New Drugs in the Development for the Treatment of Diabetes
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This is an comprehensive and extensive description of new drugs on the horizon for diabetes. Written by pharmacists, it includes excellent tables and descriptions of the unique actions of each of these anti-hyperglycemic agents.

In Brief

A variety of new agents are in development for the treatment of type 1 or type 2 diabetes. In addition to new dipeptidyl peptidase-4 inhibitors, glucagon-like peptide 1 analogs, thiazolidinediones, glinides, and new insulin formulations, there are also unique peroxisome proliferator–activated receptor agonists, selective sodium glucose cotransporter 2 inhibitors, and several other unique agents now in development.

New Drugs in Development for the Treatment of Diabetes

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The number of agents available to improve glycemic control in patients with diabetes has increased substantially in recent years. Only 15 years ago, available therapies included only sulfonylureas and insulin. Today, products from multiple additional classes, offering multiple new mechanisms and enhanced opportunities for combination therapy, have substantially increased the ability to individually tailor therapy for any given patient. And development of new products for the treatment of diabetes continues.

Many new drugs are currently in development for the treatment of diabetes, including more products with new mechanisms. This article will provide a brief overview of some of these drugs. Table 1 lists drugs in development for type 1 or type 2 diabetes by class. Table 2 lists additional drugs with unique mechanisms of action.[1–3] Drugs with applications submitted for U.S. Food and Drug Administration (FDA) approval and drugs currently in phase 3 clinical trials are summarized below.

DIPEPTIDYL PEPTIDASE 4 (DPP-4) INHIBITORS

The DPP-4 inhibitors are incretin enhancers. DPP-4 inhibitors are thought to work by slowing the inactivation of the incretin hormones glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide. These agents are released by the gastrointestinal tract in response to food and are involved with the stimulation of glucose-dependent insulin secretion. By inhibiting their inactiva-

tion, these drugs prolong the effects of these incretin hormones.

The DPP-4 inhibitors have been assessed as monotherapy and in conjunction with insulin, metformin, sulfonylureas, and thiazolidinediones in patients with type 2 diabetes. Although the DPP-4 inhibitors have been shown to improve glycemic control, as with most other new agents used in the treatment of diabetes, data have not been published addressing the effects of the DPP-4 inhibitors on key outcome measures such as mortality, diabetes complications, or health-related quality of life.[4]

Most of the DPP-4 inhibitors are structurally distinct. Alogliptin is a quinazolinone-based compound, linagliptin is a xanthine derivative, saxagliptin is a hydroxyadamantyl compound, sitagliptin is a triazole-pyrazine compound, and vildagliptin and saxagliptin are pyrrolidine-carbonitrile compounds. The first marketed DPP-4 inhibitor was sitagliptin, which was approved by the FDA in 2006. Applications for approval have also been submitted for alogliptin, saxagliptin, and vildagliptin. Dutogliptin and linagliptin are in phase 3 studies, and numerous additional DPP-4 inhibitors are in phase 2 studies (Table 1). Vildagliptin received an approvable letter from the FDA in 2007 for the treatment of diabetes; however, the FDA approvable letter requested additional data on the safety and efficacy of vildagliptin in renally impaired patients. Vildagliptin is currently available in 18 countries and

Table 1. Drugs in Development[1-3]			
Generic/Code Name	Manufacturer	Indication	Phase
DPP-4 Inhibitors			
Alogliptin/SYR-322	Takeda	Type 2 diabetes	NDA submitted
AMG 222/ALS2-0426	Amgen/Servier	Type 2 diabetes	2
Dutogliptin/PHX1149	Phenomix/Forest Laboratories	Type 2 diabetes	3
KRP-204/N-5984	Kyorin	Type 2 diabetes	2
KRP-104	Kyorin/ActivX Biosciences	Type 2 diabetes	2
Linagliptin/BI-1356	Boehringer Ingelheim	Type 2 diabetes	3
Melogliptin/GRC 8200	Glenmark Pharmaceuticals	Type 2 diabetes	2
MP-513	Mitsubishi Tanabe Pharma	Type 2 diabetes	2
PF 734200	Pfizer	Type 2 diabetes	2
R1579	Roche/Chugai	Type 2 diabetes	2
Saxagliptin/BMS-477118	Bristol-Myers Squibb/AstraZeneca	Type 2 diabetes	NDA submitted
SYR 472	Takeda	Type 2 diabetes	2
TA-6666	Mitsubishi Tanabe	Type 2 diabetes	2
Vildagliptin	Novartis	Type 2 diabetes	NDA submitted
GLP-1 Analogs			
Albiglutide/GSK716155	GSK	Type 2 diabetes	2
AVE0010/ZP-10	Sanofi-Aventis	Type 2 diabetes	3
CJC-1134-PC/PC-DAC: Exendin-4	ConjuChem	Type 2 diabetes	2
Exenatide LAR	Amylin/Alkermes/Lilly	Type 2 diabetes	3
Liraglutide/NN2211	Novo Nordisk	Type 2 diabetes	NDA submitted
LY 2189265	Lilly	Type 2 diabetes	3
NN9535	Novo Nordisk	Type 2 diabetes	2
Taspoglutide/R1583/BIM-51077	Roche/Ipsen	Type 2 diabetes	3
Biguanides			
Metformin gum/buccal	Generex/Fertin Pharma	Type 2 diabetes	2
Thiazolidinediones/PPAR-γ Agonists			
Balaglitazone/DRF-2593	Dr. Reddy's Laboratories/Rheoscience	Type 2 diabetes	3
Mitoglitazone/MDSC 0160	Metabolic Solutions Development	Type 2 diabetes	2
Netoglitazone/MCC-555	Mitsubishi Tanabe/Perlegen	Type 2 diabetes	2
Rivoglitazone/CS-011	Daiichi-Sankyo	Type 2 diabetes	3
Other PPAR Agonists			
Aleglitazar/R1439	Roche	Type 2 diabetes	2
Indeglitazar	Pexxikon/Wyeth	Type 2 diabetes	2
INT 131/AMG131	Amgen/InteKrin Therapeutics	Type 2 diabetes	2
MBX 2044	Metabolex/Ortho-McNeil	Type 2 diabetes	2
Metaglidasen/MBX 102/JNJ-39659100	Metabolex/Ortho-McNeil	Type 2 diabetes	2
ONO-5129	Ono	Type 2 diabetes	2
PLX204/PPM-204	Plexxikon/Wyeth	Type 2 diabetes	2

