

## Authors and Disclosures

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## Once-Weekly Exenatide Lowers HbA1c More Than Daily Oral Antidiabetics or Insulin Glargine

Neil Osterweil

June 27 2010 (Orlando, Florida) — Once-weekly exenatide was better at lowering glycosylated hemoglobin (HbA1c) levels in patients with type 2 diabetes in 2 randomized trials — DURATION-2 and DURATION-3 — that pitted the drug against sitagliptin, pioglitazone, and insulin glargine, reported investigators here at the American Diabetes Association (ADA) 70th Scientific Sessions.

DURATION-2 was a 26-week comparison of once-weekly exenatide (*Byetta*; Amylin and Lilly) with sitagliptin (*Januvia*; Merck & Co) or pioglitazone (*Actos*; Takeda) as an adjunct to metformin in patients with type 2 diabetes.

Patients receiving exenatide had a mean decrease in glycosylated hemoglobin (HbA1c) of  $-1.5\%$  (95% confidence interval [CI],  $-1.7$  to  $-1.4$ ) — a significantly greater decline than seen in patients receiving either sitagliptin ( $-0.9\%$ ; 95% CI,  $-1.1$  to  $-0.7$ ) or pioglitazone ( $-1.2\%$ ; 95% CI,  $-1.4$  to  $-1.0$ ), reported Richard M. Bergenstal, MD, president of medicine and science of the ADA and executive director of the International Diabetes Center at Park Nicollet in Minneapolis, Minnesota.

DURATION-3 was a 26-week comparison of once-weekly exenatide with once-daily insulin glargine (*Lantus*; Sanofi-Aventis).

Patients receiving exenatide had a  $-1.5\%$  drop in HbA1c (standard error of the mean [SE], 0.05) compared with  $-1.3\%$  (SE, 0.05) for patients receiving once-daily insulin glargine, said Michaela Diamant, MD, professor of medicine at VU University Medical Center in Amsterdam, the Netherlands.

In both studies, patients receiving exenatide also lost significantly more weight than patients receiving the comparator drugs, and there were no cases of major hypoglycemia with any of the study drugs, the investigators noted.

"We all are faced with patients who we would like to see improve their control without either weight gain or hypoglycemia, and at least in this study, when it was added to metformin, once-weekly exenatide did that better than the other agents we compared it to," Dr. Bergenstal said in an interview with *Medscape Diabetes & Endocrinology*.

The results of DURATION-2 and DURATION-3 were published June 26 in *The Lancet*.

Dr. Bergenstal said that exenatide was chosen for the study because of its clinical track record and its apparent safety, at least during 3 years of therapy — an opinion generally backed by an accompanying editorial in *The Lancet*.

"Currently, there is more promise, few disadvantages, and some unknowns about treatment with long-acting exenatide for diabetes. Despite advances in antihyperglycemic therapy, a drug which would lead to substantial prevention of macrovascular and microvascular complications, decreases mortality, and is convenient and affordable, remains the undiscovered Holy Grail of diabetes management," write Anoop Misra, MD, from Fortis Hospital in New Delhi, India, and Shashank Joshi, MD, from Lilavati and Bhatia Hospital, in Mumbai, India.

### **DURATION-2: Exenatide vs Sitagliptin or Pioglitazone**

In DURATION-2, 170 patients with type 2 diabetes were randomly assigned to receive exenatide 2 mg injected once weekly plus oral placebo once daily, 172 patients were randomly assigned to receive 100 mg oral sitagliptin once daily plus injected placebo once weekly, and 172 patients were randomly assigned to receive 45 mg oral pioglitazone once daily plus injected placebo once weekly.

Patients with type 2 diabetes were recruited from 72 sites in the United States, India, and Mexico. At baseline, the mean HbA1c level was 8.5% (SD, 1.1), which is significantly above the ADA-recommended level of less than 7.0%. The mean fasting plasma glucose level was 9.1 mmol/L (SD, 2.6), and mean weight was 88.0 kg (SD, 20.1).

The primary study outcome was change from baseline in HbA1c through 26 weeks. Other prespecified endpoints included proportion of patients achieving an HbA1c target of 6.5% (the World Health Organization standard) or 7% or lower, fasting plasma glucose (target  $\leq$  7 mmol/L), self-monitored blood glucose profile, body weight, and insulin profiles.

