Novel Treatments Target Type-2 Diabetes

Chris Fellner

Diabetes is a group of diseases characterized by elevated levels of blood glucose resulting from problems in how insulin is produced, how it works, or both. Type-1 diabetes (T1D)—previously known as insulin-dependent diabetes mellitus or juvenile-onset diabetes—develops when the cells that produce insulin in the pancreas (beta cells) are destroyed in a process initiated or mediated by the body's immune system. Insulin is required to lower blood glucose levels. Although the onset of T1D can occur at any age, the peak age for diagnosis is in the mid-teens. In adults, type-1 disease accounts for approximately 5% of all cases of diabetes.[1]

Type-2 diabetes (T2D)—previously called non–insulin-dependent diabetes mellitus or adult-onset diabetes—accounts for the vast majority (approximately 90% to 95%) of all diagnosed cases of diabetes in adults. The risk of developing T2D is associated with older age, obesity, a family history of diabetes, a history of gestational diabetes (see below), impaired glucose metabolism, physical inactivity, and race/ethnicity. The disease usually begins with insulin resistance, a disorder in which cells primarily within the muscles, liver, and fat tissue do not use insulin properly, and progresses to pancreatic beta-cell failure. For T2D to occur, both insulin resistance and inadequate insulin secretion must be present.[1–3]

Gestational diabetes is a form of glucose intolerance diagnosed during the second or third trimester of pregnancy. Other types of diabetes, such as maturity-onset diabetes of youth or latent autoimmune diabetes in adults, are caused by specific genetic conditions or by surgery, medications, infections, pancreatic disease, or other illnesses. These disorders account for 1% to 5% of all diagnosed cases of diabetes.[1]

According to the National Center for Chronic Disease Prevention and Health Promotion (a part of the Centers for Disease Control and Prevention), 29.1 million people in the U.S. (9.3% of the population) had diabetes in 2014. Of these individuals, 8.1 million (27.8%) had undiagnosed disease.[1]

Diabetes affects many parts of the body and is associated with serious complications, including heart disease, stroke, blindness, kidney failure, and lower-limb amputation.[1]

The preferred method for diagnosing diabetes is the glycated hemoglobin (HbA_{1c}) test, in which an HbA_{1c} level of 6.5% or greater indicates the presence of diabetes.[4] The HbA_{1c} test provides an average blood glucose measurement over the previous six to 12 weeks.[5]

Diabetes can be treated and managed by healthful eating, regular physical activity, and medications to lower blood glucose levels. Individuals with T1D must have insulin delivered by injection or a pump to survive. Those with T2D can control their blood glucose levels by following a healthy meal plan and a program of regular physical activity, losing excess weight, and taking medications. Insulin also is commonly used to control blood glucose in people withT2D.[1]

Metformin (dimethylbiguanide) is the standard first-line treatment when lifestyle changes, such as diet and exercise, do not achieve the desired glycemic goals. Metformin is a biguanide compound that reduces HbA_{1c} levels by inhibiting gluconeogenesis. This, in turn, reduces the production of hepatic glucose.[6] If the HbA_{1c} target is not achieved after approximately three months of metformin therapy, one of five second-line drugs may be added to the metformin regimen: a thiazolidinedione (i.e., pioglitazone [Actos, Takeda]), a sulfonylurea, a dipeptidyl peptidase 4 (DPP-4) inhibitor, a sodium-glucose cotransporter-2 (SGLT-2) inhibitor, or a glucagon-like peptide-1 receptor (GLP-1R) agonist. Basal insulin may also be added to metformin monotherapy. If HbA_{1c} targets remain unmet after dual, metformin-based treatment, diabetes patients may advance to triple therapy or to more complex injectable regimens.[4]

In July 2016, the Food and Drug Administration (FDA) approved lixisenatide (Adlyxin, Sanofi), a once-daily mealtime GLP-1R agonist injection, as an adjunct to diet and exercise for the treatment of adults with T2D.[7] The approval was based on results from the GetGoal clinical trial program and on findings from the Evaluation of Lixisenatide in Acute Coronary Syndrome (ELIXA) trial. ELIXA addressed the FDA's request for data demonstrating cardiovascular safety, which was included in a previous rejection letter. The GetGoal program, which included 13 clinical studies, evaluated the safety and efficacy of lixisenatide in more than 5,000 adults with T2D. All of the GetGoal trials successfully met the primary efficacy endpoint of HbA_{1c} reductions. The most common adverse events included nausea, hypoglycemia, and vomiting.