Table 1. Drugs in Development [1–3] *continued from p. 93*

Generic/Code Name	Manufacturer	Indication	Phase
Selective Sodium Glucose Cotransporter Inhibitors			
ASP1941	Astellas	Type 2 diabetes	2
AVE2268	Sanofi-Aventis	Type 2 diabetes	2
BI 10773	Boehringer Ingelheim	Type 2 diabetes	2
Dapagliflozin/BMS512148	AstraZeneca/Bristol-Myers Squibb	Type 2 diabetes	3
KGT-1681	GSK/Kissei	Type 2 diabetes	2
Remogliflozin/189075	GSK/Kissei	Type 2 diabetes	2
TA-7284	Mitsubishi Tanabe/Ortho McNeil	Type 2 diabetes	2
YM543	Astellas	Type 2 diabetes	2
Glinides			
Mitiglinide	Elixir Pharmaceuticals	Type 2 diabetes	3
Insulins			
Inhaled Technosphere insulin	Mannkind	Type 1 and type 2 diabetes	3
Insulin intranasal	Bentley	Type 1 and type 2 diabetes	2
Insulin intranasal	MDRNA	Type 2 diabetes	2
Oral HDV insulin	Diasome	Type 2 diabetes	2
Oral insulin spray	Generex	Type 1 and type 2 diabetes	3
NN1250 insulin analog for injection	Novo Nordisk	Type 1 and type 2 diabetes	2
NN5401 insulin analog for injection	Novo Nordisk	Type 1 and type 2 diabetes	2
Rapid-acting insulin for injection	Biodel	Type 1 and type 2 diabetes	3
Recombinant human hyaluroindase (rHuPH20)/insulin co-formulation for injection	Halozyme Therapeutics	Type 1 diabetes	2

NDA, new drug application.

Table 2. Other Drugs in Development for Diabetes [1–3]

Generic/Code Name	Manufacturer	Mechanism	Indication	Phase
AJD101	Daiichi Sankyo	Activates insulin signaling pathway	Type 2 diabetes	2
AKP-020	Akesis	Vanadium compound	Type 2 diabetes	2
AMG-108	Amgen	Interleukin-1 inhibitor	Type 2 diabetes	2
AZD6370	AstraZeneca	Glucokinase activator	Type 2 diabetes	2
Bromocriptine	VeroScience	Dopamine D2 receptor agonist	Type 2 diabetes	3
Canakinumab/ACZ885	Novartis	Anti-interleukin-1 beta antibody	Type 2 diabetes	2
Colestimide	Mitsubishi-Tanabe	Unknown	Type 2 diabetes	2
Bezafibrate + diflunisal/CRx-401	CombinatoRx	Unknown	Type 2 diabetes	2

Table 2. Other Drugs in Development for Diabetes[1–3] *continued from p. 94*				
Generic/Code Name	Manufacturer	Mechanism	Indication	Phase
DIO-902/2S,4R ketoconazole	DiObex	Cortisol synthesis inhibitor	Type 2 diabetes	2
DM-71/bethanechol and N-acetyl cysteine	Diamedica	Unknown	Type 2 diabetes	2
DM-83/combination of two generic compounds	Diamedica	Unknown	Type 2 diabetes	2
E1 INT	Transition Therapeutics	Islet regeneration factor	Type 1 and type 2 diabetes	2
Eprodisate/NC-503	Bellus Health	Serum amyloid A protein inhibitor	?	2
Ex vivo cultured adult human mesenchymal stem cells	Osiris	Mesenchymal stem cell therapy	Type 1 diabetes	2
HE3286	Hollis-Eden	Insulin sensitizer (NF-kappaB pathway/TLR4 receptor)	Type 2 diabetes	2
INCB 13739	Incyte	11-beta hydroxysteroid dehydrogenase inhibitor	Type 2 diabetes	2
INCB 19602	Incyte	GPR109A receptor agonist / HM74a agonist	Type 2 diabetes	2
INGAP peptide	Kinexum	Islet neogenesis associated protein	Type 1 and type 2 diabetes	2
ISIS 113715	Isis	PTP1B	Type 2 diabetes	2
MB 07803	Metabasis/Daiichi Sankyo	Fructose-1,6-bisphosphatase inhibitor	Type 2 diabetes	2
MK 0893	Merck	Unknown	Type 2 diabetes	2
MK 0941	Merck	Unknown	Type 2 diabetes	2
Otelixizumab/TRX4	GSK, Tolerx	Anti-CD3 MAb	Type 1 diabetes	3
rhGAD65/recombinant human glutamic acid decarboxylase	Diamyd Therapeutics	Vaccine/induces immunmotolerization	Type 1 diabetes	3
Succinobucol/AGI 1067	AtheroGenics	Antioxidant/vascular cell adhesion molecule-1	Type 2 diabetes	3
Tagatose	Spherix	Attenuates intestinal glucose absorption	Type 2 diabetes	3
Teplizumab/MGA031/ hOKT3gamma1(Ala-Ala)	Lilly/MacroGenics	Anti-CD3 MAb	Type 1 diabetes	3
TT-223	Lilly/Transition Therapeutics	Gastrin analog	Type 1 and type 2 diabetes	2

approved in 51 countries; however, Novartis, its manufacturer, does not plan to resubmit it for FDA approval at this time.[5]

Sitagliptin and the other DPP-4 inhibitors in development are orally administered. Most have long half-lives enabling once-daily administration.[6,7]

Alogliptin
Alogliptin is a highly selective inhibitor of DPP-4, demonstrating > 10,000 times more selectivity for DPP-4 than for other related proteases. After oral administration of alogliptin in a range of doses from 25 to 800 mg, mean DPP-4 inhibition ranged from 93 to 99%, with mean inhibition at 24 hours after dosing ranging from 74 to 97%.[7,8]

Very little information has been published on the clinical efficacy and safety of alogliptin, although several large studies have been presented as abstracts at scientific meetings. Alogliptin is capable of decreasing the average A1C level in patients with type 2 diabetes when used alone or in combination with insulin, metformin, a sulfonylurea, or a thiazolidinedione.[9–13] The information on common adverse reactions reported in the clinical trials with alogliptin is very limited but has included reports of hypoglycemia with an incidence similar to that of placebo.[9–13] Adverse reactions reported have also included nasopharyngitis, headache, and upper respiratory tract infection.[9] Alogliptin appears to have a neutral effect on weight and lipids.[9–13]

