EXENATIDE (EXENDIN-4) REDUCED A1C AND WEIGHT OVER 82 WEEKS IN OVERWEIGHT PATIENTS WITH TYPE 2 DIABETES

Based on a poster presented by Blonde L; Han J; Mac S; Poon T; Taylor K; Kim D
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Most patients with type 2 diabetes are overweight or obese, and most therapies for type 2 diabetes are associated with side effects, including weight gain, hypoglycemia, edema, and loss of glycemic control. Exenatide has multiple mechanisms of action that lower fasting and postprandial glycemia and improve glucose control. These actions include reduction of food intake and body weight, enhancement of glucose-dependent insulin secretion, and suppression of inappropriately elevated postprandial glucagon secretion. This study examined the long-term effects of exenatide, administered twice daily, on body weight, glycemic control, and safety over 82 weeks in 3 open-label, uncontrolled extensions in subjects unable to achieve glycemic control with metformin, a sulfonylurea, or metformin and a sulfonylurea.

Subjects were randomized into 3 groups: placebo, 5 µg of exenatide, or 10 µg of exenatide administered subcutaneously twice daily in 3 triple-blind 30-week studies. Subsequently, subjects received 5 µg of exenatide twice daily for 4 weeks, followed by 10 µg of exenatide twice daily, in the open-label uncontrolled extensions. For inclusion in the placebo-controlled trials, subjects had to have type 2 diabetes, be aged 16 to 75 years, and have undergone treatment for 3 months before screening with 1500 mg of metformin a day or greater, a maximally effective dose of sulfonylurea, or both; have A1c of 7.1% to 11.0%; fasting plasma glucose of below 240 mg/dL; body mass index of 27 to 45 kg/m²; stable body weight (± 10%) for 3 months before screening; no other clinically relevant abnormal laboratory test values; and no treatment with other antidiabetic agents or weight loss drugs within 3 months of the study. To enroll in the open-label, uncontrolled, 52-week extension studies, subjects had to complete 1 of the 30-week placebo-controlled trials.

Study results after 30 weeks indicated that treatment with exenatide reduced mean A1c (P < .002) and reduced mean body weight (P < .05). Exenatide treatment for 82 weeks resulted in durable reductions in mean A1c (-1.2%, -1.2%, and -1.1% for the placebo → 10 µg twice daily, 5 µg → 10 µg twice daily, and 10 µg twice daily arms, respectively) and progressive reductions in mean body weight (-3.3 kg, -4.7 kg, and -4.5 kg for the placebo → 10 µg twice daily, 5 µg → 10 µg twice daily, and 10 µg twice daily arms, respectively). Incidence and frequency of adverse events, including mild to moderate nausea, were similar to published data of controlled studies. Hypoglycemia was generally mild to moderate and primarily occurred in subjects treated with exenatide plus sulfonylureas.

The long-term data, which showed that exenatide elicited progressive weight reduction and sustained improvements in glycemic control, make exenatide a potential therapeutic option for patients with type 2 diabetes not adequately controlled with metformin and/or sulfonylurea therapy.

REFERENCES

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INCREASED SECRETION OF INCRETIN HORMONES AND INSULIN IN PATIENTS WITH CHRONIC PANCREATITIS AND EXOCRINE PANCREATIC INSUFFICIENCY FOLLOWING ENZYME SUBSTITUTION

Based on a poster presented by Knop FK*; Vilsboll T*; Larsen S†; Hojbjerg PV‡; Madshus SF; Holst JJ§; Krarup T*  
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It is unknown whether secretion of the incretin hormones glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) is related to digestion and/or absorption of nutrients. GLP-1 is secreted primarily from the L cells in the distal part of the small intestine, whereas GIP is secreted from the K cells in the proximal part of the small intestine. Together these hormones are responsible for 60% to 70% of the insulin response observed after ingestion of a glucose load in healthy subjects; however, in patients with type 2 diabetes, the incretin effect is reduced dramatically. Data suggest that this pathophysiological trait is caused by the absence of an effect of GIP on pancreatic β cells, and a small but significant reduction in the secretion of GLP-1. Agents that mimic the effects of GLP-1 are under development, and thus far data suggest a promising role for this new generation of drugs in the treatment of type 2 diabetes.

