ORIGINAL RESEARCH

Overview of Glucagon-Like Peptide-1 Receptor Agonists for the Treatment of Patients with Type 2 Diabetes

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BACKGROUND: It is estimated that 29.1 million people or 9.3% of the US population have diabetes, which contributes to considerable medical and financial burden. Type 2 diabetes mellitus is characterized by insulin resistance and insulin secretion impairment leading to hyperglycemia. The presence of insulin resistance is strongly correlated with obesity.

OBJECTIVE: This article reviews the available glucagon-like peptide-1 (GLP-1) receptor agonists and their role in the management of patients with diabetes, to help guide the selection of the most suitable agent for the individualized treatment of patients with type 2 diabetes.

DISCUSSION: This article reviews the evidence from phase 3 clinical trials for each of the 5 GLP-1 receptor agonists by comparing them against one another and with other existing therapies, including metformin, dipeptidyl peptidase-4 (DPP-4) inhibitors, and sulfonylureas. Incretin-based therapies have emerged as attractive agents for the treatment of type 2 diabetes. They target the GLP-1 hormone, which is partly responsible for insulin release and for attenuating hyperglycemia during meals (ie, the incretin effect). The 2 classes of incretin-based therapy currently available are GLP-1 receptor agonists and DPP-4 inhibitors, which prevent the breakdown of GLP-1. Both classes are attractive options, given their glucose-lowering effects without the adverse effects of hypoglycemia and weight gain. The different mechanisms of action of these therapies result in generally greater efficacy with GLP-1 receptor agonists, albeit at the expense of slightly increased gastrointestinal symptoms. These agents exert their effects by improving glucose-dependent insulin release, suppressing glucagon release, suppressing hepatic glucose output, and decreasing the rate of gastric emptying, thereby reducing appetite. Currently, 5 GLP-1 receptor agonists are available, including exenatide, liraglutide, albiglutide, dulaglutide, and lixisenatide; semaglutide may soon become available as the newest agent. With the exception of the investigational oral semaglutide, which has shown promising results, the other 5 agents are administered as subcutaneous injections, at different dosing intervals.

CONCLUSION: Currently, 5 GLP-1 receptor agonists are available for use in the United States. Although they are all in the same drug class, some significant differences exist among the various GLP-1 receptor agonists. The choice of a specific GLP-1 receptor agonist will depend on the patient preferences, potential adverse effects, and cost.

Stakeholder Perspective, page 187

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It is estimated that 29.1 million people or 9.3% of the US population have diabetes, which contributes to considerable medical and financial burden.[1] Type 2 diabetes mellitus is characterized by insulin resistance, and by some impairment in insulin secretion leading to hyperglycemia. The presence of insulin resistance is strongly correlated with obesity.[1]

A significant challenge in the treatment of diabetes is avoiding the development of hypoglycemia, particularly with sulfonylureas and insulin. Complications of hypoglycemia include unconsciousness, brain damage, and even death if untreated.[1] Another adverse effect associated with the treatment of diabetes is weight gain, which occurs with most antidiabetes agents, including sulfonyl-

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urea, insulin, and thiazolidinediones.[2] Because obesity is closely linked to diabetes, these agents' efficacy in treating diabetes become partly limited because of their link to weight gain.[2]

Cost is also an important consideration when selecting among the many antidiabetes medications. **Table 1** compares the costs of diabetic agents. Glucagon-like peptide (GLP)-1 receptor agonists are generally the most expensive agents. Of note, the cost of Soliqua 100/33 (insulin glargine and lixisenatide injection), which is a combination of insulin glargine and a GLP-1 receptor agonist, is comparable to other GLP-1 receptor agonists that are given as monotherapy. The cost of individual antidiabetes agents may vary depending on insurance coverage, although coupons are often available for a significant cost reduction. Although the cost of diabetes medications (and associated supplies) is significant (12% of the overall cost of treating diagnosed diabetes), the costs of treating the complications of diabetes (18%) and of diabetes-related inpatient care (43%) are even greater.[3] Therefore, it is more cost-effective for patients when their diabetes is appropriately controlled with medications, as necessary.