With the addition of alogliptin to glyburide therapy in a randomized, double-blind, placebo-controlled study enrolling 500 patients with type 2 diabetes that was adequately controlled on glyburide alone, A1C was reduced to a greater extent with alogliptin 12.5 mg (−0.38%) and alogliptin 25 mg (−0.52%) than with placebo (+0.01%; $P < 0.001$). A reduction of ≥ 1% in A1C was achieved in 28.6% of patients treated with alogliptin 12.5 mg and 30% of those treated with alogliptin 25 mg, compared to 8.7% of those treated with placebo ($P < 0.001$).[10] With the addition of alogliptin to insulin therapy in a randomized, double-blind, placebo-controlled study enrolling 390 patients with type 2 diabetes not adequately controlled on insulin alone or insulin plus metformin, A1C was reduced to a greater extent with alogliptin 12.5 mg (−0.63%) and alogliptin 25 mg (−0.71%) than with placebo (−0.13%; $P < 0.001$).[11] Similar improvements in A1C were also observed with the addition of alogliptin to pioglitazone in patients with type 2 diabetes inadequately controlled on a thiazolidinedione alone or on a thiazolidinedione with metformin or a sulfonylurea, and with the addition of alogliptin to metformin therapy.[12,13]

Dutogliptin

Dutogliptin is also an oral DPP-4 inhibitor under evaluation for once-daily dosing in patients with type 2 diabetes. To date, it has demonstrated activity in a short-term study when administered once daily in conjunction with metformin or metformin plus a thiazolidinedione; participants are now being recruited for a phase 3 study.[14,15]

Linagliptin

Linagliptin is another oral DPP-4 inhibitor under evaluation for once daily dosing in patients with type 2 diabetes. To date, it has demonstrated activity in a short-term study when administered once daily in patients with type 2 diabetes; recruitment is ongoing for a number of phase 3 studies assessing linagliptin as monotherapy and in combination with pioglitazone, metformin, or metformin plus a sulfonylurea.[16–23]

Saxagliptin

Very little information has been published on the clinical efficacy and safety of saxagliptin. Saxagliptin is capable of decreasing the average A1C level in patients with type 2 diabetes when used alone or in combination with metformin, a sulfonylurea, or a thiazolidinedione.[24–27] Treatment with saxagliptin alone has been weight neutral.[27] Common adverse reactions reported in the clinical trials with saxagliptin include nasopharyngitis, headache, diarrhea, upper respiratory infections, influenza, and urinary tract infection.[25,27]

When administered as initial therapy in patients with type 2 diabetes in a randomized, double-blind 24-week study enrolling 1,306 patients, A1C was reduced 1.69% with saxagliptin alone, 1.99% with metformin alone, and 2.49–2.53% with saxagliptin plus metformin ($P < 0.0001$ for combination vs. either monotherapy). A1C < 7% was achieved in 60% of patients treated with the combination compared to 32% of those treated with saxagliptin alone and 41% of those treated with metformin alone.[24] A1C reductions of 0.7–0.9% were observed in another study assessing saxagliptin monotherapy in drug-naïve patients with type 2 diabetes.[27] When added to a sulfonylurea in a double-blind study enrolling 768 patients with type 2 diabetes, A1C reductions were in the range of 0.54–0.64%.[25] When added to a thiazolidinedione in a double-blind study enrolling 565 patients with type 2 diabetes, A1C reductions were in the range of 0.66–0.94%, compared to 0.3% reductions with the addition of a placebo.[26]

Additional ongoing studies are assessing saxagliptin as initial monotherapy in patients with type 2 diabetes, as an addition to metformin, insulin, or insulin plus metformin, in comparison with sitagliptin when added to metformin, and in patients with renal impairment.[28–33]

Vildagliptin

Vildagliptin alone or in combination with metformin, a thiazolidinedione, or insulin is capable of decreasing fasting plasma glucose levels and improving A1C levels in patients with type 2 diabetes.

The efficacy of vildagliptin in drug-naïve patients with type 2 diabetes and "mild" hyperglycemia was evaluated in a multicenter, double-blind, randomized, placebo-controlled, parallel-group study that enrolled 306 patients. The baseline A1C for this population ranged from 6.2 to 7.5% and averaged 6.7% in the vildagliptin group and 6.8% in the placebo group. Patients were randomized to treatment with vildagliptin 50 mg or placebo once daily for 52 weeks. The change in the A1C level was −0.2% in the vildagliptin group and 0.1% in the placebo group; the between-group difference was 0.3% ($P < 0.001$). Fasting plasma glucose levels and postprandial plasma glucose levels all improved with vildagliptin compared to placebo. The patients' mean body weight decreased by 0.5 kg with vildagliptin therapy and increased by 0.2 kg with placebo. Both drug therapies were well tolerated. With continued administration for an additional year in 131 patients, the placebo-adjusted change from baseline in A1C was −0.5% ($P = 0.008$).[34,35] Additional monotherapy studies in drug-naïve patients with type 2 diabetes and baseline A1C levels of 8.3–8.7% demonstrated mean placebo-adjusted A1C reductions of 0.7–1.2% after therapy for 24 weeks at doses of 50 mg twice daily or 100 mg once daily.[36,37]

Several additional studies have assessed vildagliptin as monotherapy in comparison with other oral antidiabetic agents, including acarbose, metformin, pioglitazone, and rosiglitazone. The efficacy of vildagliptin was compared to acarbose in drug-naïve patients with type 2 diabetes in a multicenter, randomized, double-blind, parallel-arm study. Patients were given either vildagliptin 50 mg twice daily ($n = 441$) or acarbose ($n = 220$) in three equally divided doses (up to 300 mg daily) for 24 weeks. The average baseline A1C level in both groups was 8.6%. At the end of 24 weeks, the adjusted mean change from baseline was −1.4% in the vildagliptin group and −1.3% in the acarbose group. The decrease in plasma glucose was −1.2 mmol/l with vildagliptin and −1.5 mmol/l with acarbose. The body weight of the vildagliptin group remained unchanged (−0.4 ± 0.1 kg) and decreased by 1.7 ± 0.2 kg in the acarbose group.[38]

Vildaglptin has been compared to metformin as monotherapy in a 1-year study enrolling 780 drug-naïve patients with type 2 diabetes. Patients received vildagliptin 50 mg twice daily or metformin titrated to 1,000 mg twice daily. From a mean baseline A1C of 8.7%, A1C at 1 year declined by 1% with vildagliptin therapy and