This study investigated the secretion of incretin hormones among patients with chronic pancreatitis and exocrine pancreatic insufficiency. The dependence of digestion and absorption of nutrients on the secretion of incretin hormones also was determined.

The study cohort included 8 men with chronic pancreatitis and exocrine pancreatic insufficiency. The diagnosis of chronic pancreatitis was established according to the criteria of Cambridge,1 and all patients were treated with pancreatic enzyme substitution (PES). Controls were 8 healthy male subjects matched for body mass index and age (Table).

<table>
<thead>
<tr>
<th>Study Group (n = 8)</th>
<th>Control Group (n = 8)</th>
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<tbody>
<tr>
<td>Age, yrs</td>
<td>57 (46–66)</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>21.1 (15.2–27.4)</td>
</tr>
<tr>
<td>A1c, %</td>
<td>6.2 (5.1–7.7; mean range)</td>
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</table>

BMI = body mass index.

The patients with chronic pancreatitis were studied on 2 separate days in the recumbent position after an overnight fast. Arterialized venous blood was sampled over a 4-hour period after ingestion of a liquid meal (100 g NAN 1, a brand of infant milk formula manufactured in the Netherlands [2170 kJ]: 9.5% protein, 58% lactose, and 27.7% fat dissolved in 300 ml H₂O). On Day 1 the meal was supplemented with PES (2 x Creon forte, porcine pancreatin formulated as enteric-coated [acid-resistant] mini-microspheres within gelatin capsules). The healthy control subjects were studied on 1 day under similar conditions as the
patients’ regimen on Day 2 (without PES).

The data showed no significant differences between Day 1 and Day 2 in plasma glucose ($P = .755$). The secretion of GIP was significantly lower without PES ($P = .01$). Concurrently, plasma insulin and C-peptide increased after PES ($P = .019$ and $P = .005$, respectively) among the patients with chronic pancreatitis. No statistically significant difference was found between the patients with chronic pancreatitis and the control subjects in the levels of incretin hormones. Triglyceride levels were measured to determine the differences in absorption of the liquid meal with and without PES. Study data suggested a strong tendency toward increased levels of plasma triglycerides after PES (Day 1).

In conclusion, these results show preserved postprandial secretion of GIP in patients with chronic pancreatitis. Furthermore, the results suggest secretion of GIP is dependent on digestion and subsequent absorption of nutrients from the small intestine. In these patients, PES has a positive effect on the pancreatic exocrine deficit and on the secretion of insulin, and thus improves the endocrine insufficiency in patients with chronic pancreatitis.

REFERENCE


COMBINATION OF THE DPP-IV INHIBITOR VILDAGLIPTIN (LAF237) WITH PIOGLITAZONE IS SAFE AND WELL TOLERATED WITH NO PHARMACOKINETIC INTERACTION

Based on an abstract presented by Serra DB*; He Y-L*; Wang Y*; Riviere G*; Bullock J*; Schwartz S*; Ligueros-Saylan M†

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Vildagliptin, an incretin enhancer agent, is currently under development for the treatment of type 2 diabetes. This study was conducted to confirm the lack of pharmacokinetic interaction between vildagliptin and pioglitazone, demonstrate safety and tolerability of the combination, and explore the therapeutic value of this combination therapy in patients with type 2 diabetes. In this crossover study, subjects ($n = 12$) with type 2 diabetes and $\text{A1c}$ of 7% to 11% were maintained on pioglitazone (45 mg once daily) alone for 8 weeks, then randomized to receive placebo or vildagliptin (11 mg once daily) in combination with pioglitazone for 28 days. For the final open-label 7 days of the study, vildagliptin was given alone (100 mg once daily). Plasma levels of vildagliptin, pioglitazone, glucose, insulin, and glucagon-like peptide-1 (GLP-1) were all measured.

The data showed the combination therapy was safe and well tolerated, and all subjects completed the study. Peak plasma concentration and total exposure to vildagliptin and pioglitazone were unchanged when given alone or in combination.

Active GLP-1 levels following 28 days of coadministration were increased compared to pioglitazone alone. Postprandial glucose levels were significantly reduced (10%) following coadministration compared to pioglitazone alone.

In conclusion, no pharmacokinetic interaction was observed when vildagliptin and pioglitazone were coadministered. In addition, the combination was well tolerated over 28 days, and vildagliptin provided additional glycemic control when given in combination with pioglitazone.

