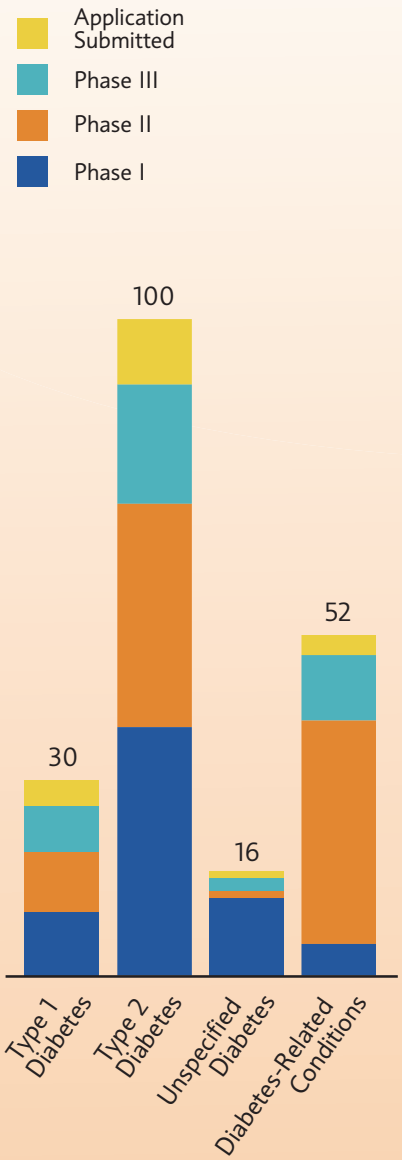
MEDICINES IN DEVELOPMENT

Diabetes

PRESENTED BY AMERICA'S BIOPHARMACEUTICAL RESEARCH COMPANIES

2014 REPORT

Medicines in Development For Diabetes



Biopharmaceutical Research Companies Are Developing 180 Medicines to Treat Diabetes and Related Conditions

Nearly 26 million Americans are affected by diabetes—including 7 million people who are unaware they have the disease. One of the top 10 causes of death in the United States, diabetes has far-reaching implications for patients and their families and our health care system.

While healthy eating and exercise can help prevent and manage type 2 diabetes, medicines play a key role in helping reduce the risk of and treat the disease. For example, one medicine was found in studies to lower the risk by 31 percent. And in recent years, eight new classes of type 2 diabetes medicines have been approved by the Food and Drug Administration (FDA), giving patients and health care providers powerful new options to treat this chronic and devastating condition.

To build on progress to date and help further meet the challenges posed by diabetes, America's biopharmaceutical research companies are **developing 180 new medicines** for type 1 and type 2 diabetes and diabetes-related conditions, such as chronic kidney failure due to diabetes and painful diabetic neuropathy.

Additionally, there are 200 active diabetes clinical trials in the United States, including 140 that have not yet started recruiting patients or are just now seeking volunteers to participate and another 60 that are active, but not recruiting new patients. In addition to the critical role these trials play in the development and testing of new treatments, they represent potentially valuable therapeutic options for patients battling diabetes and diabetes-related conditions.

According to the Centers for Disease Control and Prevention (CDC), death rates for people with diabetes fell substantially—up to 40 percent—between 1997 and 2006. CDC links this decrease to improved cardiovascular medical treatment, better management of diabetes, and some healthy lifestyle changes.

Unfortunately, while the death rates due to diabetes are declining, the rate of new cases has been rising. The number of Americans diagnosed with diabetes has more than tripled since 1980, according to the CDC. Lifestyle choices can affect this increase. The CDC-led National Diabetes Prevention Program found that

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weight loss and increased physical activity in people at high risk for diabetes reduced the development of type 2 diabetes by 58 percent in a three-year period.

According to the American Diabetes Association, most Americans with diabetes have type 2, in which relative insulin deficiency combines with the body failing to properly use insulin. Between 5 percent and 10 percent of Americans with diabetes have type 1, in which the body fails to produce insulin.