The analysis by modified intention to treat (including all patients who received at least 1 dose of a study drug) included 160 patients receiving exenatide, 166 patients receiving sitagliptin, and 165 patients receiving pioglitazone.

The difference in HbA1c reduction between exenatide and sitagliptin was  $-0.6\%$  in favor of exenatide (95% CI,  $-0.9$  to  $-0.4$ ;  $P < .0001$ ); between exenatide and pioglitazone, it was  $-0.3\%$  (95% CI,  $-0.6$  to  $-0.1$ ;  $P = .0165$ ).

Patients receiving exenatide lost a mean of 2.3 kg (95% CI,  $-2.9$  to  $-1.7$ ) compared with  $-0.8$  kg (95% CI,  $-1.4$  to  $-0.1$  kg) for those receiving sitagliptin (difference,  $-1.5$  kg; 95% CI,  $-2.4$  to  $-0.7$ ;  $P = .0002$ ). Patients receiving pioglitazone gained a mean 2.8 kg (95% CI, 2.2 - 3.4 kg; difference,  $-5.1$  kg; 95% CI,  $-5.9$  to  $-4.3$ ;  $P < .0001$ ).

Exenatide and sitagliptin were associated with nausea in 24% and 10% of patients, and with diarrhea in 18% and 10%, respectively. Pioglitazone was most frequently associated with upper respiratory tract infection (10%) and peripheral edema (8%).

### **DURATION 3: Exenatide vs Insulin Glargine**

The DURATION-3 study was a 26-week open-label trial comparing exenatide with insulin glargine in adults with type 2 diabetes who had less-than-ideal glycemic control despite maximum tolerated doses of blood-glucose-lowering drugs for at least 3 months.

A total of 456 patients from at 72 sites across the United States and Puerto Rico, the European Union, Russia, Australia, Korea, Taiwan, and Mexico were enrolled. They were randomly assigned to receive either exenatide 2 mg in a once-weekly injection or insulin

glargine in a once-daily injection at a starting dose of 10 IU, targeted to a glucose range of 4.0 to 5.5 mmol/L, in addition to their current blood-glucose-lowering regimens.

The patients were stratified by country of treatment and concomitant therapy: either 70% metformin only or 30% metformin plus a sulfonylurea.

Analysis was by intention to treat, with data analyzers (but not patients or physicians) blinded to treatment assignment. As with DURATION-2, the primary endpoint was change from baseline in HbA1c.

A total of 228 patients receiving exenatide and 220 patients receiving insulin glargine were available for the efficacy analysis.

As noted earlier, at week 26 the mean HbA1c had declined more among patients receiving exenatide than among patients receiving sitagliptin.

Beginning at week 8, exenatide was associated with a greater mean reduction in HbA1c, and this difference continued until the end of the study. The treatment difference between the groups at 26 weeks was  $-0.16$  (SE, 0.07) favoring exenatide (95% CI,  $-0.29$  to  $-0.03$ ;  $P = .017$ ).

In addition, 60% of patients receiving exenatide achieved a target HbA1c or an HbA1c level less than 7.0% compared with 48% of those receiving glargine ( $P = .01$ ). For the more ambitious 6.5% target, the numbers were 35% and 23%, respectively ( $P = .004$ ).

Patients receiving exenatide lost 2.6 kg of body weight on average during the study, whereas those receiving insulin gained 1.4 kg ( $P < .001$ ). Insulin was, however, associated with lower mean fasting serum glucose concentrations (treatment difference, 0.6 mmol/L; 95% CI, 0.2 - 1.0;  $P = .001$ ).

Adverse events were generally similar between the groups, although patients receiving exenatide had a small but significant increase in heart rate, from 75 to 79 beats per minute, compared with no increase among patients receiving insulin. The clinical significance of this change is unclear, and there were no adverse outcomes associated with the higher heart rates, Dr. Diamant said.

"I do think the data are impressive — it certainly seems as if exenatide lowers A1c as well as or better than some of the comparison drugs, and the weight loss is certainly desirable — but I think that has to be balanced against issues such as cost, and as with all drugs we have to think about all of the long-term benefits vs safety and costs," commented M. Sue Kirkman, MD, vice president of clinical affairs for the ADA, who was not involved in the study but moderated the session during which it was presented.

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