IMPROVEMENTS IN CARDIOVASCULAR RISK FACTORS ACCOMPANIED SUSTAINED EFFECTS ON GLYCEMIA AND WEIGHT REDUCTION IN PATIENTS WITH TYPE 2 DIABETES TREATMENT WITH EXENATIDE FOR 82 WEEKS

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This presentation describes the results of phase III clinical trials, which examined the impact of exenatide intervention on cardiovascular risk markers and risk factors in patients with type 2 diabetes.

Glucagon-like peptide-1 is a critical and important incretin hormone that regulates glucose homeostasis. The development of several compounds to take
advantage of this action in the management of type 2 diabetes has led to the introduction of exenatide, an incretin mimetic, for the treatment of type 2 diabetes. Exenatide exerts its antihyperglycemic effect by enhancing glucose-dependent insulin secretion and suppressing the excessive elevation in glucagon after meals. Exenatide reduces food intake and causes weight loss. It normalizes or slows gastric emptying, thereby slowing the rate of glucose appearance in the circulation following a meal. Exenatide increases β-cell mass in animal models, and has improved measures of β-cell function in human studies.

The trials from which these data were derived include all 3 of the phase III AC2993: Diabetes Management of Improving Glucose Outcomes pivotal trials involving patients with type 2 diabetes who were treated with metformin alone, sulfonylureas alone, or a combination of metformin and sulfonylureas, to which 10 µg of twice-daily administered exenatide was added. The results of these 3 trials were reported in Diabetes Care in November 2004.

More recently, 2 trials examined the effects of exenatide on glycemic control and weight in patients with type 2 diabetes. The first trial was a 30-week, double-blind, placebo-controlled study in 733 patients who were randomized to receive placebo or 5 µg subcutaneous exenatide twice daily (arms A and B) for 4 weeks. At that point, arm A remained at 5 µg twice daily, and arm B dosage was increased to 10 µg twice daily. Throughout the study, patients continued taking metformin and were randomized to maximally effective or minimum recommended doses of sulfonylurea. The 30-week study was completed by 593 patients (81%). The demographics of this study population were typical of patients with type 2 diabetes, and included patients in their mid-50s, with a body mass index (BMI) in the low-to-mid 30s, baseline hemoglobin A1C (HbA1C) of 8.3%, and duration of diabetes averaging between 5 and 10 years. Patients who received active therapy then were converted to an open-label extension analyzed out to 82 weeks of follow-up.

At 30 weeks, data from the blinded portion of the trial showed the baseline HbA1C of 8.3% reduced to levels of just under 7.3% (an approximate 1% reduction). Approximately 40% of patients achieved HbA1C targets with an average weight reduction of approximately 2 kg. The greatest decrease in body weight was in those patients receiving concomitant metformin, whereas a lesser but significant decrease in body weight was seen in patients on sulfonylurea monotherapy. Exenatide appeared to be well tolerated with mild to moderate nausea as the most common adverse event. This was most often seen early in the course of treatment, with attrition over time. There was no increase in hypoglycemia compared to placebo when exenatide was used as an add-on therapy to metformin, but the incidence of mild to moderate hypoglycemia was increased when exenatide was added to sulfonylurea-based therapies. A cohort of 265 patients treated with 10 µg of exenatide twice daily completed the 82-week open-label extension and showed sustained mean reductions in HbA1C (1.2 ± 0.1%) and weight (4.0 ± 0.3 kg).

The second study was a triple-blind, placebo-controlled, 30-week study of 336 randomized patients treated with metformin monotherapy. The study was completed by 272 patients. Inclusion criteria were screening fasting plasma glucose concentration of less than 13.3 mmol/L, BMI of 27 to 45 kg/m², and HbA1C of 7.1% to 11.0%. Metformin dose was 1500 mg or greater a day for 3 months before screening. After 4 weeks of placebo, subjects self-administered 5 µg of exenatide or placebo subcutaneously twice daily for 4 weeks, followed by 5 or 10 µg of exenatide or placebo subcutaneously twice daily for 26 weeks. HbA1C changes from baseline for each group were -0.78% ± 0.10%, -0.40% ± 0.11%, and +0.08% ± 0.10% for 10 µg, 5 µg, and placebo, respectively (P <.002).