The medicines in the pipeline today offer hope of reducing the human toll and economic costs of diabetes. Examples of some medicines now being tested include:

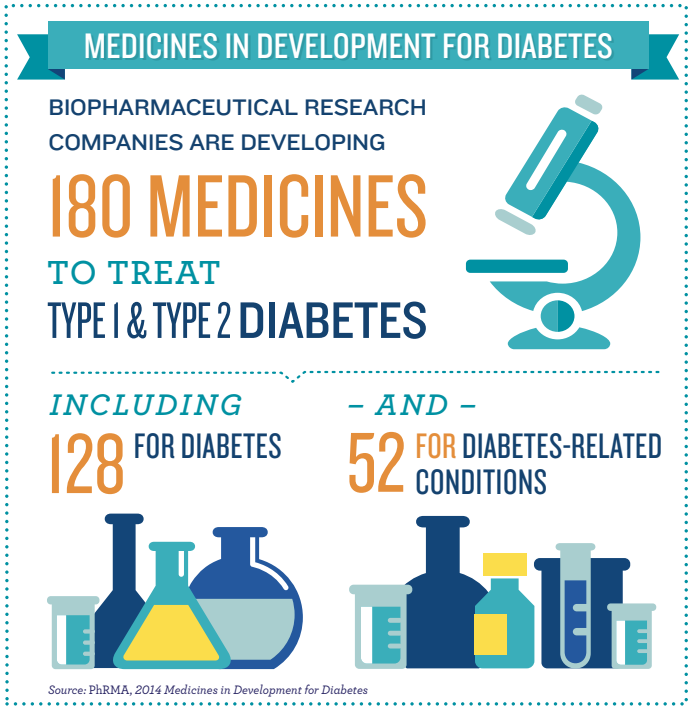
- A medicine that improves glucose-dependent insulin secretion.
- A medicine designed to inhibit an enzyme linked to diabetic neuropathy.
- A treatment designed to stimulate and enhance the regeneration of insulin-producing cells.

While diabetes remains a challenging illness, America's biopharmaceutical research companies are continuing their efforts to develop novel and more effective therapies to treat the disease and improve the quality of life for diabetes patients.

Recent Diabetes Medicine Approvals

New medicines approved by the FDA in the last year represent exciting steps forward in efforts to better treat diabetes. These include:

- **Nesina®** (alogliptin) is a new DPP-4 inhibitor designed to slow the inactivation of incretin hormones GLP-1 and GIP, resulting in more active incretins enabling the pancreas to secrete insulin and better managing blood glucose levels.
- **Invokana®** (canagliflozin) is the first sodium-glucose co-transporter 2 (SGLT2) inhibitor approved for patients with type 2 diabetes. SGLT2 inhibitors work in conjunction with the kidneys and the natural urination process to remove excess blood glucose from the body.
- **Duetact®** (pioglitazone/glimepiride) combines two previously approved type 2 diabetes medicines with complementary actions in a single tablet. One medicine targets insulin resistance while the other increases the amount of insulin produced by the pancreas.
- **Farxiga™** (dapagliflozin) is a new SGLT2 inhibitor approved to improve glycemic control in adults with type 2 diabetes.



