University of Texas Southwestern Medical School, Dallas, Texas, USA, presented findings from the study.

The primary outcome for the 24-week, randomized, multicenter trial was efficacy of specific doses of ITCA 650. Eligibility criteria included males or females aged 18 to 70 years with type 2 diabetes mellitus for ≥6 months prior to Screening Visit 1; a stable (>3 months prior to Screening Visit 1) treatment regimen of metformin monotherapy; fasting plasma glucose <240 mg/dL at Screening Visit 1; and HbA1C ≥7% and ≤10% at Screening Visit 1.

Exclusion criteria included prior treatment with exenatide, TZDs, sulfonylureas, DPP IV inhibitors, acarbose, or insulin (injected or inhaled); history of type 1 diabetes and/or diabetic ketoacidosis; body mass index ≥40 kg/m^2; and history of organ transplantation.

Subjects (n=155) were randomized to receive ITCA 650, implanted every 3 months at 20, 40, 60, or 80 mcg/day following 12 weeks of either ITCA 650 (20 or 40 mcg/day) or exenatide injections (10 mcg BID). At Week 12, the completion rate for ITCA 650 was 93% versus 89% for exenatide injections; respective withdrawals due to nausea were 3.9% versus 5.7%.

At Week 24, subjects were offered the option to continue treatment at their current dose for an additional 24 weeks; 85% of eligible subjects elected to continue treatment. During the 6-month extension, HbA1C and body weight reductions were sustained. No subjects withdrew for any reason. One patient reported nausea; none reported vomiting. No cases of hypoglycemia occurred.

Significant reductions in HbA1C ($p<0.0001$ for all does groups) and weight ($p<0.001$ for the 40 mcg/day dose and $p<0.05$ for all other doses) at Week 48 were maintained from those that were initially observed at Week 24. Desirable trends in lipids and blood pressure were also noted. Changes that were seen at 60 mcg/day, the long-term dose that was selected for future studies, were -3.1% for total cholesterol, -9.9% for triglycerides, -5.2% for low-density lipoprotein cholesterol, -1.7 mm Hg for systolic blood pressure, and -7.8 mm Hg for diastolic blood pressure. High-density lipoprotein cholesterol increased by 0.5%. Continuing treatment with ITCA 650 was very well tolerated, with minimal side effects and a completion rate of 85%.

Study delivery technology consisted of sterile, nonbiodegradable, single-use devices for continuous, subcutaneous administration of therapeutic molecules at steady rates. It is capable of delivering a wide range of therapeutic molecules for durations that range from 3 to 12 months [Rohloff CM et al. *J Diabetes Sci Technol* 2008].

This extension study shows that long-term treatment with ITCA 650 is effective in controlling glycemic parameters and weight and can also lead to potentially positive cardiovascular benefits through beneficial changes in lipids and blood pressure. In addition, tolerability is excellent, with minimal gastrointestinal side effects. Phase 3 studies will evaluate chronic treatment with ITCA 650 using devices of 6 to 12 months in duration.

Novel Agent Found to Reduce HbA1C in Type 2 Diabetes

Written by Lori Alexander

A randomized, double-blind, multicenter study demonstrated that a G-protein-coupled receptor 40 (GPR40) agonist had glucose-lowering efficacy for the treatment of type 2 diabetes. The novel agent significantly reduced HbA1C compared with placebo, with efficacy that was comparable with glimepiride but with a significantly lower rate of hypoglycemia.

Prabhakar Viswanathan, MD, PhD, State University of New York, Buffalo, New York, USA, reported the findings of the study. He first explained that the agent, TAK-875, is a highly selective and potent GPR40 agonist with glucose-dependent insulinotropic action.

The study was designed to evaluate the efficacy, safety, and tolerability of TAK-875 at 5 doses—6.25, 25, 50, 100, and 200 mg—given once daily for 12 weeks. The 426 study subjects were randomly assigned a different dose of TAK-875, glimepiride (4 mg), or placebo, with 60 to 62 subjects in each group. About 75% of the 426 patients were taking metformin at baseline.

The primary efficacy endpoint was change in HbA1C from baseline to Week 12. Several other efficacy and safety endpoints were also evaluated, including changes in HbA1C over time, fasting plasma glucose (FPG) level, 2-hour glucose level during oral glucose tolerance testing (OGTT), and incidence of hypoglycemia.

