapy fails after each medication has been titrated to its maximally effective dose then triple therapy should be initiated. • The following triple therapy regimens are considered: o Metformin + GLP-1 agonist + TZD. o Metformin + GLP-1 agonist + glinide. o Metformin + GLP-1 agonist + sulfonylurea. o Metformin + DPP-4 inhibitor + TZD. o Metformin + DPP-4 inhibitor + glinide. o Metformin + DPP-4 inhibitor + sulfonylurea. • Because of the established safety and efficacy of metformin, it is considered the cornerstone for triple therapy. • The GLP-1 agonist, exenatide, is the second preferred component of triple therapy because of its safety (low risk of hypoglycemia) and its potential for inducing weight loss. It also inhibits glucagon secretion in a glucose-dependent manner after consumption of means resulting in increased satiety and delayed gastric emptying.

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	• The third component of triple therapy is recommended in order to minimize the risk of hypoglycemia. • The combination with metformin, especially when combined with an incretin mimetic, may counteract the weight gain often associated with glinides, sulfonylureas, and TZDs. • When triple therapy fails to achieve glycemic goals, insulin therapy is needed. Management of patients with a HbA_{1c} 7.6 to 9.0% • The management of these patients is similar to that just described except patients can proceed directly to combination therapy because monotherapy is unlikely to be successful in these patients. • The following combination therapy regimens are considered: o Metformin + GLP-1 agonist. o Metformin + DPP-4 inhibitor. o Metformin + TZD. o Metformin + sulfonylurea. o Metformin + glinide. • Metformin is again considered the cornerstone of combination therapy. • A GLP-1 agonist or DPP-4 inhibitor is the preferred second component in view of the safety and efficacy of these agents in combination with metformin. Additionally, a GLP-1 agonist is given higher priority in view of its somewhat greater effect on reducing post-prandial glucose (PPG) excursions and its potential for inducing substantial weight loss. • TZDs are positioned lower due to the risks of weight gain, fluid retention, congestive heart failure, and fractures associated with their use. • Glinides and sulfonylureas are relegated to the lowest position because the greater risk of inducing hypoglycemia. • When combination therapy fails to achieve glycemic goals, triple therapy should be started. • The following triple therapy regimens are considered: o Metformin + GLP-1 agonist + TZD. o Metformin + DPP-4 inhibitor + TZD. o Metformin + GLP-1 agonist + sulfonylurea. o Metformin + DPP-4 inhibitor + sulfonylurea. o Metformin + TZD + sulfonylurea. • Metformin is the foundation to which either a TZD or sulfonylurea is added, followed by incretin-based therapy with either a GLP-1 agonist or a DPP-4 inhibitor. • The preference for metformin and the GLP-1 agonist or DPP-4 inhibitor is based on the safety of these agents and minimal associated risks of hypoglycemia. • TZDs are assigned a higher priority than a sulfonylurea because of their lower risk of hypoglycemia. • A GLP-1 agonist is assigned a higher priority than a DPP-4 inhibitor because of its somewhat greater effect on reducing PPG excursions and the possibility that it might induce considerable weight loss. • Metformin + TZD + sulfonylurea is relegated to the lowest priority due to an increased risk of weight gain and hypoglycemia. • α-glucosidase inhibitors, colesevelam, and glinides are not considered as options in these patients due to their limited HbA_{1c}-lowering potential.

Clinical Guideline	Recommendations
	• The considerations for insulin therapy in these patients are similar to those used in patients with an HbA_{1c} 6.5 to 7.5%. Management of patients with a HbA_{1c} >9.0% • Patients who are drug-naïve with an HbA_{1c} >9.0% are unlikely to achieve glycemic goals with the use of one, two, or even three agents (other than insulin). • For patients who are asymptomatic, particularly with a relatively recent onset of diabetes, there is a good chance that some endogenous β-cell function exists; implying that combination or triple therapy may be sufficient. • The following combination and triple therapy regimens are considered: o Metformin + GLP-1 agonist. o Metformin + GLP-1 agonist + sulfonylurea. o Metformin + DPP-4 inhibitor. o Metformin + DPP-4 inhibitor + sulfonylurea. o Metformin + TZD. o Metformin + TZD + sulfonylurea. o Metformin + GLP-1 agonist + TZD. o Metformin + DPP-4 inhibitor + TZD. • Metformin again provides the foundation of treatment in these patients. • An incretin-based therapy can be added with a GLP-1 agonist being preferred due to its greater effectiveness at controlling post-prandial glycemia and its potential for inducing weight loss. However the DPP-4 inhibitors in combination with metformin have also demonstrated a robust benefit for drug-naïve patients in this HbA_{1c} range. • A sulfonylurea or a TZD can also be added, with a sulfonylurea being preferred because of its somewhat greater efficacy and more rapid onset of action. • If patients are symptomatic (polydipsia, polyuria, weight loss) or if they have already failed the aforementioned treatment regimens, insulin therapy should be initiated without delay. • Insulin therapy for these patients follows the same principals as outlined previously for patients with different HbA_{1c} levels. • This algorithm favors the use of GLP-1 agonists (at the time of publication only exenatide had FDA approval) and DPP-4 inhibitors with higher priority due to their effectiveness and overall safety profiles. Additionally, due to the increasing amount of literature indicating the serious risks of hypoglycemia, these agents are becoming preferred in most patients in place of secretagogues. • The algorithm moves sulfonylureas to a lower priority due to the risks of hypoglycemia and weight gain associated with their use, as well as the failure of these agents to provide improved glycemic control after use for a relatively short period. • A TZD is considered a “well-validated” effective agent due to demonstrated extended durability of action, but these agents have a lower priority for many patients in light of their potential side effects. • The three classes of medications; α-glucosidase inhibitors, colesevelam, and glinides, are considered in relatively narrow, well-defined clinical situations, due to their limited efficacy.
American Association of Clinical Endocrinologists: **Medical Guidelines for**	Glycemic management-all patients with diabetes • Encourage patients to achieve glycemic levels as near normal as possible without inducing clinically significant hypoglycemia. Glycemic