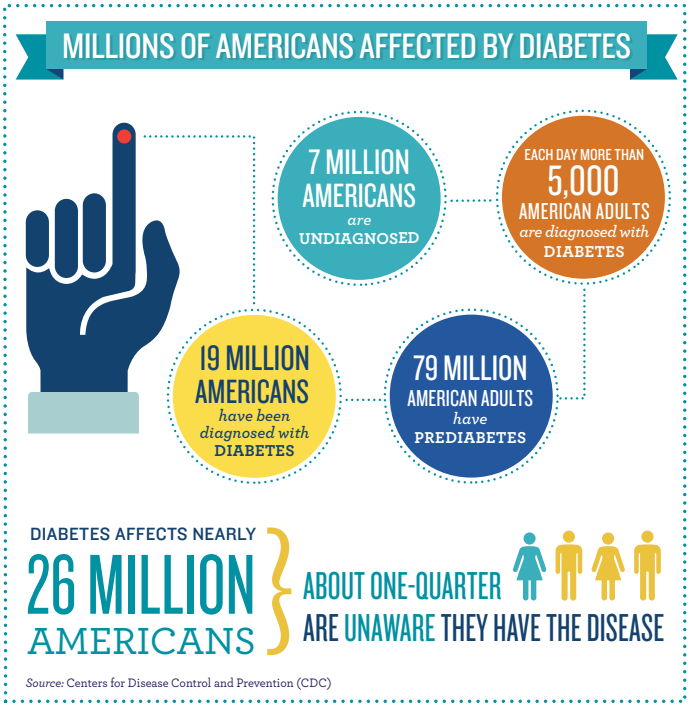
Diabetes Medicines in the Pipeline

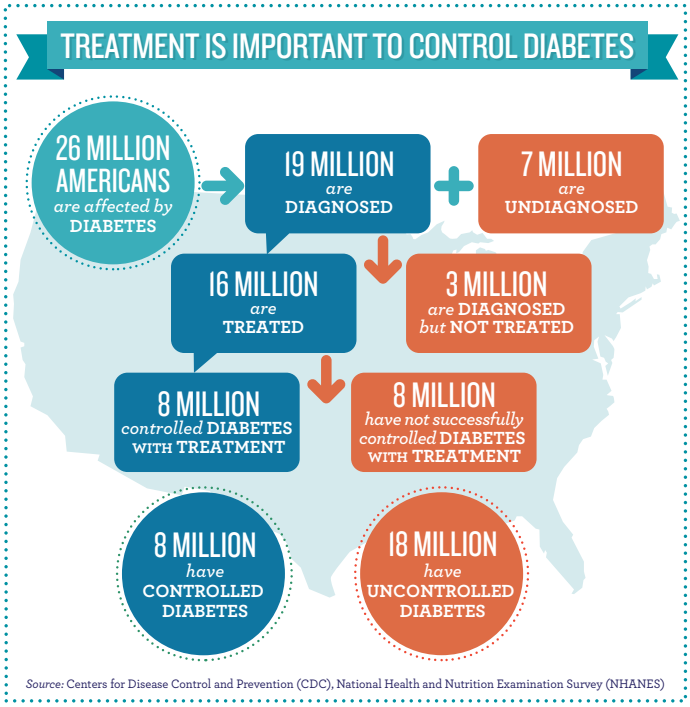
America's biopharmaceutical research companies continue to explore many different approaches to battle diabetes and related-conditions. Some potential innovations from the 180 medicines in development today, include:

Stimulating the Formation of Insulin Producing Cells—A potential first-in-class treatment for type 1 diabetes is designed to stimulate and enhance the regeneration of insulin-producing cells (islets). The treatment is a human peptide consisting of the bioactive part of a gene responsible for regenerating pancreatic islets. In diabetes, there are often too few insulin-producing islets to keep up with the demand for insulin.

Next-Generation Oral Treatment—A medicine in development for the treatment of type 2 diabetes is part of the DPP-4 inhibitor class, but chemically distinct from other approved medicines in this class. DPP-4 inhibitors work by stimulating the production of insulin and producing less glucose. In clinical trials, the medicine was able to inhibit more than 80 percent of its target enzyme for seven days, making it potentially a once-weekly treatment versus daily.

Once-Weekly Treatment—A medicine in development is in the same class of drugs as some other approved medicines for type 2 diabetes, but with a longer therapeutic life that





may make it suitable for once-weekly dosing. The medicine is a human glucagon-like peptide (GLP-1) analogue that lowers blood glucose and reduces body weight.

