Table 2. Summary of Adverse Events

Category	Once-Weekly Exenatide	Twice-Daily Exenatide
All patients with AEs	162 (70.7)	108 (74.0)
AEs in ≥5% of patients		
Nausea	22 (9.6)	31 (21.2)
Injection site nodule	29 (12.7)	1 (0.7)
Diarrhea	12 (5.2)	17 (11.6)
Headache	13 (5.7)	9 (6.2)
Upper respiratory tract infection	13 (5.7)	5 (3.4)
Vomiting	8 (3.5)	9 (6.2)
Serious AEs	6 (2.6)	7 (4.8)
AEs leading to withdrawal	5 (2.2)	7 (4.8)

AEs=adverse events. Data are n (%).

The prevalence of adverse events (AEs) was overall similar between the study arms (Table 2). However, the prevalence of nausea and diarrhea was lower but the presence of an injection-site nodule was far more common in the once-weekly exenatide arm as compared with the twice-daily arm.

The present results were similar to those of the previous DURATION-5 study [Blevins T et al. *J Clin Endocrinol Metab* 2011]. This featured administration of exenatide QW, which required reconstitution and administration with a syringe. The researchers concluded that a weekly autoinjection of exenatide that does not require reconstitution provides statistically superior reduction in HbA_{1c} and fewer gastrointestinal AEs than the regimen of exenatide given by twice-daily injection.

Empagliflozin Reduces BP in Hypertensive Type 2 Diabetics

Written by Brian Hoyle

Empagliflozin, an investigational drug to treat type 2 diabetes that is being developed by Boehringer Ingelheim Pharma, lowered blood pressure (BP) in hypertensive type 2 diabetics and reduced blood glucose levels during 12 weeks of treatment. Afshin Salsali, MD, University of Medicine and Dentistry of New Jersey, Newark, New Jersey, USA, presented findings of the 12 Week Efficacy and Safety Study of Empagliflozin (BI 10773) in Hypertensive Patients With Type 2 Diabetes Mellitus [EMPA-REG BP; NCT01370005], a placebo-controlled Phase 3 trial (randomized, double-blind).

Prior 24-week Phase 3 clinical trials (randomized, double-blind) established the efficacy of empagliflozin (10 and 25 mg) in reducing systolic BP compared with placebo among patients with type 2 diabetes [Häring H-U et al. *Diabetes Care* 2014; Kovacs CS et al. *Diabetes Obes Metab* 2014; Häring H-U et al. *Diabetes Care* 2013; Roden M et al. *Lancet Diabetes Endocrinol* 2013]. The effect on blood sugar remained unclear.

The present study involved 823 subjects with type 2 diabetes and high BP (130/80 to 159/99 mm Hg) who were randomly assigned to receive placebo (n=271), empagliflozin–10 mg (n=276), and empagliflozin–25 mg (n=276). The baseline demographics and clinical characteristics of the randomized patients were similar (Table 1).

At baseline, the majority (63%) had an estimated glomerular filtration rate of 60 to 90 mL/min/1.73 m^2. All patients wore an ambulatory BP cuff that monitored systolic and diastolic BP every hour for 24 hours at baseline (before treatment) and after 12 weeks of treatment. Blood samples were also acquired at baseline and 12 weeks to determine HbA_{1c} levels as a measure of long-term blood sugar control.

The 24-hour pattern of systolic BP was almost identical for the 3 subject groups at baseline. At Week 12, while the 24-hour systolic BP curves for the 3 groups were similar in shape, the placebo group consistently displayed higher BP than either empagliflozin group.

Table 1. Baseline and Clinical Characteristics of the 3 Patient Groups

		Empagliflozin	
	Placebo	10 mg	25 mg
Subjects	271	276	276
Male	168 (62.0)	171 (62.0)	156 (56.5)
Age, y	60.3 ± 8.8	60.6 ± 8.5	59.9 ± 9.7
Body mass index, kg/m^2	32.4 ± 4.9	32.4 ± 5.3	33.0 ± 5.0
HbA_{1c}, %	7.9 ± 0.7	7.9 ± 0.8	7.9 ± 0.7

Values in number (%) or mean±standard deviation.

Empagliflozin–25 mg produced slightly lower 24-hour systolic BP than empagliflozin–10 mg.