1.4% with metformin therapy (both $P < 0.001$ vs. baseline). Body weight was unchanged with vildagliptin (0.3 kg; $P = 0.17$), but was reduced 1.9 kg ($P < 0.001$) in the metformin group.[39]

Vildagliptin was compared to pioglitazone and the combination of the two agents in another 24-week double-blind study enrolling 607 drug-naïve patients with type 2 diabetes. From baseline (A1C ~ 8.7%), A1C was reduced 1.4% in the group receiving pioglitazone 30 mg once daily as monotherapy, 1.7% in the group received vildagliptin 50 mg plus pioglitazone 15 mg once daily, 1.9% in the group received vildagliptin 100 mg plus pioglitazone 30 mg once daily, and 1.1% in the group received vildagliptin 100 mg once daily as monotherapy.[40]

Vildagliptin was compared to rosiglitazone as monotherapy in another 24-week, double-blind study enrolling 786 drug-naïve patients with type 2 diabetes. Patients received vildagliptin 50 mg twice daily or rosiglitazone 8 mg once daily. A1C was reduced 1.1% in the vildagliptin group and 1.3% in the rosiglitazone group (both $P < 0.001$ vs. baseline). Body weight was unchanged (0.3 kg) in the vildagliptin group and increased 1.6 kg in the rosiglitazone group ($P < 0.001$ vs. vildagliptin).[41]

Vildagliptin has also been assessed when added to metformin in patients with type 2 diabetes with inadequate glycemic control. Addition of vildagliptin 50 mg daily and 100 mg daily for 24 weeks in a randomized, double-blind, placebo-controlled study enrolling 544 patients resulted in a placebo-adjusted reduction in A1C of 0.7% at the 50-mg dose ($P < 0.001$) and 1.1% in the 100-mg dose ($P < 0.001$).[42] Addition of vildagliptin 50 mg once daily for 52 weeks in a randomized, placebo-controlled, double-blind study enrolling 107 patients resulted in a placebo-adjusted reduction in A1C of 0.7% at 12 weeks ($P < 0.0001$) and 1.1% at 52 weeks ($P < 0.0001$).[43] Another 24-week double-blind study compared vildagliptin and pioglitazone when added to metformin in 576 patients with type 2 diabetes. A1C was reduced from a mean baseline value of 8.4% by 0.9% in the vildagliptin group and 1% in the pioglitazone group.[44]

Patients whose diabetes was inadequately controlled with a sulfonylurea were treated with either vildagliptin or placebo in another multicenter, randomized, double-blind, placebo-controlled study. All 515 type 2 diabetic patients enrolled in this trial received glimepiride 4 mg once daily plus their assigned study medication for 24 weeks. The vildagliptin was given either as 50 mg once daily or 50 mg twice daily. Both vildagliptin doses were better than placebo in improving the patients' A1C levels. The between-group difference (vildagliptin vs. placebo) for the A1C was −0.6% with vildagliptin 50 mg once daily and −0.7% with vildagliptin 50 mg twice daily ($P < 0.001$ vs. placebo).[45]

Similar improvements in A1C of ~ 0.5–1% were observed with the addition of vildagliptin to therapy with pioglitazone and the addition of vildagliptin to insulin.[46,47]

Adverse reactions reported in the clinical trials have generally been similar to those reported with placebo and have included cough, nasopharyngitis, headache, hypoglycemia, dizziness, dyspepsia, nausea, constipation, and diarrhea. Vildagliptin had no impact on patient weight in the majority of studies.

A study of the safety of vildagliptin in patients with type 2 diabetes and severe renal insufficiency, as required by the FDA, is currently underway.[48]

GlUCAGON-LIKE PEPTIDE 1 (GLP-1) ANALOGS

The GLP-1 analogs induce their activity through a glucose-dependent stimulation of insulin secretion, inhibition of glucagon secretion, slowing of gastric emptying, and reduction in appetite. The first marketed GLP-1 analog was exenatide, which was approved by the FDA in 2005. Exenatide is currently used as adjunctive therapy in type 2 diabetes in patients currently using metformin, a sulfonylurea, a combination of metformin and sulfonylurea, or a combination of metformin and a thiazolidinedione; an application for use of exenatide as monotherapy in type 2 diabetes is under FDA review.

An application for approval has been submitted for liraglutide. Several other GLP-1 analogs are in phase 3 studies, including AVE0010/ZP-10, LY2189265, taspoglutide, and the once-weekly exenatide formulation called exenatide LAR.

Exenatide is administered subcutaneously twice daily. Most of the other products in development are administered subcutaneously once daily (liraglutide, AVE0010/ZP-10) or once weekly (exenatide LAR, LY2189265, albiglutide, NN9535, taspoglutide).[49,50]

AVE0010/ZP-10

Limited clinical data are available for AVE0010. Study results from a dose-ranging study including 542 patients with type 2 diabetes treated with metformin have been presented in abstract form at a scientific meeting. A1C was reduced 0.28% to 0.69% compared to placebo in a range of doses from 5 mμ once daily to 30 mμ twice daily administered subcutaneously. Efficacy was similar with once-daily and twice-daily regimens. Greater weight loss with AVE0010 than with placebo was observed at doses of 20 and 30 mμ once daily and 30 mμ twice daily. Nausea and vomiting were the most common adverse effects.[50] Recruitment is ongoing for a number of phase 3 studies evaluating AVE0010 as monotherapy and in addition to basal insulin, metformin, a sulfonylurea, or pioglitazone in patients with type 2 diabetes, as well as a study comparing AVE0010 and exenatide in association with metformin in patients with type 2 diabetes.[51–57]

Exenatide LAR

The slow-release or long-acting release (LAR) formulation of exenatide is in phase 3 development. It is intended for once-weekly subcutaneous administration for the treatment of type 2 diabetes.