Facilitating Glucose Regulation—A potential medicine in development for type 2 diabetes is a gut sensory modulator (GSM) delivered directly to the stomach where it intensifies the body's natural food-driven signals that facilitate glucose regulation. The medicine, a delayed-release formulation of metformin (a medicine used to treat diabetes alone or in combination with other medicines), targets the lower gut to avoid systemic absorption in the bloodstream, making it potentially useful to diabetes patients with renal impairment who are unable to use metformin due to the risk of building metformin up in the blood (lactic acidosis).

Painful Nerve Damage—Nerve damage is a common symptom of diabetes. About half of all people with diabetes have some form of nerve damage, or neuropathy, according to the American Diabetes Association. Over time, blood glucose can injure the walls of tiny blood vessels that nourish nerves causing pain, especially in the legs. One medicine in development is designed to improve the symptoms of diabetic neuropathy by inhibiting the activity of an enzyme that causes the accumulation of intracellular sorbitol (a sugar alcohol) that causes diabetic neuropathy.

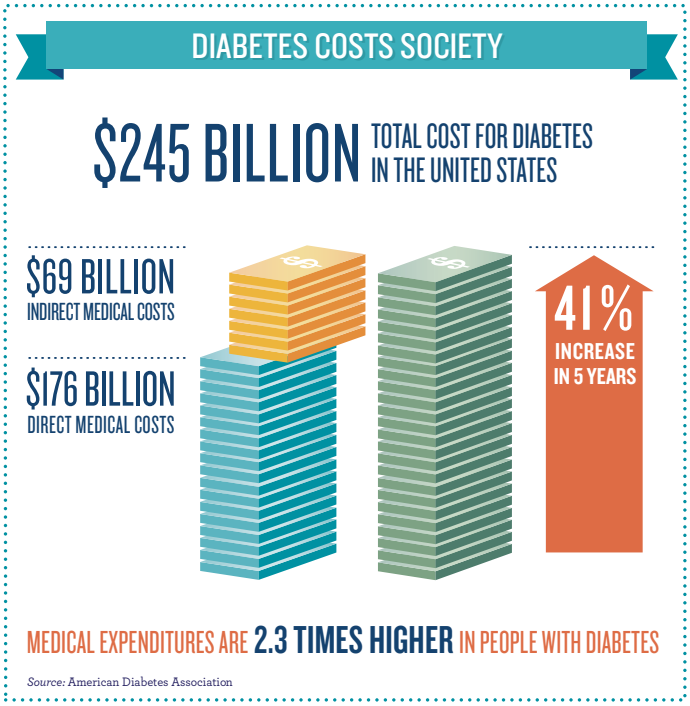
Diabetic Kidney Disease—A potential first-in-class medicine is in development for the treatment of diabetic nephropathy —a chronic progressive kidney disease that is the leading cause of end-stage renal disease (ESRD) or kidney failure. From 1990 to 2006, ESRD due to diabetic nephropathy increased 2.5 times. The medicine has demonstrated the potential to protect kidney function and slow disease progression when added to existing therapy.

