Drugs in Phase 3 Clinical Trials for Type 2 Diabetes

By Alice Goodman, Medical Writer

This article outlines some of the novel therapies recently approved by the US Food and Drug Administration (FDA) or are furthest along in clinical trials for type 2 diabetes.

Dipeptidyl Peptidase-4 Inhibitors

Linagliptin belongs to the dipeptidyl peptidase (DPP)-4 inhibitors class that was recently approved by the FDA for type 2 diabetes and has the potential to replace sulfonylureas in the future. Linagliptin is not excreted renally, and therefore no dose adjustments are needed in patients with renal impairment. With sulfonylureas, patients need to be taught to self-measure blood glucose, which involves substantial costs; this is not necessary with linagliptin, which could result in cost-savings.

Alogliptin (Nesina) is another DPP-4 agent in late-stage development. In 2008 alogliptin was submitted to the FDA, which requested additional cardiovascular (CV) safety information. A clinical trial is now underway examining the CV safety profile.

Glucagon-Like Peptide-1 Receptor Agonists

Exenatide is being investigated as 2 new formulations—once weekly (Bydureon) and once monthly. A twice-daily formulation (Byetta) was approved by the FDA in 2005. Exenatide mimics the effect of incretins, such as glucagon-like peptide (GLP)-1 receptor agonists that increase the secretion of insulin from the pancreas, slow the absorption of glucose, and reduce the action of glucagon. GLP-1 agents also reduce appetite.

The 3-year data from DURATION-1 and 84-week data from DURATION-2 trials plus 3 additional studies demonstrated that the once-weekly formulation of exenatide achieved a significant 1.6% reduction from baseline in hemoglobin (Hb) A1c and weight (5.1 lb).

Cardiometabolic risk markers also improved, including systolic blood pressure (~2.1 mm Hg), total cholesterol (~9.9 mg/dL), low-density lipoprotein cholesterol (~7.0 mg/dL), and triglyceride levels (~12%). Bydureon was approved in the European Union in June 2011.

Lixisenatide (Lyxumia) achieved positive results in patients not achieving glycemic goal with oral therapies or basal insulin. In the GetGoal-X trial, once-daily lixisenatide achieved noninferiority results in HbA1c reduction versus twice-daily exenatide; both drugs were used as add-on to metformin in patients inadequately controlled with metformin.

A second study, GetGoal-L Asia, showed that Asian patients with type 2 diabetes who were inadequately controlled with basal insulin with and without sulfonylurea were significantly improved with lixisenatide once daily versus placebo at week 24, as reflected by the improvement in HbA1c level, with a target of <6.5% or <7.0%.

Sodium-Glucose Cotransporter-2 Inhibitors

Sodium-glucose cotransporter (SGLT)-2 inhibitors represent a promising new class of drugs for treatment of type 2 diabetes. These drugs work by inhibiting reabsorption of endogenously produced glucose in the proximal tubules of the kidney.

Results from a phase 3 trial showed that the investigational SGLT-2 inhibitor dapagliflozin added to metformin sustained reductions in HbA1c from 52 weeks to 104 weeks in adults with type 2 diabetes compared with glipizide (a frequently used sulfonylurea) plus metformin. Adverse events were similar in frequency between the 2 treatment arms. These results are from an extension phase of the original 52-week trial. Weight reduction was sustained at 104 weeks, and hypoglycemic episodes were 10 times more frequent in patients treated with glipizide plus metformin than with dapagliflozin plus metformin (45.8% vs 4.2%, respectively). Genital and urinary tract infections were more frequent with dapagliflozin than with glipizide.

Canagliflozin is safe and generally well tolerated at doses up to 300 mg twice daily when added to stable doses of insulin in subjects with type 2 diabetes, based on a randomized, double-blind, placebo-controlled, parallel-group, multidose study. Canagliflozin reduced the renal threshold for glucose excretion, improved glycemic control, and was associated with weight loss. A trend toward blood pressure reduction was observed, with no orthostatic symptoms.

Ultra-Long-Acting Insulin Degludec

The activity of the investigational ultra-long-acting basal insulin degludec lasts for up to 40 hours and may be able to reduce the insulin dosing frequency. In two phase 3, 52-week trials, it reduced the rates of hypoglycemia compared with insulin glargine.

A late-breaking 26-week study presented at ADA 2011 showed that insulin degludec could be dosed at different times from day to day.