The Rationale for GLP-1 Receptor Agonists

The pathology of type 2 diabetes involves inherited traits and environmental factors. The vast majority of patients with type 2 diabetes have a genetic risk for insulin resistance; however, the risk for diabetes also worsens with increasing age and weight.[2] Obese patients have more adipocytes, which release leptin, adiponectin, tumor necrosis factor–alpha, and resistin, and these hormones are thought to further contribute to insulin resistance.

During periods of hyperglycemia, there is an increase in glucose transport into beta-cells of the pancreas, which leads to insulin secretion. It is well-recognized that continued poor control of hyperglycemia leads to a decline in beta-cell function, which is likely a result of decreased insulin gene expression and decreased production of insulin. Therefore, it is important that lifestyle changes and treatments are implemented to maintain euglycemia. Uncontrolled diabetes will eventually lead to complications, such as microvascular disease (ie, retinopathy, nephropathy, and neuropathy), and cardiovascular (CV) events and hypertension.

Insulin secretion occurs in 2 phases. The first phase occurs after a meal, manifested as an immediate rise in insulin lasting approximately 10 minutes. This is followed by a second phase, in which insulin is released more slowly for a prolonged period. Patients with type 2 diabetes have markedly reduced first-phase insulin secretion, which likely explains why the majority have persistently elevated postprandial glucose concentrations despite relatively normal fasting glucose levels.[4,5] The beta-cells in the pancreas respond to this by increasing second-phase insulin response.[6] However, prolonged elevation of insulin from persistent hyperglycemia leads to beta-cell toxicity and ultimately contributes to insulin resistance.[7] Interventions that mimic normal first-phase insulin secretion, rather than the second phase, have been correlated with improved glucose tolerance.[8]

GLP-1 is a naturally occurring hormone responsible for the incretin effect. The incretin effect is a response to release more insulin because of high glucose levels after a meal. Studies suggest that patients with type 2 diabetes have an attenuated incretin effect, possibly because of reduced levels of active GLP-1.[9] Evidence shows that GLP-1 regulates the expression of beta-cell genes by inhibiting beta-cell apoptosis, preventing beta-cell glucolipotoxicity, and improving beta-cell function.[10] GLP-1 has been shown to suppress glucagon release and hepatic glucose output.[10] GLP-1 also decreases the rate of gastric

KEY POINTS

- This article reviews the available glucagon-like peptide-1 (GLP-1) receptor agonists and their role in the management of patients with diabetes.
- Clinical trials demonstrate the superiority of GLP-1 receptor agonists to other antidiabetes drugs in HbA_{1c} reduction, blood pressure reduction, and weight loss, without hypoglycemia risk.
- The 5 GLP-1 receptor agonists available include exenatide, liraglutide, albiglutide, dulaglutide, and lixisenatide.
- A new, oral agent, semaglutide, is currently under FDA review and may soon become available as the newest GLP-1 receptor agonist.
- The GLP-1 receptor agonists are valuable options for the treatment of type 2 diabetes as adjunctive therapy or as monotherapy.

Table 1 Costs of Diabetes Medications, by Class

Drug/drug class	Cost of 30-day supply, range, $
Metformin	5-9
Insulin	145-650
Sulfonylureas	9-15
Pioglitazone	12-17
DPP-4 inhibitors	173-397
SGLT-2 inhibitors	432-443
GLP-1 receptor agonists	492-684

DPP-4 indicates dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; SGLT-2, sodium-glucose cotransporter-2.
Source: Cost obtained from GoodRx based on 30-day supply.