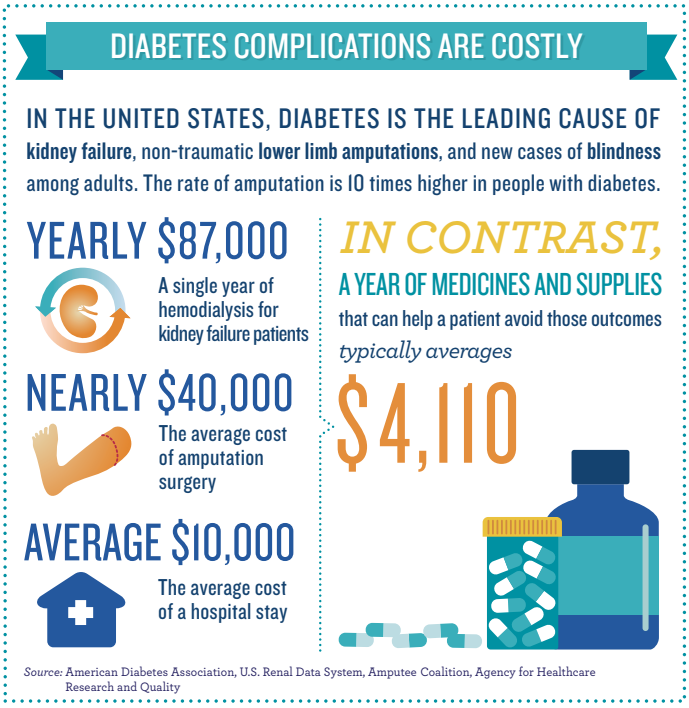
Early Diabetes Breakthroughs

Basic research is important to finding new treatments and possibly a cure for diabetes. Recent research discoveries offer hope that they can one day lead to new effective treatments. Some of the new discoveries include:

- Researchers at the Harvard Stem Cell Institute discovered a hormone that can stimulate production of insulin-secreting pancreatic beta cells up to 30 times the normal rate in mice. These new cells only produce insulin when the body needs it, potentially leading to a natural regulation of insulin.
- Scientists at London's Imperial College have manipulated a patient's own stem cells into insulin-secreting cells. Further research aims to inject patients with 100 percent of insulin-producing cells that would release insulin for up to one year. Other scientists at the Walter and Eliza Hall Institute of Medical Research in Australia have isolated stem cells from the pancreas and turned them into insulin-producing cells for the treatment of type 1 diabetes.

- A type 1 diabetes vaccine created by researchers at Stanford University shuts down certain segments of the human immune system. Most vaccines aim to boost the immune system to fight a virus, but the Stanford vaccine turns off portions of the immune system that are malfunctioning. Type 1 diabetes is an autoimmune disease where the pancreas produces too little or no insulin.
- Researchers at the University of Tokyo have identified a molecule that functions similarly to the hormone adiponectin, which is secreted by fat cells and helps to regulate glucose and insulin effectiveness. But the hormone was destroyed by the digestive system when taken orally. The new molecule can be taken orally and was found to be effective when studied in mice.
- Doctors at Boston Children's Hospital have isolated a pathway in animals that triggers T cells to attack the pancreas. With more research, the newly discovered pathway could lead to better treatments or even a cure for type 1 diabetes.





Diabetes Medications—Improving Adherence

Improved adherence to diabetes medications can lead to better health outcomes and reduced costs. According to recent research, diabetes patients who do not consistently take their medicines as prescribed are 2.5 times more likely to be hospitalized than those who follow their prescribed treatment regimens more than 80 percent of the time. In addition, a recent study in *Health Affairs* projected that improved adherence to diabetes medications could avert more than 1 million emergency room visits and close to 620,000 hospitalizations annually, for a total potential savings of $8.3 billion annually. There are several recent studies showing the cost effectiveness of treating diabetes with medication. Some of those include:

- Medicare Part A and B costs associated with poor medication adherence are estimated to be up to $840 per month for beneficiaries with diabetes. The most expensive beneficiaries were episodic medication users including discontinuers, delayed initiators, and individuals with long gaps in use, according to a study published in *Health Affairs*.
- Insurance plans that perform low on adherence metrics could save $2.1 billion annually for diabetes patients by improving the adherence of their enrollees to even a moderate level. In fact, adherence at a high level could save $19.3 billion, according to a new study.