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Clinical Practice for the Management of Diabetes Mellitus (2007)[55]	targets include the following: o HbA_{1c} ≤6.5%. o FPG <100 mg/dL. o Two-hour PPG <140 mg/dL. • Refer patients for comprehensive, ongoing education in diabetes self-management skills and nutrition therapy. • Initiate self-monitoring blood glucose levels. <u>Glycemic management-patients with type 2 diabetes</u> • Aggressively implement all appropriate components of care at the time of diagnosis. • Persistently monitor and titrate pharmacologic therapy until all glycemic goals are achieved. o First assess current HbA_{1c} level, fasting/pre-prandial glycemic profile, and two-hour PPG profile to evaluate the level of control and identify patterns. o After initiating pharmacologic therapy based on the patterns identified in the profile, persistently monitor and titrate therapy over the next two to three months until all glycemic goals are achieved. o If glycemic goals are not achieved at the end of two to three months, initiate a more intensive regimen and persistently monitor and titrate therapy over the next two to three months until all glycemic goals are achieved. o Recognize that patients currently treated with monotherapy or combination therapy who have not achieved glycemic goals will require either increased dosages of current medications or the addition of a second or third medication. o Consider insulin therapy in patients with HbA_{1c} >8.0% and symptomatic hyperglycemic, and in patients with elevated fasting blood glucose levels or exaggerated PPG excursions regardless of HbA_{1c} levels. o Initiate insulin therapy to control hyperglycemia and to reverse glucose toxicity when HbA_{1c} >10.0%. Insulin therapy can then be modified or discontinued once glucose toxicity is reversed. o Consider a continuous subcutaneous insulin infusion in insulin-treated patients. • Instruct patients whose glycemic levels are at or above target while receiving multiple daily injections or using an insulin pump to monitor glucose levels at least three times daily. Although monitoring glucose levels at least three times daily is recommended, there is no supporting evidence regarding optimal frequency of glucose monitoring with or without insulin pump therapy. • Instruct insulin-treated patients to always check glucose levels before administering a dose of insulin by injection or changing the rate of insulin infusion delivered by an insulin pump. • Instruct patients whose glycemic levels are above target while being treated with oral agents alone, oral agents plus once-daily insulin, or once-daily insulin alone to monitor glucose levels at least two times daily. There is no supporting evidence regarding optimal frequency of glucose monitoring in these patients. • Instruct patients who are meeting target glycemic levels, including those treated non-pharmacologically, to monitor glucose levels at least

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	once daily. • Instruct patients whose glycemic levels are above target or who experience frequent hypoglycemia to monitor glucose levels more frequently. Monitoring should include both pre-prandial and two-hour PPG levels and occasional 2:00 to 3:00 AM glucose levels. • Instruct patients to obtain comprehensive pre-prandial and two-hour PPG measurements to create a weekly profile periodically and before clinician visits to guide nutrition and physical activity, to detect post-prandial hyperglycemia, and to prevent hypoglycemia. • Instruct patients to monitor glucose levels anytime there is a suspected (or risk of) low glucose level and/or before driving. • Instruct patients to monitor glucose levels more frequently during illness and to perform a ketone test each time a measured glucose concentration is >250 mg/dL. <u>Clinical support-clinical considerations in patients with type 2 diabetes</u> • Combining therapeutic agents with different modes of action may be advantageous. • Use insulin sensitizers, such as metformin or TZDs, as part of the therapeutic regimen in most patients unless contraindicated or intolerance has been demonstrated. • Insulin is the therapy of choice in patients with advanced chronic kidney disease. • Metformin, TZDs, and incretin mimetics do not cause hypoglycemia. However, when used in combination with secretagogues or insulin, these medications may need to be adjusted as blood glucose levels decline. • The weight gain associated with TZDs in some patients may be partly offset by combination therapy with metformin. • Carefully assess PPG levels if the HbA_{1c} level is elevated and pre-prandial glucose measurements are at target levels. • Instruct patients to assess PPG levels periodically to detect unrecognized exaggerated PPG excursions even when the HbA_{1c} level is at or near target. • Individualize treatment regimens to accommodate patient exercise patterns. • Administer basal insulin in the evening if fasting glucose is elevated. • Long-acting insulin analogs are associated with less hypoglycemia than neutral protamine Hagedorn insulin.