Lixisenatide is available in a disposable prefilled pen in a single dose of 20 mcg. Patients also will receive a disposable prefilled pen in a single dose of 10 mcg that they should initiate once daily for 14 days. On day 15, patients will increase the dosage to 20 mcg once daily.

Table 1 lists key branded treatments for T2D in the U.S.[8] In addition, several promising drugs are in the T2D pipeline. These medications are discussed below.

Ertugliflozin (Pfizer/Merck), an oral, once-daily SGLT-2 inhibitor, demonstrated significant HbA_{1c} reductions in two phase 3 studies (VERTIS Mono and VERTIS Factorial) in subjects with T2D.[9] The study results showed statistically significant reductions in HbA_{1c} for the two ertugliflozin dosages tested (5 mg daily and 15 mg daily).

In the 26-week VERTIS Mono trial, which evaluated ertugliflozin as monotherapy, patients randomly assigned to receive ertugliflozin 5 mg or 15 mg had significantly greater HbA_{1c} reductions of 0.99% and 1.16%, respectively, compared with placebo ($P < 0.001$ for both comparisons). In addition, significantly more patients receiving ertugliflozin 5 mg and 15 mg achieved the

Chris Fellner is a medical writer and the Editor of PTCommunity.com.

Table 1 Key Branded Treatments for T2D in the U.S.[7,8]

Class	Brand (Company)	Year Launched
DPP-4 inhibitors	Onglyza (AstraZeneca)	2009
	Nesina (Takeda)	2013
	Tradjenta (Boehringer Ingelheim)	2011
GLP-1R agonists	Adlyxin (Sanofi)	2016
	Byetta (AstraZeneca)	2005
	Bydureon (AstraZeneca)	2012
	Januvia (Merck)	2006
	Lyxumia (Sanofi)	2015
	Tanzeum (GlaxoSmithKline)	2014
	Trulicity (Eli Lilly)	2014
	Victoza (Novo Nordisk)	2010
Insulin analogues	Afrezza (MannKind)	2015
	Apidra (Sanofi)	2006
	Humalog (Eli Lilly)	1996
	Humalog 200 (Eli Lilly)	2015
	Lantus (Sanofi-Aventis)	2001
	Levemir (Novo Nordisk)	2006
	NovoLog (Novo Nordisk)	2000
	Toujeo (Sanofi-Aventis)	2015
SGLT-2 inhibitors	Farxiga (AstraZeneca)	2013
	Invokana (Mitubishi Tanabe)	2013
	Jardiance (Boehringer Ingelheim/Eli Lilly)	2014
Thiazolidinedione	Actos (Takeda)	1999

DPP-4 = dipeptidyl peptidase 4; GLP-1R = glucagon-like peptide-1 receptor; SGLT-2 = sodium-glucose cotransporter-2; T2D = type-2 diabetes.

HbA_{1c} treatment goal of less than 7.0% (28.2% and 35.8%, respectively) compared with placebo (13.1%; $P < 0.001$ for both comparisons), which was a secondary endpoint.[9]

VERTIS Factorial, another 26-week study, evaluated the coadministration of ertugliflozin and the DPP-4 inhibitor sitagliptin (Januvia, Merck). This study also met its primary endpoint, with greater reductions in HbA_{1C} in patients treated with ertugliflozin in combination with sitagliptin compared with those given ertugliflozin or sitagliptin alone. An HbA_{1c} reduction of 1.5% was observed with both combinations studied (ertugliflozin 5 mg or 15 mg with sitagliptin 100 mg) compared with reductions of 1.0% with ertugliflozin 5 mg alone, 1.1% with ertugliflozin 15 mg alone, and 1.1% with sitagliptin 100 mg alone ($P < 0.001$ for both combinations versus individual treatments).[9]

As an SGLT-2 inhibitor, ertugliflozin lowers blood glucose levels by causing the kidneys to remove glucose from the body through the urine.[10] Ertugliflozin is rapidly absorbed and is eliminated primarily via glucuronidation.[11] In May 2015, the FDA warned that treatment with the currently available SGLT-2 inhibitors, such as canagliflozin (Invokana, Janssen), dapagliflozin (Farxiga, AstraZeneca), and empagliflozin (Jardiance, Boehringer Ingelheim), may lead to ketoacidosis.[12]

If approved, ertugliflozin faces stiff competition in the SGLT-2 inhibitor market, which is already populated by well-established products such as those mentioned above. No head-to-head comparisons have been conducted between any of the SGLT-2 inhibitors; therefore, no individual product, including ertugliflozin, can claim a clinical advantage over another. There are plans, however, to use ertugliflozin in combination with other therapies, including Merck's sitagliptin. The anticipated launch date for ertugliflozin is 2017.[8]