Table 2 Phase 3 DURATION Trials with Exenatide ER[16-22]

Trial	Study drug	Exenatide ER outcomes vs comparator drugs
DURATION-1	Exenatide ER 2 mg vs exenatide 10 mcg twice daily	Greater HbA_{1c} reduction: –1.9% vs –1.5% Greater reduction in lipid profile, total cholesterol, triglycerides Better glucose control, body weight reduction, systolic blood pressure reduction Reduced nausea
DURATION-2	Exenatide ER vs pioglitazone vs sitagliptin; all agents taken with metformin	Greater HbA_{1c} reduction w/ exenatide ER: –1.5% vs –0.9% vs –1.2% Greater weight loss: –2.3 kg vs –0.8 kg vs +2.8 kg Less nausea (5% vs 10.8% vs 9.6%) No hypoglycemia w/ exenatide ER
DURATION-3	Exenatide ER vs insulin glargine, titrated to goal <100 mg/dL	Greater HbA_{1c} reduction w/ exenatide ER: –1.5% vs –1.3% 3 × lower hypoglycemia rate w/ exenatide ER
DURATION-4	Exenatide ER vs metformin vs pioglitazone vs sitagliptin; all in treatment-naïve patients	HbA_{1c} reduction: –1.53% vs 1.48% vs 1.63% vs 1.15% Weight loss: –2.0 kg vs –2.0 kg vs +1.5 kg vs –0.8 kg Nausea & diarrhea: 11.3% and 10.9% w/ exenatide ER No major hypoglycemia occurred
DURATION-5	Exenatide ER vs exenatide; this is similar to DURATION-1	At 24 weeks, greater HbA_{1c} reduction: –1.6% vs –0.9% Greater fasting glucose reduction: –35 mg/dL vs –12 mg/dL Similar weight reduction, adverse effects
DURATION-6	Exenatide ER vs liraglutide	Greater HbA_{1c} reduction w/ liraglutide: –1.48% vs –1.28% More patients reached goal w/ liraglutide: 60% vs 53% Greater weight loss w/ liraglutide

ER indicates extended-release; HbA_{1c}, glycated hemoglobin.

emptying and acid secretion, thereby reducing appetite and contributing to weight loss. GLP-1 is degraded by dipeptidyl peptidase (DPP)-4, resulting in a shorter half-life, as shown in patients with type 2 diabetes and in healthy volunteers.[11] This has led to the development of DPP-4 inhibitors, which inhibit the degradation of GLP-1. GLP-1 had been considered a treatment modality, but it has a very short half-life and would require continuous infusions.[11] This has led to the development of GLP-1 receptor agonists, which are structurally similar to the natural hormone to provide beneficial effects but differ structurally to prevent breakdown by DPP-4.

This article reviews the evidence available for current GLP-1 receptor agonists.

Exenatide

Exenatide (Byetta) is a synthetic derivative of exendin-4 (isolated from salivary secretions of the Gila monster lizard) with a 53% amino acid sequence overlap.[12] In 2005, it became the first GLP-1 receptor agonist to receive approval by the US Food and Drug Administration (FDA) for the treatment of type 2 diabetes. As an agonist of pancreatic beta-cells and resistance from DPP-4 inactivation, exenatide has a longer duration of action than GLP-1 and more than 1000-fold potency for lowering glucose than GLP-1.[12] Exenatide has been shown to stimulate insulin production in response to blood glucose concentration, inhibit postprandial glucagon release, slow the rate of gastric emptying, slow the rate of nutrient absorption in the bloodstream, and reduce appetite.[12] It is also found to promote the proliferation of beta-cells and islet-cell neogenesis from precursor cells.[12]

Exenatide was first introduced as a twice-daily injection of 5 mcg for 1 month followed by 5 mcg or 10 mcg. Pharmacokinetics demonstrated a plasma level reaching peak concentrations at 2 to 3 hours after administration with levels remaining detectable for 6 hours after administration. Patients with type 2 diabetes who were inadequately controlled with a sulfonylurea and/or metformin were given 0.08-mcg/kg subcutaneous injections of exenatide, which showed significant reductions in postprandial plasma glucose (PPG) and glycated hemoglobin (HbA_{1c}).[12]