In a randomized, placebo-controlled study enrolling 45 patients with type 2 diabetes suboptimally controlled on metformin or diet and exercise, exenatide LAR administered subcutaneously once weekly for 15 weeks reduced A1C 1.4% (0.8 mg dose) and 1.7% (2 mg dose; both $P < 0.0001$). An A1C of ≤ 7% was achieved in 86% of subjects receiving the 2-mg dose. Patients in this dose group also experienced a 3.8-kg weight loss in this 15-week study ($P < 0.05$).[58]

In a non-inferiority study comparing exenatide LAR 2 mg once weekly with exenatide 10 mμ twice daily in 295 patients with type 2 diabetes, patients treated with exenatide LAR had a greater reduction in A1C at 30 weeks than those treated with exenatide twice daily (−1.9% vs. −1.5%; 95% CI −0.54 to −0.12%;

$P = 0.0023$). A1C of ≤ 7% was achieved in 77% of patients treated with exenatide LAR compared to 61% of those treated with exenatide twice daily ($P = 0.0039$). Weight loss was similar in the two groups. Nausea and injection site pruritus were the most common adverse effects.[59] After 30 weeks, 258 patients entered an open-label treatment with exenatide LAR. Improvements in A1C were sustained in patients continuing therapy with exenatide once weekly for 52 weeks (–2% from baseline) and were similar in those switched to once-weekly therapy (–2% from baseline). Patients in both groups lost ~ 4 kg of weight by week 52, and blood pressure and lipid profiles were improved in both groups.[60]

Liraglutide
Liraglutide is under evaluation for use in the treatment of patients with type 2 diabetes as an adjunct to diet and exercise, either as monotherapy or in combination with commonly used diabetes medications, including sulfonylureas and metformin. In clinical trials, liraglutide has been associated with a reduction in A1C and fasting plasma glucose with either weight loss or no change in body weight. Significant reductions in A1C have been observed at doses of 0.1–2 mg administered subcutaneously once daily.

A randomized, double-dummy study has compared the addition of liraglutide to glimepiride therapy with glimepiride monotherapy or the addition of rosiglitazone to glimepiride in 1,041 patients with type 2 diabetes and baseline A1C of 8.4%. Patients received liraglutide 0.6, 1.2, or 1.8 mg/day in combination with glimepiride, placebo plus glimepiride 2–4 mg per day, or rosiglitazone 4 mg daily plus glimepiride for 26 weeks. A1C was reduced 1.08% with liraglutide 1.2 mg and by 1.13% with liraglutide 1.8 mg, compared with a reduction of 0.44% with the addition of rosiglitazone and an increase of 0.23% with glimepiride monotherapy ($P < 0.0001$). A1C < 6.5% was achieved in 22% treated with liraglutide 1.2 mg plus glimepiride and 21% of those treated with liraglutide 1.8 mg plus glimepiride, compared to 4% of those treated with glimepiride monotherapy, and 10% of those treated with rosiglitazone plus glimepiride ($P ≤ 0.0003$).[61] A 52-week study also compared liraglutide and glimepiride

as monotherapy in 746 patients with type 2 diabetes. At 52 weeks, A1C was reduced 0.51% with glimepiride 8 mg daily, 0.84% with liraglutide 1.2 mg once daily ($P = 0.0014$), and 1.14% with liraglutide 1.8 mg once daily ($P < 0.0001$).[62]

Liraglutide has also been evaluated in combination with metformin therapy in a randomized, double-blind study enrolling 1,091 patients with type 2 diabetes and baseline A1C of 8.4%. Patients received liraglutide 0.6, 1.2, or 1.8 mg once daily added to metformin 1 g twice daily, placebo plus metformin, or glimepiride 4 mg once daily added to metformin for 26 weeks. A1C was reduced 0.7% with liraglutide 0.6 mg and 1% with liraglutide 1.2 mg and 1.8 mg plus metformin, compared to an increase of 0.1% with metformin monotherapy and a reduction of 1% with glimepiride plus metformin ($P < 0.05$ vs. liraglutide plus metformin vs. placebo plus metformin). A1C < 6.5% was achieved in 11.3% of patients treated with liraglutide 0.6 mg plus metformin, 19.8% of those treated with liraglutide 1.2 mg plus metformin, 24.6% of those treated with liraglutide 1.8 mg plus metformin, compared to 4.2% of those treated with placebo plus metformin and 22.2% of those treated with glimepiride plus metformin. Weight loss was greater in all three liraglutide plus metformin groups than in the glimepiride plus metformin group.[63]

In another 26-week study enrolling 533 patients, liraglutide was added to metformin and rosiglitazone. A1C was reduced 1.48% in the groups treated with liraglutide 1.2 mg once daily and liraglutide 1.8 mg once daily in conjunction with metformin and rosiglitazone, compared to reductions of 0.54% in patients receiving placebo with metformin and rosiglitazone ($P < 0.05$ for both liraglutide doses vs. placebo). A1C < 7% was achieved in 58% of patients treated with liraglutide 1.2 mg and 54% of those treated with liraglutide 1.8 mg, compared to 28% of those treated with placebo ($P < 0.05$ for both liraglutide doses vs. placebo). Weight loss was also greater in the liraglutide groups (–1.02 and –2.02 kg vs. +0.6 kg).[64]

Liraglutide has also been compared to insulin glargine as add-on to therapy with metformin and glimepiride in a study enrolling 581 patients with type 2 diabetes and a baseline A1C

of 8.2%. Patients received liraglutide 1.8 mg once daily, placebo, or insulin glargine in addition to metformin 1 g twice daily and glimepiride 2–4 mg once daily for 26 weeks. A1C was reduced 1.33% with the addition of liraglutide, 0.24% with the addition of placebo, and 1.09% with the addition of insulin glargine ($P < 0.05$ for liraglutide vs. placebo and insulin glargine). A1C < 6.5% was achieved in 37.1% of those treated with liraglutide compared to 10.9% of those in the placebo group and 23.6% of those in the insulin glargine group. A weight loss of 1.81 kg was observed in the liraglutide group compared to a loss of 0.42 kg in the placebo group and a weight gain of 1.62 kg in the insulin glargine group.[65]

Adverse effects associated with liraglutide therapy have included headache, dizziness, nausea, and vomiting.

