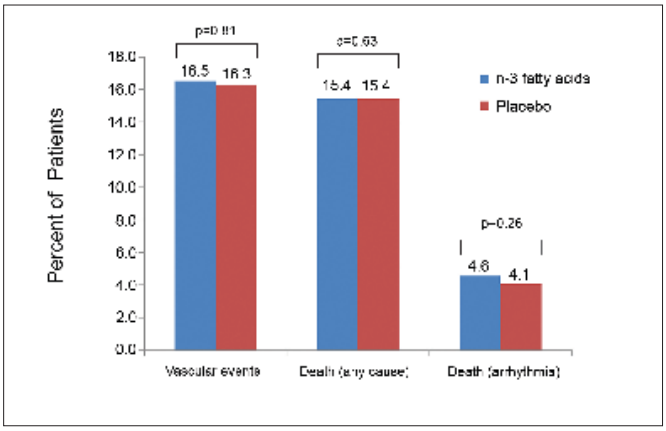
Figure 1. Event Rates.



Matthew C. Riddle, MD, Oregon Health & Science University, Portland, Oregon, USA, presented new ORIGIN trial subgroup data. The findings indicate that target-directed intervention early in dysglycemia can maintain baseline HbA1C levels for at least 5 years and that the glargine-based regimen is more likely to keep HbA1C <6.5% than standard care.

The main independent predictors of maintaining mean HbA1C <6.5% up to 5 years were type 2 diabetes versus no type 2 diabetes, baseline HbA1C per 1%, alcohol use >2 times/week, and glargine versus standard treatment ($p<0.001$ for all).

The data showed that <50% of diabetic patients had HbA1C levels <6.5% at baseline, but this figure rose to 60% at 5 years among those randomized to glargine and dropped to 45% among those on standard therapy. In the group without diabetes, 91% of patients had baseline HbA1C levels <6.5%. This number fell to 87% at 5 years in those randomized to glargine and to 79% at 5 years among those on standard therapy.

Both titrated glargine and a standard care approach kept HbA1C levels near baseline values for at least 5 years. According to Dr. Riddle, more data and further analyses are needed to define the benefits versus the risks of the two approaches.

For more information, please see the MD Conference Express review of the ORIGIN presentation in our ADA Report.

Exenatide Once Weekly Sustained Improvement in Glycemic Control with Weight Loss Through 4 Years

Written by ***Rita Buckley***

The once-weekly formulation of exenatide, a glucagon-like peptide-1 receptor agonist, is associated with clinically sustained improvement in glycemic control, continued improvements in cardiometabolic risk factors and weight loss after 4 years of treatment in type 2 diabetes mellitus (T2DM) patients. Results of the open-label extension of the Effects of Exenatide Long-Acting Release on Glucose Control and Safety in Subjects with Type 2 Diabetes Mellitus [DURATION-1; NCT00308139] clinical trial were presented by Leigh MacConell, PhD, Amylin Pharmaceuticals, San Diego, California, USA.

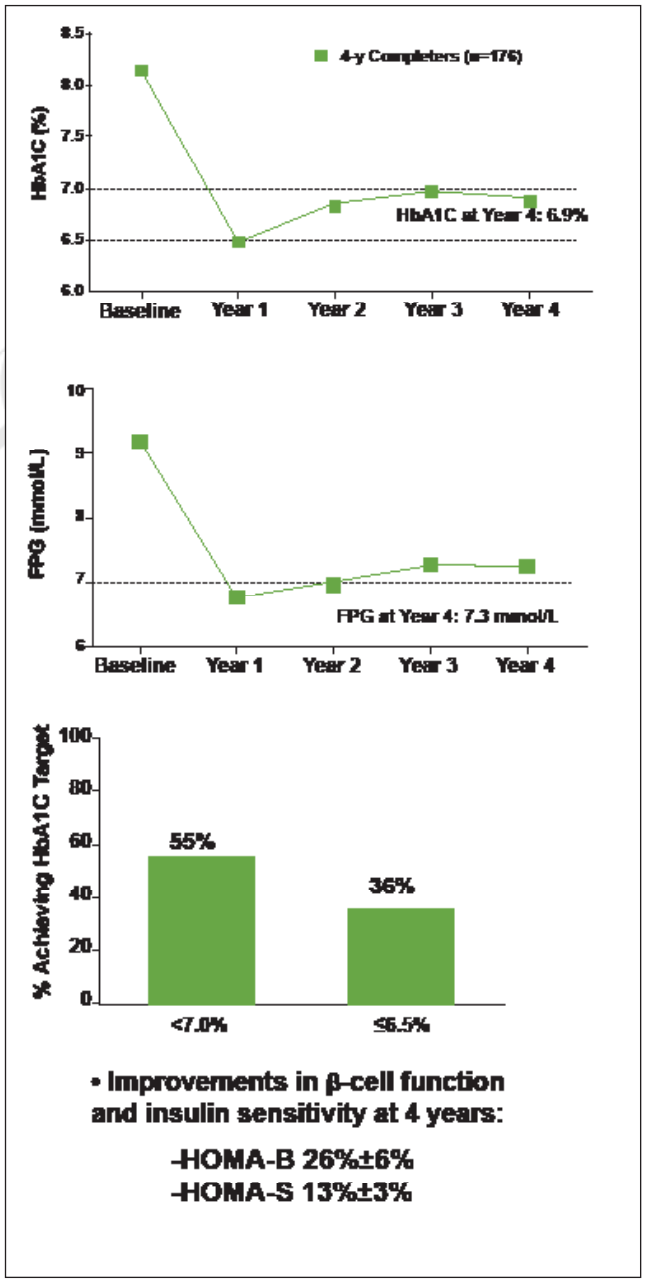
In the DURATION-1 trial, treatment with exenatide once weekly (EQW) for 30 weeks significantly reduced HbA1C compared with twice-daily exenatide in patients with T2DM [Drucker DJ et al. *Lancet* 2008]. The study included patients with T2DM and HbA1C 7.1% to 11.0%, who were treated with diet and exercise and/or a stable dose of metformin, sulfonylurea, thiazolidinedione, or a combination of these therapies. Patients were randomized to receive EQW (2 mg) or exenatide BID (5 µg for 4 weeks, then 10 µg for 26 weeks). The primary endpoint (HbA1C) was assessed at 30 weeks, after which all patients received EQW (2 mg).

