DURATION-3 was an open-label, randomized, controlled study of patients with type 2 diabetes mellitus comparing once-weekly injection of exenatide, a glucagon-like peptide-1 receptor agonist, to titrated insulin glargine. Michael Trautmann, MD, Diabetologist and Consultant, Hamburg, Germany, reported the 3-year results, noting that this study was unique in that it compared the two injectable therapies over 3 years in patients who had not achieved an HbA1C level of <7% during treatment with metformin alone or in combination with sulfonylurea.

The 456 enrolled patients were randomized to exenatide 2 mg QW (n=233) or titrated insulin glargine QD (n=223). All patients received metformin with or without sulfonylurea. The study consisted of a 26-week core study period followed by a 130-week controlled extension period. A substantial proportion of participants completed the 156-week regimen (60% in the exenatide arm and 66% in the insulin glargine arm). The baseline characteristics of the intention-to-treat (ITT) subjects and the completers were similar, notably concerning HbA1C level (~8.3%) and duration of diabetes (~8 years).

Dr. Trautmann reported that in the ITT population, mean HbA1C levels at 3 years were significantly lower with exenatide (7.3±0.07%) versus insulin glargine (7.5±0.07%; p=0.033; Figure 1). Similarly, in the completer population, mean HbA1C levels at 3 years were significantly lower with exenatide (7.1±0.08%) versus insulin glargine (7.4±0.08%; p=0.022). The similarity of the findings in the ITT and completer populations emphasizes the representative nature of the 3-year data. Furthermore, significantly more patients in the exenatide arm achieved HbA1C targets of ≤6.5% at 3 years (24% vs 15%; p=0.02 [ITT population]; 28% vs 18% [completer population]).

Patients in the exenatide group gained body weight (mean, −2.49±0.28 kg) while those receiving insulin glargine lost body weight (mean, +2.01±0.28 kg). There was a significant difference between the groups for the change in body weight from baseline to 3 years (mean difference, −4.51±0.37 kg; p<0.001).

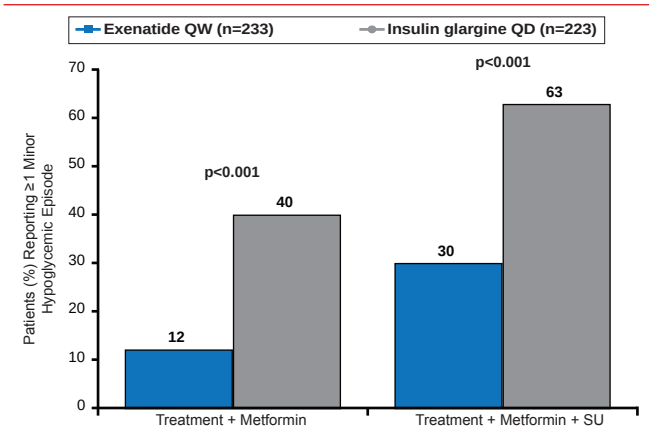
Sixty-eight percent of patients in the exenatide arm displayed both reduced HbA1C and body weight at 3 years compared with only 34% in the insulin glargine arm. Fasting serum glucose was also significantly decreased in patients receiving exenatide (mean, −31.16 mg/dL) versus those receiving insulin glargine (mean, −47.74 mg/dL; p<0.001).

The safety profile of both drugs at 3 years echoed the previous 26- and 84-week results. While subjects receiving exenatide were more prone to gastrointestinal maladies including nausea, vomiting, and diarrhea than those receiving insulin glargine (16% vs 2%; 6% vs 3%; 14% vs 7%, respectively), most adverse events occurred in the first 26 weeks in the exenatide group. Consistent with the better longer-term tolerance of exenatide, the positive rate for anti-exenatide antibodies decreased from 56% at 26 weeks to 19% at 3 years.

Exenatide was associated with significantly fewer incidents of hypoglycemia than insulin glargine when used in combination with metformin alone (p<0.001) or with metformin plus sulfonylurea (p<0.001; Figure 1).

Dr. Trautmann concluded that exenatide is superior to insulin glargine in terms of sustained glycemic control and weight loss, and in lessening the risk of hypoglycemia.