Exenatide was studied in the phase 3 clinical trials AMIGO I, II, and III.[12,13] In all 3 trials, the continuation of previous therapy (with metformin alone, sulfonylurea alone, or the combination of both) was compared between the addition of exenatide and placebo. The exenatide treatment group demonstrated a significant reduction in PPG concentrations and HbA_{1c} compared with the placebo group. Nausea was the most common adverse effect, with an increased rate of nausea in the exenatide groups versus the placebo groups. The rates of hypoglycemia in AMIGO I, which included patients who had received metformin, were equal between the exenatide and the placebo groups; however, in the AMIGO III study, which included patients who had received sulfonylurea and metformin combination therapy, patients receiving 10-mg exenatide had increased hypoglycemia (28% vs 13% in the placebo group). No changes in heart rate, blood pressure, and electrocardiograms were noted. The small increase in cortisol levels normalized by day 28.[12,13]

Buse and colleagues compared exenatide 5 µg twice daily for 4 weeks and then 10 µg twice daily thereafter with placebo in patients receiving insulin glargine.[14] Insulin glargine was titrated to achieve a fasting glucose of <100 mg/dL on the basis of the Treat-to-Target Trial algorithm. The study showed an HbA_{1c} reduction of 1.74% with exenatide versus 1.04% with placebo. No significant increase in hypoglycemia or weight gain occurred. Similar to the AMIGO trials, exenatide was associated with more events of nausea (41% vs 8%, respectively) and vomiting (18% vs 4%, respectively) than placebo.[14]

Exenatide ER

A new formulation of exenatide, exenatide extended-release (ER; Bydureon) 2-mg once-weekly injection was approved by the FDA in 2012 as an adjunct therapy or monotherapy in patients with type 2 diabetes.[15] Exenatide ER reaches therapeutic levels after 2 weeks, and after 6 weeks the drug attains a maximum concentration

higher than that attained by a single injection of exenatide 10 mcg.[15] Six weeks after stopping treatment, the serum concentration of exenatide once weekly declines to insignificant levels.

The phase 3 clinical trials of exenatide ER included the DURATION series, and are summarized in **Table 2**.[16-22] DURATION-1 and -5 compared exenatide twice daily versus exenatide ER, showing that exenatide ER had a greater HbA_{1c} reduction and better glucose control compared with the twice-daily formulation. DURATION-2 and -4 compared exenatide ER with other diabetic oral medications, including pioglitazone, sitagliptin, and metformin, which demonstrated comparable efficacy in reducing HbA_{1c} and significantly reducing weight.[16-21]

Exenatide was associated with an increase in gastrointestinal (GI) adverse effects, including nausea, vomiting, and diarrhea,[16-21] as is expected of the GLP-1 class. Nausea was most notable during the first few weeks of therapy and was minimized by gradual dose titration. In DURATION-2 and -4, no significant differences were reported in the rates of hypoglycemia between exenatide ER and metformin, pioglitazone, or sitagliptin.[18,20] DURATION-3 compared exenatide ER with insulin glargine, showing 3 times fewer hypoglycemic events with the GLP-1 inhibitor than in the insulin glargine group.[19]

Mild injection-site pruritus was observed more often with exenatide ER, but it resolved with treatment continuation.[17] Despite concerns for a possible association of exenatide and the other GLP-1 receptor agonists with increased risk for pancreatitis, this was not observed in the DURATION trials.[15]