LY2189265
Results of studies with LY2189265 have not been published. Recruitment is currently ongoing for a phase 2/3 study comparing LY2189265 with sitagliptin in patients with type 2 diabetes on metformin.[66]

Taspoglutide
Taspoglutide administered subcutaneously once weekly has been associated with reductions in fasting blood glucose, improvement in A1C, and weight loss when added to metformin therapy in patients with type 2 diabetes in short-term studies.[67,68] Recruitment is ongoing for studies assessing taspoglutide as initial monotherapy and in conjunction with metformin, metformin plus pioglitazone, metformin plus a sulfonylurea, or metformin plus a thiazolidinedione. In several of these studies, taspoglutide is being compared head-to-head with exenatide, insulin glargine, and sitagliptin.[69–73]

PEROXISOME PROLIFERATOR–ACTIVATED RECEPTOR (PPAR) AGONISTS
The PPAR-γ agonists act as insulin sensitizers, reducing fasting glucose and A1C. The thiazolidinediones were the first class of PPAR-γ agonists to be approved for use in diabetes. Balaglitazone and rivoglitazone are thiazolidinediones in phase 3 studies in patients with type 2 diabetes. Balaglitazone is a partial agonist; rivoglitazone is a full agonist. The

partial PPAR-γ agonists, also known as selective PPAR modulators, have been developed in an attempt to minimize the side effects of the full agonists while maintaining the therapeutic effect.[74–76] Insufficient data are available at this time to determine if the selective PPAR modulators will have fewer adverse effects. In light of the recent experience with rosiglitazone, long-term studies will likely be required for approval of any new drugs in this class.

Other PPAR agonists in early-phase development include the dual agonists or glitazars, which stimulate both PPAR-α and -γ receptors, resulting in effects on insulin resistance and dyslipidemia, and pan agonists, which act at the α, γ, and δ PPAR receptors and may have activity in diabetes, dyslipidemia, and obesity.[74]

Balaglitazone
Balaglitazone is a selective partial PPAR-γ agonist. It has been suggested that partial PPAR-γ agonists may have a favorable adverse effect profile relative to the full PPAR-γ agonists pioglitazone and rosiglitazone. However, results of clinical studies directly comparing these agents are not yet available.[75] A phase 3 study assessing the efficacy and safety of balaglitazone compared to pioglitazone in patients with type 2 diabetes receiving stable insulin therapy is currently enrolling patients.[77]

Rivoglitazone
Rivoglitazone is a potent PPAR-γ agonist currently under evaluation in a phase 3 study comparing it to placebo and pioglitazone in patients with type 2 diabetes not adequately controlled with diet and exercise or with nonthiazolidinedione antihyperglycemic monotherapy.[78] In an earlier open-label comparative 6-week study, rivoglitazone 2-mg and 5-mg doses once daily were associated with greater reductions in fasting plasma glucose than pioglitazone 30 mg; however, these rivoglitazone doses were also associated with a greater incidence of peripheral edema and weight gain.[79] In a double-blind 26-week study comparing rivoglitazone and pioglitazone in patients with type 2 diabetes, rivoglitazone doses of 2 mg and 3 mg were associated with greater reductions in A1C than pioglitazone 45 mg; however, rivoglitazone was again associated with higher incidence

of peripheral edema and weight gain.[80] The ongoing study is comparing rivoglitazone 1-mg and 1.5-mg doses with pioglitazone 45 mg.[78]

SELECTIVE SODIUM GLUCOSE COTRANSPORTER 2 INHIBITORS
The selective sodium glucose cotransporter 2 inhibitors are a new class of agents. The sodium glucose cotransporter type 2 (SGLT2) located in the plasma membrane of cells lining the proximal tubule mediates the majority of renal glucose reabsorption from the tubular fluid. Blood glucose is continuously filtered by the renal glomeruli and then reabsorbed in the renal proximal tubules by SGLT2, and to a lesser extent SGLT1, preventing the loss of glucose in the urine. Competitive inhibitors of SGLT2 provoke renal excretion of glucose, potentially lowering elevated blood glucose levels in patients with diabetes.[80] These agents are expected to improve plasma glucose levels and decrease body weight in patients with type 2 diabetes without causing hypoglycemia.[81] Dapagliflozin is the only agent in this class in phase 3 studies.

Dapagliflozin
Dapagliflozin is in the early portion of phase 3 development for use as a monotherapy agent or in combination with other oral hypoglycemic agents. The drug has been well tolerated in early clinical studies with the most common adverse reactions being urinary tract infection, dizziness, headache, fatigue, back pain, and nasopharyngitis.[82]

In a randomized, double-blind, placebo-controlled, dose-ranging 12-week study enrolling 389 treatment-naïve patients with type 2 diabetes, dapagliflozin doses from 2.5 to 50 mg once daily were associated with greater reductions in A1C than placebo (–0.55% to –0.9% vs. –0.18%; $P < 0.01$). Fasting plasma glucose was reduced at doses from 5 to 50 mg once daily compared with placebo (–19.3 to –30.5 vs. –5.8 mg/dl; $P < 0.01$). Urinary glucose excretion ranged from 51.8 to 85 g/day at week 12 in the dapagliflozin arms compared with 5.8–10.9 g/day at baseline and 5.7 g/day at 12 weeks in the placebo group. Mean weight loss at week 12 ranged from 2.5 to 3.2% in the dapagliflozin groups compared with 1.2% in the placebo group.[82,83]

Dapagliflozin is currently under evaluation in a number of phase 3 studies assessing the agent as monotherapy in patients with type 2 diabetes not adequately controlled with diet and exercise, as well as studies assessing dapagliflozin in conjunction with metformin, a sulfonylurea, a thiazolidinedione, or insulin.[84–91]

GLINIDES
The glinides, including nateglinide, repaglinide, and mitiglinide, are agents that enhance mealtime insulin secretion and reduce postprandial hyperglycemia. Nateglinide and repaglinide have been available in the United States since 2000 and 1997, respectively.

Mitiglinide
Mitiglinide has been available in Japan since 2004 and is currently in phase 3 studies in the United States. It has been reported to have a more β-cell–selective effect on the adensine triphosphate-dependent potassium channels than nateglinide and repaglinide and to have no active metabolites or cytochrome P450 drug interactions.[92,93]

Several recently published studies conducted in Japan have assessed premeal mitiglinide combined with once-daily insulin glargine and twice-daily premixed insulin.[94–96] In a study comparing mitiglinide with acarbose in elderly patients, glycemic control was better maintained in the mitiglinide group at 6 months (A1C 7.43% in the mitiglinide group and 7.75% in the acarbose group; $P < 0.001$).[92] In a study assessing mitiglinide in combination with metformin compared with metformin alone or mitiglinide alone, glycemic control was better in the group receiving the combination at 7 months (A1C 7.13% vs. 7.7% on metformin alone, $P < 0.001$).[92,93] An additional ongoing study is assessing mitiglinide in combination with metformin compared to metformin alone.[97]

INSULINS
A variety of insulin formulations are currently in development including inhaled formulations, intranasal formulations, oral formulations, and injectable analogs.

