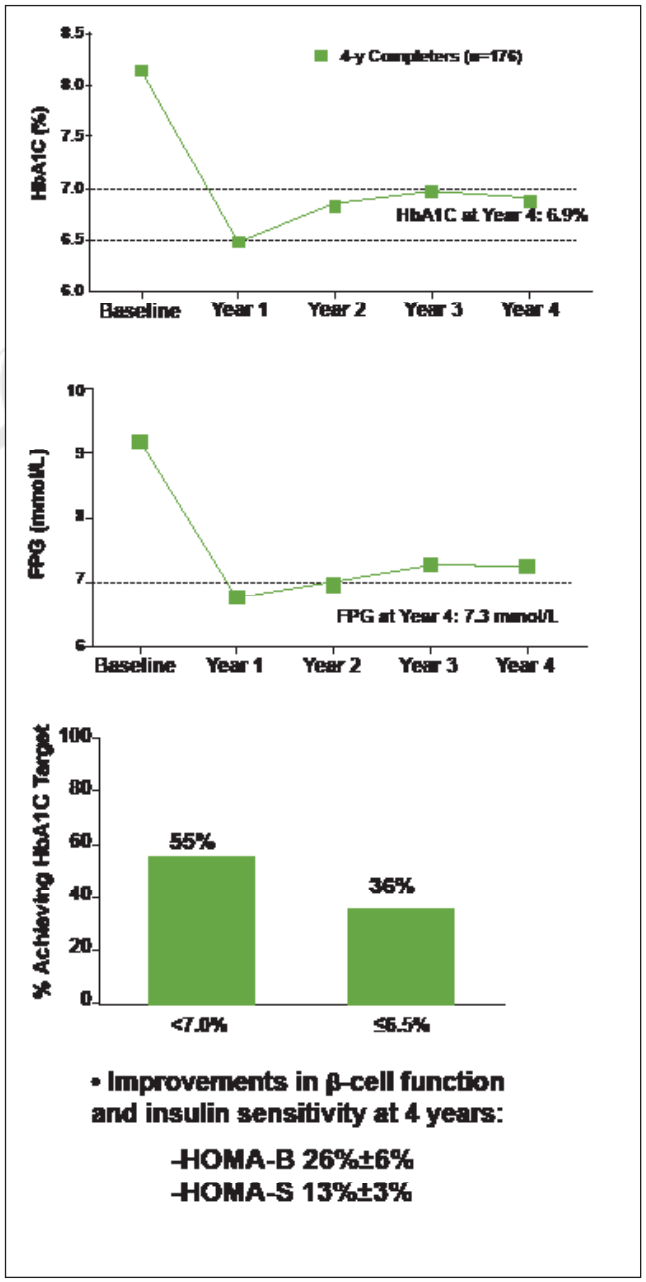
function and insulin sensitivity were indicated by increases in the Homeostasis Model Assessment for β-cell function (HOMA-B; 26%±6%) and for insulin sensitivity (HOMA-S; 13%±3%). These changes from baseline were observed at Year 1 and maintained thereafter.

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].

DIA-AID 1 was a 2-year double-blind study conducted in 42 medical centers in 11 countries in Europe, South Africa, and Israel. It included 457 patients aged 16 to 45 years with newly diagnosed T1D (<3 months) and residual β-cell function fasting C-peptide ≥0.22 nmol/L.

The peptide DiaPep227 is an immunodominant epitope of heat shock protein 60 that is found in insulin secretory granules of β cells. It is thought to be an autoantigen and induces T regulatory cells via toll-like receptors [Gupta S. *Med Clin N Am* 2012].

Patients were randomized 1:1 to receive a total of 9 injections of either 1 mg DiaPep277 or placebo administered quarterly at a medical center. The primary outcome was the change in stimulated C-peptide area under the curve (AUC) from baseline to Month 24 as measured by a 20-minute glucagon-stimulated test. Secondary outcomes included the change in stimulated C-peptide AUC from baseline to Month 24 as measured by the mixed-meal tolerance test (MMTT), the proportion of patients who maintained HbA1C levels ≤7% at the end of the study, and the change in fasting C-peptide from baseline to Month 24.

The primary efficacy endpoint in the modified intention-to-treat population (mITT) showed a trend that became significant (p=0.037) at 24 months, with a 23.4% decline in progression in the DiaPep277 group versus placebo. The difference was even more pronounced in the per-protocol (PP) population, with a relative treatment effect of 29.2% (p=0.011).

Among the secondary endpoints, there was no significant difference between the placebo and treatment groups in change in stimulated C-peptide AUC from baseline to Month 24 as measured by the MMTT. Although there was a trend toward a treatment effect in the change from baseline in fasting C-peptide, the difference between the treatment and placebo groups was not significant.

A significantly greater number of treated patients in the mITT population maintained HbA1C levels ≤7% at the end of the study versus those who received placebo (p=0.03), with an even greater difference between the 2 groups in the PP population (p=0.0082). The number of patients with at least 1 treatment emergent adverse advent (TEAE) was 173 (76.9%) in the DiaPep277 group and 164 (71%) in the placebo group. The number of patients with at least 1 life-threatening TEAE was the same for both groups (2; 0.9%). The most common TEAEs were nasopharyngitis, influenza, upper respiratory tract infection, gastroenteritis, headache, pyrexia, and back pain.

Outcomes from a continuous glucose monitoring substudy conducted on 78 patients at 17 sites showed a significantly lower number of hyperglycemic excursions per patient (defined by glucose levels >140 mg/dL) in the DiaPep277-treated group compared with those who received the placebo (11.5 vs 14.4; p=0.032). In the treated group, the duration of hypoglycemia was shorter and the magnitude of the events showed a strong trend of less severity.

Linagliptin Proves Safe and Effective as Add-on Therapy to Basal Insulin

Written by ***Rita Buckley***

Linagliptin may be a treatment option in patients with type 2 diabetes mellitus (T2DM) taking basal insulin, especially in those prone to hypoglycemia and/or declining renal function, according to Hannele Yki-Järvinen, MD, PhD, University of Helsinki, Helsinki, Finland, who presented results from a 52-week, multicenter, randomized, placebo-controlled, Phase 3 clinical trial.

The objective of the Efficacy and Safety of Linagliptin in Combination with Insulin in Patients with Type 2 Diabetes study was to determine the efficacy of the dipeptidyl peptidase-4 inhibitor linagliptin after 24 weeks, and long-term safety after 52 weeks as add-on therapy to basal insulin alone or in combination with metformin and/or pioglitazone in patients with T2DM [NCT00996658]. The primary endpoint was change in HbA1C from baseline to Week 24. Secondary endpoints were changes from baseline in fasting plasma glucose, basal insulin dose, and body weight after 24 and 52 weeks, ie, sustained glucose control and long-term safety data with an emphasis on hypoglycemia.

A total of 1261 patients inadequately controlled on insulin glargine, insulin detemir, or neutral protamine Hagedorn insulin were randomized 1:1 to receive either linagliptin 5 mg QD or placebo QD for at least 52 weeks. The background dose of basal insulin was kept stable up to 24 weeks but could then be freely adjusted. Inclusion criteria were male and female subjects at least 18 years of age with T2DM, body mass index (BMI) ≤45 kg/m^2, detectable C-peptide, pretreatment with basal insulin and/or metformin and/or pioglitazone, and HbA1C of 7% to 10% [Yki-Järvinen H et al. EASD 2012 Abstract 6].