Liraglutide

Liraglutide (Victoza) is an acylated analog of GLP-1 that has 97% amino acid sequence identity to the endogenous GLP-1 analog. In 2009, it was the second GLP-1 agonist to be approved by the FDA for the treatment of type 2 diabetes. Liraglutide is a long-acting GLP-1 receptor agonist that is administered once daily as a subcutaneous injection in contrast to twice-daily injections of the first exenatide formulation.[23] Liraglutide has been reported to increase beta-cell mass in animal models via increased beta-cell replication and reduced apoptosis.[24] In a study with normal-weight and obese rats, liraglutide was associated with a reduction in food intake, resulting in weight loss of approximately 15%.[25] Preclinical studies showed improvement in first- and second-phase insulin secretion, implying that liraglutide leads to improved biphasic insulin secretion in response to hyperglycemia.[26,27]

The Liraglutide Effect and Action in Diabetes (LEAD) program is comprised of 6 phase 3 clinical trials, which are summarized in **Table 3**.[28-33] Liraglutide, given as adjunct therapy and as monotherapy, was associated with significant reductions in HbA_{1c} levels, blood pressure, fasting plasma glucose (FPG), and PPG levels.[28-33] Liraglutide is superior to insulin glargine and to twice-daily exenatide in HbA_{1c} reduction. Weight loss was similar between the liraglutide and the exenatide groups, but greater weight loss was seen with liraglutide compared with insulin glargine.[28-33]

The LEAD trials showed that the risk for hypoglycemia is low with liraglutide and is significantly lower than with a sulfonylurea or twice-daily exenatide.[28-33] Like exenatide, liraglutide was associated with increased GI side effects, including nausea and vomiting, which were generally mild and transient. A total of 3.4% of the patients receiving liraglutide in the phase 3 trial withdrew because of nausea.[30] In general, the GI adverse effects can be managed by starting at lower doses of liraglutide and then gradually increasing the dose. Liraglutide was

Table 3 Phase 3 LEAD Trials with Liraglutide[28-33]

Trial	Study drug	Liraglutide outcomes vs comparator drugs
LEAD-1	Liraglutide 1.2 mg & 1.8 mg once daily vs rosiglitazone 4 mg once daily; all concurrently taking sulfonylurea	Significant HbA_{1c} reduction w/ liraglutide 1.2 mg & 1.8 mg: 1.1% vs –0.4% w/ rosiglitazone 4 mg Significant decrease in FPG & PPG w/ liraglutide vs rosiglitazone Minor hypoglycemia, <10%; nausea, <11%; vomiting, <5%; diarrhea, <8%
LEAD-2	Liraglutide 1.2 mg & 1.8 mg vs glimepiride 4 mg; all concurrently taking metformin	Noninferior HbA_{1c} reduction in liraglutide groups: mean decrease, –1% Body weight –2.8 kg w/ 1.8-mg liraglutide vs +1.0 kg w/ glimepiride Less hypoglycemic events in liraglutide groups: 3% vs 17% w/ glimepiride Increased nausea in liraglutide groups
LEAD-3	Liraglutide 1.2 mg & 1.8 mg once daily vs glimepiride 8 mg once daily	HbA_{1c} reductions: –0.84% & –1.23% w/ liraglutide 1.2 mg & 1.8 mg vs 0.51% w/ glimepiride 8 mg No major hypoglycemic events Significantly less minor hypoglycemia: 8% & 12% vs 24%
LEAD-4	Liraglutide 1.2 mg & 1.8 mg vs placebo; all concurrently taking metformin and rosiglitazone	HbA_{1c} reduction: –1.5% vs –0.5% Significant FPG and PPG reductions w/ 1.2-mg & 1.8-mg liraglutide Body weight reductions: –1.0 kg & –2.0 kg w/ liraglutide 1.2 mg & 1.8 mg vs +0.6-kg weight gain w/ placebo Systolic BP reductions: –6.7 mm Hg & –5.6 mm Hg w/ liraglutide 1.2 mg & 1.8 mg vs –1.1 mm Hg w/ placebo Minor hypoglycemia: 7.9% & 9% vs 5.1% No major hypoglycemic events
LEAD-5	Liraglutide 1.8 mg vs insulin glargine; all concurrently taking metformin and glimepiride	Significantly greater HbA_{1c} reduction: –1.33% vs –1.09% Significantly greater weight loss w/ liraglutide: –1.39 kg vs +3.43 kg Systolic BP reduction: –4 mm Hg vs +0.5 mm Hg Major & minor hypoglycemia rates: 0.06 & 1.2 vs 0 & 1.3 events/patient annually
LEAD-6	Liraglutide 1.8 mg vs exenatide 10 µg twice daily, all concurrently taking metformin and sulfonylurea	Significant HbA_{1c} reduction: –1.12% vs –0.79% Greater FPG reduction vs exenatide Weight loss: 3.24 kg vs 2.87 kg (difference not significant) Significantly less minor hypoglycemia w/ liraglutide: 25.5% vs 33.6% 2 patients taking exenatide & sulfonylurea had major hypoglycemia Less nausea w/ liraglutide