Inhaled Technosphere Insulin
Inhaled Technosphere insulin is an inhaled insulin in development for administration using a palm-sized

handheld breath-activated inhaler. The Technosphere particles are composed of human regular insulin loaded into a diketopiperazine molecule. The particles dissolve rapidly at physiological pH, providing for rapid insulin absorption from the lungs.[98] Technosphere insulin is absorbed within 15 minutes, has an onset of action of ~ 25–30 minutes, and has a duration of action of ~ 2–3 hours.[98]

In a study comparing inhaled Technosphere insulin and insulin lispro as prandial insulin in conjunction with basal insulin glargine in a 12-week study enrolling 111 patients with type 1 diabetes, inhaled insulin was associated with fewer postprandial glucose excursions, less late postprandial hypoglycemia, and greater weight loss. A1C was improved in both groups but did not differ between groups.[99] In a 12-week study assessing inhaled Technosphere insulin in 126 patients with type 2 diabetes not adequately controlled with oral agents, inhaled insulin reduced the mean A1C by 0.72% compared to a reduction of 0.3% in the placebo group ($P = 0.003$). Postprandial glucose excursions were reduced 56%. Body weight was unchanged.[98] In other smaller studies, inhaled Technosphere insulin was associated with improvements in postprandial glycemic control in patients with type 2 diabetes and glycemic control without weight gain in both type 1 and type 2 diabetes.[100,101]

Other studies are assessing inhaled Technosphere insulin compared to insulin aspart in type 1 diabetes, with basal insulin glargine compared to a regimen of insulin lispro and insulin glargine in type 1 diabetes, with basal insulin compared to subcutaneous premixed insulin therapy in type 2 diabetes, and in combination with metformin or compared to oral antidiabetic agents in patients with type 2 diabetes.[102–105]

Inhaled Technosphere insulin did not affect pulmonary function in a 6-month study enrolling 306 patients with type 2 diabetes.[106] An additional 2-year study is currently assessing pulmonary outcomes in patients with type 1 or type 2 diabetes treated with Technosphere insulin.[107]

Oral Insulin Spray
An oral insulin spray in development by Generex Biotechnology is in phase 3 studies in the United States but has already been approved in Ecuador and India. The insulin is absorbed buccally following administration with a proprietary RapidMist device that resembles the metered-dose inhalers used in the treatment of asthma. The formulation is tasteless and odorless.[108]

Compared to preprandial subcutaneous injection of regular insulin, preprandial oral insulin spray was associated with similar pre- and postmeal glucose concentrations.[109] Compared to a regimen of premeal subcutaneous regular insulin and twice-daily NPH insulin, a regimen of mealtime (half-dose before meal and half-dose after meal) oral insulin spray plus twice-daily NPH insulin was associated with greater reduction in A1C.[110] Compared to a regimen of once-daily subcutaneous insulin glargine and premeal insulin lispro, a regimen of twice-daily NPH insulin plus mealtime oral insulin spray was also associated with lower premeal glucose, A1C, and fructose during a 372-day treatment period.[111] Additional small preliminary studies have assessed mealtime oral insulin spray in adolescents with type 1 diabetes, in adults with type 2 diabetes requiring insulin injections, in conjunction with metformin in patients with type 2 diabetes not adequately controlled with oral agents, and as initial therapy in patients with type 2 diabetes not adequately controlled with diet and exercise.[108,112]

A 26-week phase 3 study is currently underway comparing oral insulin spray to subcutaneous regular human insulin in patients with type 1 diabetes receiving twice-daily NPH insulin. The oral insulin is administered as half the dose immediately before meals and half the dose immediately after meals. Subcutaneous regular human insulin is administered 30 minutes before meals. All patients receive twice-daily NPH insulin.[113]

Rapid-Acting Insulin for Injection (VIAject)
VIAject is a novel ultra-fast insulin formulation composed of human soluble insulin and ingredients designed to increase the rate of absorption (EDTA and citric acid). These ingredients pull the zinc ions away from human insulin hexamers and mask charges on the surface of the insulin molecule, causing the insulin hexamers to dissociate and preventing re-association to the hexameric state with subcutaneous administration.[114] VIAject has exhibited a quicker onset of action than insulin lispro and human soluble insulin (time to early half-maximal activity 33 minutes with VIAject vs. 51 minutes with insulin lispro and 66 minutes with human soluble insulin; $P < 0.05$).[114] When administered immediately before a meal, VIAject was associated with improved postprandial blood glucose control, reduced hyperglycemia in the first 3 hours after a meal, and reduced hypoglycemia through 8 hours compared to regular human insulin.[115]

Phase 3 studies comparing insulin VIAject and regular human insulin in patients with type 1 and type 2 diabetes have recently been completed.[116,117]

Other AGENTS
A wide variety of other agents are also in development for the treatment of type 1 or type 2 diabetes.

Bromocriptine
Bromocriptine is a dopamine D2 receptor agonist that is approved for the treatment of dysfunctions associated with hyperprolactinemia, acromegaly, and Parkinson's disease and has been in development for the treatment of type 2 diabetes for several years. A new drug application for a quick-release formulation was granted approvable status by the FDA in 2006. However, at least one additional safety study was necessary before the drug could be approved.[118]

Results of the studies submitted in support of approval have not been published. In one small study in patients with type 2 diabetes, bromocriptine was associated with reduced fasting plasma glucose and reduced A1C.[119] The required 1-year randomized, double-blind, placebo-controlled safety study enrolled 3,070 patients with type 2 diabetes. A1C was reduced 0.6% more in the bromocriptine-treated subjects than in the placebo-treated subjects compared to baseline. Target A1C of ≤ 7% was achieved in 32% of the bromocriptine group compared to 10% of the placebo group ($P = 0.0001$). Reductions were consistently greater in the bromocriptine group than in the placebo group when combined with multiple oral hypoglycemic agents, including metformin, sulfonylureas, thiazolidinediones, and combinations of these oral hypoglycemic agents.[120]

Otelixizumab

Otelixizumab is a humanized anti-CD3 monoclonal antibody currently being evaluated in clinical studies in patients with new-onset type 1 diabetes. Otelixizumab binds to the CD3/TCR complex and blocks full T-cell activation, proliferation, and cytokine release. It has been hypothesized that otelixizumab's downregulation of T effector cells via binding of the T-cell receptors will result in inhibition of the autoimmune attack on β-cells in the pancreatic islets and establishment of longlasting operational tolerance by the generation and expansion of regulatory T-cells, which prevent further autoimmune destruction.[121]