The effect on body weight also was assessed in the blind portion of this trial. Patients in the active therapy arm demonstrated a decrease in body weight over the entire course of study from a baseline weight of approximately 100 kg. An average loss of 2 kg per patient was observed during the blind portion of the study, and the weight loss continued during the observational period, averaging to approximately 4.5 kg lost over the entire treatment interval.

The effect of this therapy on cardiovascular risk factors was noted to be a result of changes in body weight and improvements in glycemic control. Significant reductions were observed in low-density lipoprotein cholesterol, triglycerides, and diastolic blood pressure, in addition to improvements in high-density lipoprotein (HDL) cholesterol, Apo-B, and systolic blood pressure. Based on these observations, it was determined that assessing the impact of exenatide therapy on lipid measures and blood pressure in...
patients who lost substantial amounts of weight or who had minimal weight loss was important. The average weight loss by quartile of treated patients was followed out to 82 weeks and had approximately 66 individuals in each group. A total of 83% of patients followed in this blind and open-label follow-up lost weight during the course of treatment. Those patients with the greatest degree of weight loss experienced a mean weight loss of approximately 12 kg. More moderate degrees of weight loss were observed, but 3 of 4 quartiles demonstrated weight loss.

The impact of change in weight was seen across 3 of the quartiles. Even modest degrees of weight loss with this compound resulted in a decrease in diastolic blood pressure. The relationship between weight loss quartiles and standard measures of dyslipidemia in diabetes showed that those patients who lost the most weight had the greatest reduction in triglycerides. There was an increase in HDL cholesterol across all weight-loss quartiles, with the greatest increase seen in those patients who had lost the most weight and who also had experienced the greatest beneficial effect on triglycerides.

The agent exenatide was generally well tolerated in this open-label extension. Adverse events were consistent with those seen in the blinded, randomized, and controlled trials. Mild to moderate nausea was the most frequent adverse event reported when therapy was initiated. Withdrawal because of nausea was less than 4%.

The authors concluded that this 82-week extension of pivotal trials to evaluate exenatide demonstrated that therapy with this compound resulted in sustained improvements in glycemia, clinically meaningful increases in HDL cholesterol, and lowered plasma triglycerides and blood pressure. Many patients had these improvements in cardiovascular risk factors; the greatest improvement was seen in those with the greatest weight loss.

REFERENCES


HEAD-TO-HEAD COMPARISON OF THE DPP-IV INHIBITOR VILDAGLIPTIN WITH EXENDIN-4 IN A MODEL OF PANCREATIC β-CELL INJURY

Based on an oral presentation by Duttaroy A; Voelker F; Ren X; Zhang X; Merriam K; Qin L; Chen H; Burkey B
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This study compared the dipeptidyl peptidase-IV (DPP-IV) inhibitor vildagliptin with exendin-4 in a mouse model of pancreatic β-cell injury. Vildagliptin, previously known as LF237, is an orally active DPP-IV inhibitor. DPP-IV is the enzyme that inactivates glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP). DPP-IV inhibitors increase endogenous incretin levels and are commonly referred to as incretin enhancers. Clinical studies have shown that vildagliptin improved glycemia in patients with type 2 diabetes. Exenatide, an incretin mimetic also known as exendin-4, is an injectable GLP-1 agonist that also improves glycemia in patients with type 2 diabetes. Preclinical studies show that exenatide increases β-cell mass in rodents by enhancing β-cell neogenesis and suppressing apoptosis.

Dipeptidyl peptidase-IV inhibitors and GLP-1 agonists produce GLP-1 actions in different ways. When a meal is ingested, an instantaneous release of GLP-1 from intestinal L cells produces a rise in blood levels of endogenous active GLP-1, but it is immediately deactivated by DPP-IV. By blocking this conversion, a DPP-IV inhibitor raises the level of circulating active GLP-1 and maintains its effects. However, the actions of the inhibitor are limited by the amount of endogenous GLP-1 production. On the other hand, the effects of GLP-1 agonists are only limited by the exogenous dose of the drug and tolerance to the compound. This point is important, as previous studies with GLP-1 agonists show that β-cell growth requires a high dose or sustained exposure to the compound. One could hypothesize that because the effects of a DPP-IV inhibitor is limited by endogenous GLP-1 production, treatment with the DPP-IV inhibitor vildagliptin may be less effective than exenatide or another GLP-1 agonist in increasing β-cell growth. The following study specifically compares the effect of vildagliptin and exenatide on the maintenance of β-cell mass.