Novo Nordisk is developing FIAsp (ultra-rapid insulin aspart), a faster-acting version of the company's NovoLog, to help protect NovoLog from generic erosion to biosimilars. FIAsp is designed to provide a better match to the physiological profile of prandial insulin and to produce a better response to the rapid increase in the need for insulin after a meal compared with NovoLog.[8]

In December 2015, Novo Nordisk submitted a new drug application for FIAsp to the FDA for the treatment of adults with T1D or T2D. The filing was based on results from the phase 3a ONSET 1 and ONSET 2 trials, which involved approximately 2,100 adults with T1D or T2D, respectively. Both studies evaluated the efficacy and safety of mealtime and after-meal FIAsp in reducing HbA_{1c} levels and in providing postprandial blood glucose control.[13] In both trials, FIAsp was compared with NovoRapid (the name for NovoLog outside the U.S.).[14]

In the T2D study (ONSET 2), FIAsp was shown to be noninferior to NovoRapid in lowering HbA_{1c}. A total of 881 patients with T2D inadequately controlled on a combination of basal insulin and oral antidiabetes drugs had their basal therapy optimized during an eight-week run-in period. The 689 patients who reached the prespecified HbA_{1c} target of 7.0% to 9.5% during the run-in phase were randomly assigned to the addition of either FIAsp or NovoRapid as mealtime insulin for 26 weeks. At the end of the study, the mean HbA_{1c} had improved from approximately 7.9% to approximately 6.6% in both the FIAsp and NovoRapid groups.[14]

If FIAsp is approved by the FDA, Novo Nordisk intends to make it available in the FlexTouch prefilled delivery device and a 10-mL vial.[13] The anticipated launch date is 2017.[8]

Intarcia Therapeutics is developing ITCA 650 (continuous subcutaneous delivery of exenatide) for the treatment of patients with T2D. The investigational therapy employs a subcutaneous osmotic mini-pump about the size of a matchstick to provide continuous exenatide drug therapy

Table 2 Promising Drugs in the T2D Pipeline[8]

Product *Developer(s)*	Therapeutic Class	Mode of Administration	Expected Pricing Strategy	Anticipated U.S. Launch Date
Ertugliflozin *Pfizer/Merck*	SGLT-2 inhibitor	Oral tablet (once daily)	Priced at 10% discount to marketed SGLT-2 inhibitors	2017
FIAsp* *Novo Nordisk*	Insulin (ultra-rapid insulin aspart)	SC injection (before meal)	Priced at a 10% premium to NovoLog	2017
ITCA 650 *Intarcia Therapeutics*	Technology platform: continuous SC delivery of exenatide	Implanted SC osmotic mini-pump	Priced at 20% premium to Victoza	2017
OG217SC (oral semaglutide) *Novo Nordisk*	GLP-1R agonist	Oral tablet (once weekly)	Priced at 15% premium to Victoza	2020
Semaglutide *Novo Nordisk*	GLP-1 agonist	SC injection (once weekly)	Priced at 10% discount to dulaglutide	2018

* Fast-acting version of NovoLog.

DPP-4 = dipeptidyl peptidase 4; GLP-1 = glucagon-like peptide-1; GLP-1R = GLP-1 receptor; SC = subcutaneous; SGLT-2 = sodium-glucose cotransporter-2; T2D = type-2 diabetes.

for up to one year. Exenatide is a GLP-1R agonist that is currently marketed globally as twice-daily and once-weekly self-injection therapies for patients with T2D.[15]

The FREEDOM clinical trial program for ITCA 650, which consisted of four global phase 3 studies, recently concluded. FREEDOM-1 was a nine-month, placebo-controlled, double-blind trial comparing ITCA 650 (40 mcg/day and 60 mg/day) plus standard of care (SoC) with placebo plus SoC in 450 adults (18 to 80 years of age) with T2D.[16] Significant HbA_{1c} reductions ranging from a mean of 1.4% to 1.7% were observed across the majority of patients, with the highest reductions in patients receiving background metformin. Patients with a starting baseline HbA_{1c} greater than 8.5% had mean reductions of up to 2.1%. Both the 40-mcg/day and 60-mcg/day mini-pumps demonstrated statistically significant results versus control.[17]