BP indicates blood pressure; FPG, fasting plasma glucose; HbA_{1c}, glycated hemoglobin; PPG, postprandial glucose.

Table 4 Phase 3 HARMONY Trials with Albiglutide[39-46]

Trial	Study drug	Albiglutide outcomes vs comparator drugs
HARMONY-1	Albiglutide 30 mg vs placebo	HbA_{1c}: –0.8% vs –0.1% Hyperglycemia events: 24.4% vs 47.7% No significant differences in weight change All GI events: 31.3% vs 29.8% Diarrhea: 11.3% vs 8.0% Nausea: 10.7% vs 11.3% Vomiting: 4% vs 4%
HARMONY-2	Albiglutide 30 mg vs albiglutide 50 mg vs placebo	HbA_{1c}: –0.84% vs –1.04% No significant changes in weight w/ 2 albiglutide doses Similar nausea, diarrhea, vomiting, hypoglycemia rate in all groups, including placebo
HARMONY-3	Albiglutide 30 mg vs sitagliptin 100 mg vs glimepiride 2 mg vs placebo; all concurrently taking metformin	HbA_{1c}: –0.9% vs –0.4% vs –0.3% (vs placebo) Weight change: –1.21 kg vs –0.86 kg vs +1.17 kg vs –1.0 kg Hyperglycemia rates: 25.8% vs 36.4% vs 32.7% vs 59.2% Diarrhea: 12.9% vs 8.6% vs 10.9% (vs placebo) Nausea: 10.3% vs 6.2% vs 10.9% (vs placebo)
HARMONY-4	Albiglutide vs insulin glargine titrated to fasting plasma glucose goal of 100 mg/dL	HbA_{1c}: –0.7% vs –0.8% Weight change: –1.0 kg vs +1.5 kg Hypoglycemia: 17.5% vs 27.4%
HARMONY-5	Albiglutide 30 mg titrated up to 50 mg vs pioglitazone 30 mg titrated up to 50 mg; all concurrently taking metformin ± glimepiride 4 mg	HbA_{1c} reduction: –0.87% vs placebo HbA_{1c} +0.25 vs pioglitazone: not meeting noninferiority criteria Hypoglycemia: 14% vs 25% vs 14% Weight change: –0.42 kg vs +4.4 kg vs –0.4 kg
HARMONY-6	Albiglutide 30 mg titrated up to 50 mg vs insulin lispro 3 × daily adjusted per glucose level	HbA_{1c}: –0.82% vs –0.66% Weight change: –7.3 kg vs +0.81 kg Severe hypoglycemia: 0 vs 2 events Nausea: 11.2% vs 1.4% Vomiting: 6.7% vs 1.4% Injection-site reaction: 9.5% vs 5.3%
HARMONY-7	Albiglutide 30 mg titrated up to 50 mg vs liraglutide 0.6 mg titrated up to 1.8 mg; all concurrently taking metformin ± sulfonylurea ± thiazolidinedione	HbA_{1c}: –0.78% vs –0.99% Injection-site reaction: 12.9% vs 5.4% GI adverse effects: 35.9% vs 49%
HARMONY-8	Albiglutide vs sitagliptin with GFR >60 mL/min, GFR 30-59 mL/min, GFR 15-29 mL/min; all ± oral diabetes drugs	HbA_{1c}: –0.83% vs –0.52% Time to hyperglycemic rescue longer w/ albiglutide All adverse events: 51.7% vs 25.2% Diarrhea: 10% vs 6.5% Nausea: 4.8% vs 3.3% Vomiting: 1.6% vs 1.2% Hypoglycemia: 24.1% vs 15.9% (sulfonylurea: 22.5% vs 14.2%; no sulfonylurea: 4% vs 4%) Weight change: –0.79 kg vs –0.19 kg