Conclusions

The glucagon-like peptide-1 receptor agonists, or incretin mimetics, exenatide (Bydureon®, Byetta®) and liraglutide (Victoza®), are incretin-based antidiabetic therapies that are Food and Drug Administration-approved as adjunctive therapy to diet and exercise in adult type 2 diabetics.[2-4] These agents work in a glucose-dependent manner and maintain glucose homeostasis through several different mechanisms. Incretin mimetics enhance insulin secretion from the pancreatic β cell in the presence of elevated glucose, suppress inappropriately elevated glucagon secretion, and slow gastric emptying, all of which result in improved fasting plasma glucose (FPG).[1-4,6]

The incretin mimetics are available as subcutaneous (SC) injections to be administered in the abdomen, thigh, or upper arm. Specifically, exenatide (Byetta®) is administered twice-daily (60 minutes prior to meals), liraglutide (Victoza®) is administered once-daily (independent of meals), and ER extended-release (ER) (Bydureon®) is administered once weekly (independent of meals).[2-4] The extended formulation of

exenatide (Bydureon®), was developed by adding the biodegradable polymer poly D, L-lactic-co-glycolic acid to exenatide. As a result, microspheres are formed and after administered, continued infiltration of water into the microspheres causes them to swell and release exenatide in a slow predictable fashion. Patients who administer exenatide ER will have a palpable SC nodule at the injection site that dissipates as the medication is released.[7] In terms, of adverse events, the most commonly reported with the incretin mimetics are gastrointestinal-related, and all of the agents are associated with risk of developing pancreatitis.[2-4] Exenatide ER and liraglutide have a black boxed warning regarding the risk for thyroid C-cell tumors.[3,4]

The incretin mimetics have been evaluated in clinical trials and have consistently demonstrated positive effects on glycosylated hemoglobin, FPG, post-prandial glucose (PPG), body weight, and blood pressure. In general, the incretin mimetics have been evaluated as add-on therapy to treatment regimens of established antidiabetic agents. The most commonly reported adverse events associated with the incretin mimetics within clinical trials were gastrointestinal-related.[8-50] According to current clinical guidelines, metformin remains the cornerstone of most type 2 diabetes treatment regimens. The incretin mimetics are recommended as a potential second-line treatment option to be added to or used in combination with metformin in patients not achieving glycemic goals. Clinical guidelines note a lower rate of hypoglycemia, established efficacy and safety profile when used in combination with metformin, demonstrated effectiveness in reducing PPG, and the potential for weight loss as advantages associated with the incretin mimetics compared to other antidiabetic agents. No one incretin mimetic is recommended or preferred over another.[51-55]

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DIVISION OF HEALTH CARE FINANCING AND POLICY
NEVADA MEDICAID
DRUG USE REVIEW (DUR) BOARD
PROPOSED PRIOR AUTHORIZATION CRITERIA

Byetta® (exenatide), Bydureon® (exenatide extended-release) and Victoza® (liraglutide) are a covered benefit of Nevada Medicaid for recipients who meet the criteria for coverage.

1. Coverage and Limitations:
Authorization will be given if the following criteria are met and documented:

a. The recipient is 18 years of age or older.
AND
b. The recipient has a diagnosis of type 2 diabetes mellitus.
AND
c. The recipient is currently taking metformin and/or a sulfonylurea.
AND
d. The recipient has failed to achieve glycemic control despite an appropriate trial with metformin and/or a sulfonylurea.

2. PA Guidelines:
Prior Authorization approval will be for 6 months.

3. Quantity Limits:
Byetta: 1 pen per rolling 25 days
Bydureon: 4 vials (one-time use) per rolling 25 days
Victoza: 3 pens per rolling 25 days

2012 Q1 and Q2 Bydureon and Victoza Utilization

YearMonth Submitted	Drug Label Name	Claim Count	Sbm Qty Dispense	Sbm Days Supply	App Dispensing	App Total Amount
201201	BYDUREON INJ	-	-	-	$ -	$ -
201202	BYDUREON INJ	-	-	-	$ -	$ -
201203	BYDUREON INJ	-	-	-	$ -	$ -
201204	BYDUREON INJ	-	-	-	$ -	$ -
201205	BYDUREON INJ	-	-	-	$ -	$ -
201206	BYDUREON INJ	1	4	90	$ -	$ 3.30
201201	VICTOZA INJ 18MG/3ML	26	240	956	$ 109.48	$ 5,195.34
201202	VICTOZA INJ 18MG/3ML	22	171	656	$ 95.20	$ 3,689.13
201203	VICTOZA INJ 18MG/3ML	28	210	824	$ 76.16	$ 5,441.94
201204	VICTOZA INJ 18MG/3ML	33	315	1,233	$ 99.96	$ 8,903.56
201205	VICTOZA INJ 18MG/3ML	36	300	1,156	$ 119.00	$ 9,662.19
201206	VICTOZA INJ 18MG/3ML	23	174	761	$ 71.40	$ 5,448.40