Figure 1. Incidence of Minor Hypoglycemia at 3 Years



QD=once daily; QW=once weekly; SU=sulfonylurea.

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Empagliflozin Improves Glycemic Parameters and Cardiovascular Risk Factors in Patients With Type 2 Diabetes Mellitus

Written by Wayne Kuznar

Patients with type 2 diabetes mellitus (T2DM) who are treated with empagliflozin, a sodium glucose cotransporter 2 inhibitor, as monotherapy or add-on antihyperglycemic therapy experience clinically meaningful improvements in glycemic parameters and several cardiovascular risk factors, according to Thomas Hach, MD, Boehringer Ingelheim Pharma GmbH & Company KG, Ingelheim, Germany. Prof. Hach presented the results of a pooled analysis of four randomized, placebo-controlled Phase 3 trials in which the effects of 24 weeks of empagliflozin were evaluated in 2477 T2DM patients.

In the four trials, patients with HbA1C values ranging from 7% to 10% at screening were randomized to empagliflozin 10 mg (n=831) or 25 mg (n=821) QD or placebo (n=825) for 24 weeks as either monotherapy, add-on to metformin, add-on to metformin plus a sulfonylurea, or add-on to pioglitazone with or without metformin. The

patient population had a mean age of 55.6 years and a mean body mass index of 28.7 kg/m^2; 45.5% of the participants were female.

Relative to placebo, HbA1C levels significantly decreased by 0.62% and 0.68% in the empagliflozin 10- and 25-mg groups at Week 24 ($p<0.001$ for both vs placebo). Among patients with baseline HbA1C ≥7.0%, significantly more who were assigned to empagliflozin at either dose achieved an HbA1C levels <7.0% at Week 24 compared with placebo (empagliflozin 10 mg, 31.5%; empagliflozin 25 mg, 37.2%; placebo, 10.5%; $p<0.001$ for both vs placebo).

Over 24 weeks, fasting plasma glucose (FPG) declined by 20.5 mg/dL in the empagliflozin 10-mg group and by 23.2 mg/dL in the 25-mg group, while it increased by 7.4 mg/dL in the placebo group. The difference in FPG at Week 24 was significantly different between the two empagliflozin groups and placebo ($p<0.001$ for both vs placebo).

Confirmed hypoglycemic adverse events were more frequent with empagliflozin 10 mg (5.2%) and 25 mg (4.0%) versus placebo (2.9%); however, no hypoglycemic event required assistance.

Systolic blood pressure (BP) and diastolic BP decreased significantly more from baseline to Week 24 in patients randomized to empagliflozin 10 mg or 25 mg compared with placebo ($p<0.001$ for both vs placebo). The percentage of patients with uncontrolled hypertension (BP ≥130/80 mm Hg) at baseline whose BP was controlled at Week 24 was 18.6% with placebo, 33.3% with empagliflozin 10 mg, and 35.2% with empagliflozin 25 mg ($p<0.001$ for both doses vs placebo).

Empagliflozin 25 mg was associated with a significant increase from baseline in total cholesterol compared with placebo ($p<0.001$). Patients assigned to empagliflozin 10 mg had a significant decrease from baseline in triglyceride level when compared with placebo ($p<0.05$). Compared with placebo, low-density lipoprotein cholesterol levels increased substantially in both empagliflozin groups, but this change was only statistically significant in the 25-mg group ($p<0.008$). The level of high-density lipoprotein cholesterol increased significantly in both empagliflozin groups compared with placebo ($p<0.001$ for both vs placebo).

The changes from baseline to Week 24 in uric acid levels were +1.03 µmol/L in the placebo group, –28.95 µmol/L with empagliflozin 10 mg ($p<0.001$), and –29.55 µmol/L with empagliflozin 25 mg ($p<0.001$ for both vs placebo).

Relative to placebo, body weight declined by 1.81 kg in patients randomized to empagliflozin 10 mg and by 2.01 kg in those randomized to empagliflozin 25 mg ($p<0.001$ for both vs placebo).

In conclusion, the findings of this pooled analysis show that empagliflozin QD at 10 mg or 25 mg for 24 weeks is clinically superior to placebo in patients with T2DM.