GFR indicates glomerular filtration rate; GI, gastrointestinal; HbA_{1c}, glycated hemoglobin.

associated with a lower antibody formation than exenatide, likely because of the greater (97%) amino acid sequence identity than human GLP-1.[34] Exenatide has a lower sequence identity than liraglutide, which may explain the incidence of anti-exenatide antibody formation in up to 43% of exenatide-treated patients.[35]

There have been few case reports of liraglutide-associated pancreatitis. Studies in rodents have shown that liraglutide induces C-cell proliferation and medullary thyroid adenomas and carcinomas via GLP-1 receptor agonist activation and calcitonin release, but this pattern was not seen in humans. Follow-up studies have been inconclusive to definitively define a cause-and-effect relationship between liraglutide and pancreatitis, because patients with type 2 diabetes already have a 3-fold increased risk for pancreatitis.[36] In the LEADER trial, liraglutide taken for 3.5 years was associated with a 23% reduction in CV events, a 22% reduction in CV mortality, and a 15% reduction in all-cause mortality.[37]

Albiglutide

Albiglutide (Tanzeum) is a GLP-1 agonist that was approved by the FDA in 2014 as an adjunct treatment for diabetes; it is administered as a weekly injection.[38] Albiglutide has 97% homology to the amino acid sequence of GLP-1. A single amino acid substitution (alanine to glycine) renders albiglutide resistant to DPP-4–mediated protein degradation, resulting in a longer half-life. After subcutaneous injection of a single 30-mg dose, patients with type 2 diabetes achieved mean maximum plasma concentration 3 to 5 days after administration. Plasma concentrations reach steady state within 3 to 5 weeks of repeated once-weekly administrations. Albiglutide is currently available as a 30-mg and a 50-mg once-weekly injection.[38]

Albiglutide was tested in the HARMONY phase 3 clinical trials, which comprised 8 studies (**Table 4**).[39-46] HARMONY-2 demonstrated the superiority of albiglutide monotherapy to diet and exercise in glycemic control.[40] In HARMONY-3, once-weekly albiglutide add-on therapy was noninferior to once-daily sitagliptin and once-daily glimepiride at reducing HbA_{1c} levels in patients inadequately controlled with metformin alone,[41] whereas HARMONY-4 and -6 demonstrated that albiglutide was noninferior to insulin therapy in patients inadequately controlled with oral antidiabetes therapy.[42,44] However, in HARMONY-5, albiglutide was found to be inferior to pioglitazone in HbA_{1c} reduction.[43] HARMONY-8 revealed that albiglutide was superior to sitagliptin in patients with and without renal impairment.[46]

Albiglutide demonstrated greater weight loss in all studies compared with sitagliptin, glimepiride, pioglitazone, and insulin therapy, although more GI adverse effects were reported with albiglutide compared with other agents.[39-46] All trials demonstrated no significant differences in rates of hypoglycemia, except in patients with impaired renal disease who used albiglutide and a sulfonylurea.[39-46]

Dulaglutide

Dulaglutide (Trulicity) is a once-weekly subcutaneously administered GLP-1 receptor agonist approved by the FDA in 2014 as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes.[47] The initial dosage is 0.75 mg administered subcutaneously once weekly, which may be increased to 1.5 mg

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