FREEDOM-1 High Baseline (HBL) was a nine-month, open-label study of 75 adults (18 to 80 years of age) from the FREEDOM-1 trial with baseline HbA_{1c} levels greater than 10%.[16] The study showed sustained reductions in HbA_{1c} levels of 3.4% from a mean starting baseline of 10.8%. When ITCA 650 was added, 25% of the patients reached an HbA_{1c} goal of less than 7% at week 39.[17]

FREEDOM-2 was a 12-month, active-comparator-controlled, double-blind, double-dummy study in 500 adults (18 to 80 years of age) with T2D who had failed on metformin therapy. ITCA 650 20 mcg/day (for 13 weeks) plus ITCA 650 60 mcg/day (for 39 weeks) was compared with sitagliptin 100 mg/day (for 52 weeks) in these patients.[16] Patients treated with ITCA 650 60 mcg experienced a nearly twofold greater reduction in HbA_{1c} (–1.5% versus –0.8%; $P < 0.001$) and a threefold greater reduction in weight (–4.0 kg [8.8 lbs] versus –1.3 kg [2.8 lbs]; $P < 0.001$) compared with patients treated with sitagliptin 100 mg. In addition, significantly more patients treated with ITCA 650 60 mcg achieved the recommended HbA_{1c} target of less than 7.0% compared with sitagliptin (61% versus 42%, respectively; $P < 0.001$).[18]

FREEDOM-CVO was a placebo-controlled cardiovascular outcomes study examining the safety of ITCA 650 (60 mcg/day) in approximately 4,000 adults (40 years of age or older) with T2D receiving treatment with a variety of approved antidiabetes therapies.[16] The study met its primary and secondary endpoints by demonstrating FDA-required noninferiority for preapproval cardiovascular safety.[19]

Regulatory filing of ITC 650 is targeted for the third quarter of 2016. If approved, ITCA 650 would be the first once- or twice-yearly, injection-free GLP-1 therapy[15]—a significant advantage in a market crowded with "me too" drugs.[8] The product's anticipated launch date is 2017.[8]

OG217SC (Novo Nordisk) is a once-daily oral formulation of the once-weekly injectable GLP-1R agonist semaglutide (see below). It is being developed as a tablet formulation, with an absorption-enhancing excipient called sodium N-(8-[2-hydroxybenzoyl] amino) caprylate. Currently, there are no marketed oral GLP-1R agonists, so if OG217SC is eventually approved, it has the potential to become a blockbuster drug.[8]

In August 2015, Novo Nordisk announced the decision to initiate a phase 3a clinical trial program with OG217SC. The decision followed encouraging results from a proof-of-concept phase 2 study. The PIONEER program consists of seven trials involving approximately 8,000 patients with T2D. Six of the studies will evaluate the safety and efficacy of OG217SC, and one study will look specifically at the drug's cardiovascular safety profile. All of the studies are expected to get under way before the end of 2016.[20]

The first trial in the program, initiated in February 2016, is investigating the efficacy and long-term safety of once-daily OG217SC doses of 3 mg, 7 mg, and 14 mg, compared with that of 100 mg once-daily oral sitagliptin in an estimated 1,860 patients. The study's expected completion date is March 2018.[21]

If OG217SC gains FDA approval, its anticipated launch date is 2020. As mentioned, the drug is expected to achieve blockbuster status because all other GLP-1R agonists on the market are injectable products. OG217SC may face some competition, however, from ITCA 650, with its continuous subcutaneous delivery of exenatide.[8]

Semaglutide (Novo Nordisk) is also being developed as a once-weekly

subcutaneous injection for patients with T2D. Several injectable drugs in this class are already on the market, including AstraZeneca's exenatide (Byetta) and extended-release exenatide (Bydureon), and Novo Nordisk's liraglutide (Victoza).[8]

In June 2016, Novo Nordisk reported the results from two phase 3a studies of semaglutide in adults with T2D. In the SUSTAIN 2 trial, semaglutide (0.5 mg and 1.0 mg) administered once weekly significantly improved glycemic control compared with sitagliptin (100 mg). In the SUSTAIN 3 trial, semaglutide (1.0 mg) administered once weekly significantly improved glycemic control compared with extended-release exenatide (2.0 mg).[22]

If approved, semaglutide would be the fourth-to-market once-weekly GLP-1R agonist; it is not expected to capture a big piece of the T2D market. Its anticipated launch date is 2018.[8]

The current T2D market is crowded with generic, branded, biosimilar, and "me too" drugs. All of these agents, however, tend to lose efficacy after three or four years of treatment. The novel products expected to reach the market over the next 10 years (Table 2) have an opportunity to revolutionize T2D therapy if they can demonstrate the ability to provide more-durable glycemic control compared with traditional treatments.[8]

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