A phase 3 study is currently underway assessing whether an 8-day series of otelixizumab infusions will lead to greater improvement in insulin secretion than placebo in adults 18–35 years of age with new-onset type 1 diabetes.[122]

Recombinant Human Glutamic Acid Decarboxylase-65 (rhGAD65)

RhGAD65 is a vaccine that induces immunotolerization and may thereby slow or prevent autoimmune destruction of pancreatic islet cells.[123] Antibodies against GAD are present at the time of diagnosis in 80–90% of patients with type 1 diabetes.[124] In patients with adult-onset autoimmune diabetes and the presence of antibodies against GAD, administration of rhGAD65 has been associated with reduced A1C and increased fasting and stimulated C-peptide levels for 2 years.[124,125]

Two phase 3 studies were recently initiated to assess whether rhGAD65 formulated in alum preserves the body's own insulin-producing capacity in patients recently diagnosed with type 1 diabetes. One study will enroll subjects 10–20 years of age; the other will enroll subjects 8–45 years of age. Results will not be available for several years.[123,126]

Succinobucol

Succinobucol is an oral antioxidant lipid peroxidation inhibitor and vascular cell adhesion molecule antagonist that is in phase 3 development for the treatment of atherosclerosis and type 2 diabetes. It is a monosuccinate ester of probucol, a previously approved lipid-lowering agent.[127]

The first of these studies failed to achieve its primary endpoint in the treatment of patients with acute coronary syndrome. The double-blind, placebo-controlled multicenter trial was designed to evaluate the efficacy of succinobucol in the treatment of acute coronary syndrome in 6,144 patients. Patients were randomized to succinobucol 300 mg/day or placebo. The primary endpoint for the study was the composite of cardiovascular death, resuscitated cardiac arrest, myocardial infarction, stroke, unstable angina, or coronary revascularization. The secondary endpoints were primary composite endpoint with all-cause death, primary composite endpoint without coronary revascularization, and primary composite endpoint without coronary revascularization or unstable angina. After 24 months of treatment, the primary endpoint of the study was the same in both the succinobucol and placebo groups (17.2% vs. 17.3%, respectively; $P = 0.99$). However, the secondary endpoint of cardiovascular death, cardiac arrest, myocardial infarction, or stroke was lower in patients randomized to succinobucol (6.7% vs. 8.2%, $P = 0.028$). New-onset atrial fibrillation occurred more frequently in the succinobucol group (hazard ratio [HR] 1.87, 95% CI 1.67–2.09; $P = 0.0002$). New-onset diabetes occurred less frequently in the succinobucol group (HR 0.37, 95% CI 0.24–0.56; $P < 0.0001$).[128] This study included 2,271 patients with type 2 diabetes at study entry with a mean A1C of 7.2% who were followed for an average of 2 years. A1C was reduced in the succinobucol treatment group. An A1C of < 7% was achieved in 68.9% in the succinobucol group compared to 57.8% of the placebo group ($P < 0.001$).[129]

The manufacturer has reported preliminary results from a recently completed phase 3 study enrolling 999 patients with type 2 diabetes treated with succinobucol or placebo. The primary endpoint for the study was the change in A1C at the end of 6 months of therapy. A1C was reduced 0.6% in the succinobucol 150 mg group ($P < 0.001$) and 0.4% in the succinobucol 75 mg group ($P = 0.016$) compared to baseline, whereas A1C was reduced 0.2% in the placebo group. Succinobucol was not associated with weight gain or hypoglycemia. Liver enzyme elevations were observed in a small number of succinobucol-treated patients.[130,131]

Tagatose

Tagatose is a naturally occurring, sweet-tasting, low-calorie monosaccharide hexoketose found in dairy products. It is the epimer of D-fructose. Tagatose was originally developed as a sugar substitute for calorie and weight control. It was granted "Generally Recognized as Safe" status for use as a sweetener in foods and beverages by the FDA in 2001.[132]

The product in development by Spherix for the treatment of diabetes is produced by isomerization of galactose, which is produced by the hydrolysis of lactose derived from whey.[132] Oral administration of this product decreases the postprandial glucose peaks seen in patients with type 2 diabetes when it is administered before meals.[133] Administration three times a day with meals in patients with type 2 diabetes has been associated with weight loss, reduced A1C, and increased HDL cholesterol levels.[134] It is believed to exert its effect on postprandial glucose by attenuating glucose absorption in the intestine, as well as increasing glycogen synthesis and decreasing glycogen utilization.[132,133] Adverse effects have primarily included diarrhea, nausea, and flatulence.[133,134] The current 1-year clinical trial to demonstrate the efficacy of tagatose as monotherapy in the treatment of type 2 diabetes is scheduled for completion in 2009.[132,135]

Teplizumab

Teplizumab is a humanized anti-CD3 monoclonal antibody. Like otelixizumab, teplizumab is hypothesized to minimize cytokine release and prevent the progressive destruction of β-cells.[136]

Teplizumab was administered to 12 patients with new-onset type 1 diabetes in a placebo-controlled phase 1/2 study. Teplizumab was administered as a daily intravenous injection for 14 consecutive days within 6 weeks after diagnosis. After 1 year, insulin production was maintained or improved in 9 of the 12 patients treated with teplizumab compared to 2 of 12 placebo recipients ($P = 0.01$). A1C levels and insulin doses were reduced and C-peptide responses were maintained in the teplizumab group compared to the placebo group at 1 year and 2 years after treatment. Adverse effects included fever, rash, and anemia.[137,138]

A phase 3 study is currently evaluating the effects of 14 days of intravenous teplizumab in patients 8–35 years of age with new-onset type 1 diabetes, followed by retreatment at 6 months. The primary study endpoint is a successful clinical response as assessed by subjects' total daily insulin usage and A1C at 1 year.[136,139]

CONCLUSION

A wide range of agents are in development for use in the treatment of type 1 or type 2 diabetes. All of these agents appear to be effective in improving glycemic control, but it is unknown whether they will have an impact on the course of the disease or alter the micro- and macrovascular consequences of uncontrolled diabetes. One of the DPP-4 inhibitors is most likely to reach market next, as well as possibly liraglutide or mitiglinide. The PPAR-γ agonists and SGLT2 inhibitors are still early in phase 3 development.

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