This study was undertaken in a mouse model of β-cell injury inflicted by streptozotocin (STZ). Study
parameters included β-cell replication, apoptosis, overall change in a mass neogenesis marker, β-cell differentiation, and pancreatic gene expression. An oral glucose tolerance test (OGTT) was carried out to determine the corresponding functional changes.

β-cell injury was produced in C57Bl/6 mice by injecting STZ once daily from day 1 to day 5. Injured mice were pretreated with vildagliptin or exenatide that was administered at a cumulative dose for 5 days before to STZ injury and continued to day 15. Thus, there were 4 groups: STZ only, STZ and vildagliptin, STZ and exenatide, and noninjury controls. β-cell parameters were measured by tissue harvesting using several cohorts of mice at day 6 (24 hours after the end of the STZ injury) and at day 16 (24 hours after the end of drug treatment). To measure corresponding functional changes, another cohort of mice was given an OGTT at the end of drug treatment (day 16). To observe long-term changes, mice received no drug treatment for 10 days after completing the drug doses. An OGTT was then done and tissue was harvested.

At the end of STZ dosing, β-cell mass was significantly reduced, and there was a progressive loss compared to the noninjury control mice. Severe apoptosis also was noted at this point. The corresponding insulin mRNA level was decreased significantly throughout the study compared to vehicle control (P < .05 vs vehicle). At the end of STZ injury there was a significant increase in blood glucose level, which doubled as the study continued. These results indicated that STZ inflicted β-cell loss and made the mice diabetic.

To determine the effect of drug treatment on β-cell injury, β-cell proliferation was measured at day 6 using bromodeoxyuridine incorporation into β cells, a marker of β-cell replication. With STZ treatment alone, the marker of β-cell replication increased significantly compared to noninjury control mice—the incorporation of bromodeoxyuridine enhanced the replication. This was a characteristic recovery induced by STZ-driven β-cell loss. The effect was blocked by vildagliptin and exenatide at this point, and at the same time, both drugs also increased pancreas duodenum homeobox gene-1 (PDX-1) mRNA, a marker of β-cell differentiation, compared to mice treated with STZ alone. At this time point, vildagliptin and exendin had similar effects; therefore, they blocked STZ-produced replication and enhanced differentiation. At day 16, after dosing for 10 more days, there was a significant increase in ductal β cells, a marker of the presence of newer islets. Again, this occurred with vildagliptin- and exenatide-treated mice as compared to the STZ mice; therefore, drug treatment induced replication, β-cell differentiation, and eventually produced neogenesis.

Corresponding functional changes were measured by OGTTs on day 16. Compared with the noninjury control mice, STZ animals had significantly increased blood glucose levels and impaired glucose tolerance (P = .05). Drug treatment significantly decreased plasma glucose level and improved glucose tolerance in STZ animals. The degree of improvement was similar with vildagliptin and exendin. This study was done 24 hours after the last dose, at the time when there was no acute effect with either agent.

When compared to the noninjury vehicle control, an OGTT conducted on day 24 after the washout period when the drug was completely gone, STZ animals still had increased blood glucose and impaired glucose tolerance. Again, the drug treatments decreased glucose level and improved glucose tolerance; the degree of improvement was similar for vildagliptin and exendinatide.

Vildagliptin and exenatide reduced the STZ-induced proliferative response, a protective effect against β-cell injury. The drugs promoted differentiation of pancreatic progenitor cells, which was demonstrated by an increase in the PDX-1 mRNA level. Eventually, increased formation of ductal β cells marked islet neogenesis. Vildagliptin and exenatide had identical effects on β-cell regulation, and both drugs improved glucose tolerance to a similar extent in the diabetic animals. The effect was maintained for both drugs even after clearance.

The authors concluded that the incretin enhancer vildagliptin promoted neogenesis in this mouse model as effectively as the incretin mimetic exenatide. Increased β-cell differentiation and maturation of β cells also were accompanied by a similar improvement in glucose tolerance with both drugs. Therefore, treatment with either of these 2 classes of drug in an animal model slowed progression of type 2 diabetes by increasing functional β-cell mass.