Dr. Viswanathan reported that all doses of the drug led to greater reductions in HbA1C at 12 weeks than placebo, with the efficacy of the drug reaching a plateau at the 50-mg dose. Doses ≥50 mg of TAK-875 led to reductions that were comparable with those found with glimepiride. The mean reduction in HbA1C was significantly different by the time of the first testing (4 weeks), and the difference remained significant at all time points. Nearly

one-third of patients who were treated with TAK-875 had a decrease in HbA1C of 1.5% or more at Week 12, a rate that was comparable with that for the glimepiride group and significantly better than that for the placebo group ($p<0.05$).

TAK-875 rapidly reduced the FPG, with a substantial difference by Week 1. The mean reduction in the 2-hour glucose level during OGTT was significantly greater with doses of TAK-875 ≥25 mg compared with placebo ($p<0.05$). β-cell function also appeared to improve, with significantly higher HOMA-β scores for TAK-875 at doses ≥50 mg compared with placebo ($p<0.05$).

All doses were well tolerated over the course of the study. The incidence of hypoglycemia in all of the TAK-875 groups was similar to that in the placebo group (2.0% vs 3.3%) and was significantly lower than that in the glimepiride group (16.1%; $p<0.05$).

The rates of treatment-emergent adverse events in the TAK-875 groups ranged from 1.0% (hyperglycemia) to 5.3% (urinary tract infection). The rate of any adverse event was lower for TAK-875 compared with glimepiride (48.7% vs 61.3%).

TAK-875 is the first agent in its class to reach clinical development for the treatment of type 2 diabetes. The drug is being developed as an adjunct therapy to diet and exercise for improving glycemic control in patients with type 2 diabetes.

Intensive Lifestyle Intervention and Metformin Are Cost-Effective for Diabetes Prevention

Written by Rita Buckley

The Diabetes Prevention Program (DPP) was a multicenter trial that examined the impact of an intensive lifestyle intervention or metformin to prevent or delay the development of diabetes in a high-risk population with impaired glucose tolerance (IGT). The DPP ended early, demonstrating that lifestyle modification reduced diabetes onset by 58% versus 31% by metformin [Diabetes Prevention Program Research Group. *N Engl J Med* 2002].

The Diabetes Prevention Program Outcomes Study (DPPOS; NCT00038727) followed participants for another 7 years. The main objective was to assess the longer-term outcomes, including cost-effectiveness of the lifestyle and metformin interventions, with an intent-to-treat analysis that spanned the combined 10 years of DPP/DPPOS. William H. Herman, MD, MPH, University of Michigan, Ann Arbor, Michigan, USA, presented findings from the study.

Data on resource utilization, cost, and quality of life (QoL) were collected prospectively during DPP and DPPOS. Economic analyses were performed from a health system perspective that considered direct medical costs. Sensitivity analyses were performed from a societal perspective that considered both direct medical costs and direct nonmedical costs (diet- and activity-related costs, participant time, and transportation).

The DPP randomized overweight adults with IGT and an elevated fasting glucose level to intensive lifestyle (ILS), metformin (MET), or placebo (PBO) for an average of 3 years. During the DPPOS, ILS and MET participants were encouraged to continue those interventions, and all were offered a modified lifestyle intervention.

An analysis demonstrated that the beneficial effects of ILS and MET on the incidence of type 2 diabetes persisted 10 years after randomization [DPP Research Group. *Lancet* 2009].

During DPP, the costs of ILS were greater than the cost of MET, which were greater than the cost of PBO. During DPPOS, the costs of ILS and MET were substantially lower than during DPP, and the costs of PBO were higher than during DPP.

Over 10 years, the cumulative, undiscounted, per capita direct medical costs of the interventions were greater for ILS and MET than for PBO ($4601 ILS vs $2300 MET vs $769 PBO). The direct medical costs of care outside the DPP/DPPOS increased over time for all groups but were highest for PBO. The cumulative undiscounted, per capita, direct medical costs of nonintervention-related medical care were greater for PBO ($27,468) than MET ($25,616) or ILS ($24,563).

The undiscounted, per capita, total direct medical costs over 10 years were $29,164 for ILS, $25,616 for MET, and $28,236 for PBO. Quality of life was better for ILS compared with MET or PBO, and the undiscounted quality-adjusted life-years (QALYs) that accrued over 10 years were greater for ILS (6.81) than MET (6.69) or PBO (6.67). From a payer perspective, MET was less expensive and more effective than PBO, and ILS cost only about $1000 per QALY.

From a payer perspective, the MET intervention was cost-saving, and the lifestyle intervention was cost-effective compared with PBO. The increased cost of the ILS, relative to PBO, was largely offset by lower nonintervention-related medical care costs. Health policy should support the funding of intensive lifestyle and metformin for diabetes prevention in high-risk adults.