Similar results were found for diastolic BP. On average, systolic and diastolic BP among subjects who received the 25 mg of empagliflozin decreased by 4.2 mm Hg ($p < .001$) and 1.7 mm Hg ($p < .01$), respectively, compared with placebo. The average decrease in systolic and diastolic BP among patients who received the 10 mg of empagliflozin was 3.4 mm Hg ($p < .001$) and 1.4 mm Hg ($p < .01$), respectively, compared with placebo.

From baseline to Week 12, the average HbA_{1c} level dropped by 0.62% and 0.65% with 10 and 25 mg of empagliflozin, respectively, compared with placebo. Subjects tolerated empagliflozin well, with no increased rate of side effects compared with placebo. Most adverse events that occurred in all 3 groups were mild.

The authors speculate that the improved blood sugar levels evident in subjects receiving empagliflozin reflect reduced glucose reabsorption in the kidneys, which leads to glucose elimination in the urine. The findings suggest the potential of empagliflozin to reduce the risk of cardiovascular events with longer-term treatment. This possibility is being addressed in the long-term EMPA-REG OUTCOME trial [Zinman B et al. *Cardiovasc Diabetol* 2014], which is expected to finish in 2015. The primary end point of the latter trial is the time to first occurrence of cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke.

Table 1. Patient Demographics and Characteristics

	Placebo (n = 207)	Empagliflozin 10 mg (n = 217)	Empagliflozin 25 mg (n = 213)
Male	116 (56.0)	125 (57.6)	120 (56.3)
Age, y	56.0 ± 9.7	55.5 ± 9.9	55.6 ± 10.2
Race			
Asian	92 (44.4)	99 (45.6)	98 (46.0)
White	113 (54.6)	112 (51.6)	113 (53.1)
Other	2 (1.0)	6 (2.8)	2 (0.9)
Time since T2DM diagnosis, years			
≤1	19 (9.2)	20 (9.2)	19 (8.9)
> 1-5	83 (40.1)	78 (35.9)	69 (32.4)
> 5-10	65 (31.4)	68 (31.3)	74 (34.7)
> 10	40 (19.3)	51 (23.5)	51 (23.9)
HbA_{1c}, %	7.90 ± 0.88	7.94 ± 0.79	7.86 ± 0.87
Body weight, kg	79.7 ± 18.6	81.6 ± 18.5	82.2 ± 19.3
Blood pressure, mm Hg			
Systolic	128.6 ± 14.7	129.6 ± 14.1	130.0 ± 15.1
Diastolic	78.1 ± 7.9	79.6 ± 8.0	78.4 ± 8.4

Data are expressed as number (%) or mean±standard deviation.
T2DM=type 2 diabetes mellitus.

Reductions in HbA_{1c} and Weight in Type 2 Diabetics With the Empagliflozin Add-On Regimen

Written by Brian Hoyle

Empagliflozin, 10 or 25 mg, used as an add-on to metformin therapy for ≥ 76 weeks among patients with type 2 diabetes mellitus (T2DM) produces significant and sustained decreases in glycated hemoglobin (HbA_{1c}), body weight, and systolic blood pressure (SBP), compared with placebo. The results of the extension portion of a randomized Phase 3 trial involving 637 patients were reported by Ludwig Merker, MD, Diabetes- und Nierenzentrum, Dormagen, Germany.

Empagliflozin is a potent and selective inhibitor of sodium glucose cotransporter 2 [Grempler R et al. *Diabetes Obes Metab* 2012]. A prior Phase 3 trial [EMPA-REG MET; Häring H-U et al. *Diabetes Care* 2014] showed improved glycemic control as measured by HbA_{1c} and fasting plasma glucose, as well as body weight and blood pressure, among T2DM patients who received empagliflozin, 10 or 25 mg, as an add-on to metformin therapy over 24 weeks of treatment, compared with placebo. The present extension study, the Safety and Efficacy of Empagliflozin (BI 10773) and Sitagliptin Versus Placebo Over 76 Weeks in Patients With Type 2 Diabetes study [EMPA-REG EXTEND MET; NCT01289990], assessed the long-term safety, tolerability, and efficacy of the empagliflozin add-on regimen.

The full analysis population included 637 patients with HbA_{1c} between 7.0% and 10% despite a diet and exercise regimen. All patients received metformin (≥ 1500 mg daily) and were randomly assigned to receive a daily add-on of placebo (n = 207); empagliflozin, 10 mg (n = 217); or empagliflozin, 25 mg (n = 213). The main outcomes were changes from baseline to Week 76 of treatment in HbA_{1c}, body weight, and SBP. Safety was assessed among 463