The objectives of the current analysis were to examine the long-term safety and efficacy of EQW over 4 years in patients with T2DM. Study endpoints included change from baseline to Year 4 in HbA1C, fasting plasma glucose (FPG), weight, blood pressure (BP), and lipid profile. Sixty percent (n=176) of the intention-to-treat (ITT) population completed 4 years of EQW treatment. The efficacy results are based on the 176 study completers. Safety data are based on the ITT population (n=295). Baseline characteristics were consistent between the ITT and completer populations: mean age 56 years, 54% men, mostly white, mean HbA1C 8.2%, mean FPG 9.2 mmol/L, and duration of diabetes 7 years. Most study participants received metformin (33%) or combination therapies (39%).

At 4 years, mean HbA1C (± standard error) was 6.9% (±0.1%), with 55% of patients achieving HbA1C <7.0% and 36% achieving HbA1C ≤6.5% (Figure 1). Clinically significant ($p<0.05$) improvements in FPG (–1.9 mmol) and weight (–2.5 kg) were observed. Improvements in β-cell

function and insulin sensitivity were indicated by increases in the Homeostasis Model Assessment for β-cell function (HOMA-B; 26%±6%) and for insulin sensitivity (HOMA-S; 13%±3%). These changes from baseline were observed at Year 1 and maintained thereafter.

Figure 1. Once-Weekly Exenatide Associated with Improved HbA1C and Fasting Plasma Glucose Through 4 Years.



FPG=fasting plasma glucose; HOMA-B=Homeostasis Model Assessment B-cell function; HOMA-S=Homeostasis Model Assessment, insulin sensitivity; SE=standard error.

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Improvements (baseline to 4 years) were also observed for cardiovascular risk markers: systolic BP (–1.6 mm Hg; -8.7 mm Hg in patients with abnormal baseline systolic BP), diastolic BP (–2.7 mm Hg), total cholesterol (–0.30 mmol/L), low-density lipoprotein cholesterol (–0.20 mmol/L), high-density lipoprotein cholesterol (+0.05 mmol/L), and triglycerides (–13%). Maximum response was seen at Year 2 and maintained thereafter. Seventy-one percent of patients lost weight (–2.5 kg mean weight loss at Year 4).

Nausea and injection-site pruritus—the most common adverse events (AEs)—decreased in incidence with ongoing therapy, as did vomiting and diarrhea. The annual event rate for nausea and injection-site pruritus was 15/100 years and 6/100 years patient exposure over the 4-year study duration. Cardiac and renal/urinary disorders occurred at event rates of 5 and 6 per 100 years patient exposure, respectively. Twenty percent of EQW patients experienced serious AEs (no identifiable pattern of types of events) and 3 patients died (none due to treatment). Withdrawal rates over the 4-year duration due to AEs were low (8%); gastrointestinal AEs led to withdrawal in few (2%) patients. There was no major hypoglycemia. Minor hypoglycemia increased minimally after 1 year of exenatide therapy. There were few minor hypoglycemia events in patients not using concomitant sulfonylurea.

Long-term exenatide treatment was associated with significant, sustained improvement in glycemic control and improvements in cardiometabolic measures, with no unexpected safety findings.

DiaPep277® Shows Promise as a Therapeutic Strategy for Type 1 Diabetes

Written by Maria Vinall

Administration of DiaPep277® is safe and represents a promising therapeutic strategy in patients with recent-onset type 1 diabetes (T1DM). Results of two large Phase 3 trials will determine if this therapy might change the current approach to treating newly diagnosed T1DM patients [Tuccinardi D et al. *Expert Opin Biol Ther* 2011].

Itamar Raz, MD, Hadassah Medical Center, Jerusalem, Israel, reported outcomes from 1 of these trials—a multinational, randomized, double-blind, placebo-controlled, parallel-group study to investigate the clinical Efficacy and Safety of DiaPep277 in Newly Diagnosed Type 1 Diabetes Patients [DIA-AID 1; NCT00615264].