ADHERENCE IS KEY TO IMPROVED HEALTH

DIABETES PATIENTS
who DID NOT consistently take medications are

2.5 TIMES MORE LIKELY TO BE HOSPITALIZED

than those who followed their prescribed treatment regimens

Source: Diabetes Care

ADHERENCE CREATES SAVINGS

IMPROVED ADHERENCE TO DIABETES MEDICATIONS COULD RESULT IN:

1,082,000
fewer emergency room visits

618,000
fewer hospitalizations annually

$8.3 BILLION
in potential annual savings

Source: Health Affairs

Treatment Intensification and Clinical Inertia in Diabetes Care

Diabetes is a complex, chronic illness that requires consistent medical care and treatment to help control blood sugar levels and prevent acute or long-term complications of the disease, such as kidney failure and amputations.

Despite the availability of effective treatments and clinical guidelines, many individuals with diabetes do not achieve optimal blood glucose levels. One reason is that patients may not receive appropriate and timely changes to or intensification of their medication regimen. Multiple studies have found that there are significant delays in treatment intensification in people with type 2 diabetes despite poor glycemic control.

There are several factors that may contribute to optimal glycemic control and influence treatment success. However, understanding appropriate intensification of diabetes treatment is critical in achieving clinical goals and value to our overall healthcare system.

DIABETES AND MINORITIES IN THE UNITED STATES

Racial and ethnic minority populations in the United States are disproportionately affected by diabetes. According to the U.S. Department of Health and Human Services Office of Minority Health, as compared to non-Hispanic whites:

- *African-American adults are twice as likely to be diagnosed with diabetes.*
- *Hispanic adults are 1.7 times more likely to have diabetes.*
- *American Indians and Alaska Natives are twice as likely to be diagnosed with the disease.*
- *Native Hawaiians and Pacific Islanders are three times more likely to be diagnosed with diabetes.*

According to the CDC, of people diagnosed with diabetes, 7.1 percent are non-Hispanic whites, while 8.4 percent are Asian Americans, 12.6 percent are African Americans, 11.3 percent are Hispanic Americans, and 16.1 percent are American Indians/Alaska Natives.

Facts About Diabetes in the United States

Prevalence[1]

- Nearly 26 million Americans—8.3 percent of the population—are affected by diabetes; including 7 million who are unaware they have the disease.
- One in 10 adults has diabetes now. If current trends continue, as many as one in three will be facing the disease by 2050 due to an aging population more likely to develop type 2 diabetes, increases in minority groups at high risk for the disease, and longer lifespans among diabetes patients.
- Of the nearly 25.6 million adults with diabetes, 13 million are men and 12.6 million are women.
- In 2010, 10.9 million people aged 65 years and older had diabetes.
- About 215,000 people under the age of 20 had diabetes in 2010.
- In 2010, 1.9 million patients were newly diagnosed with diabetes.
- As many as 79 million people may have prediabetes.

Types of Diabetes[2]

- Type 1 diabetes accounts for 5 percent of all diagnosed cases of diabetes. This type of diabetes is usually diagnosed in children and young adults.
- Type 2 diabetes accounts for 95 percent of all diagnosed cases of diabetes in adults.
- Between 2 percent to 10 percent of pregnant women will develop gestational diabetes during pregnancy. And, women who have had gestational diabetes have a 35 percent to 60 percent chance of developing type diabetes within the next 20 years.

Mortality

- Diabetes is the seventh leading cause of death in the United States.[1]
- In 2011, 73,282 Americans died as a result of diabetes.[1]
- Death rates for heart disease and stroke are as many as four times higher among people with diabetes compared to those without the disease.[3]

Diabetes-Related Conditions

- Diabetes is the leading cause of kidney failure, non-traumatic lower limb amputations, and new cases of blindness among adults.[1]
- The rate of amputation is 10 times higher in people with diabetes than those without the disease.[2]

Economic Impact[3]

- In 2012, the cost of diagnosed diabetes in the United States was $245 billion—$176 billion for direct medical costs (hospital and emergency care, office visits and medications) and $69 billion in reduced productivity. That represents an increase of 41 percent since 2007.
- Average medical expenditures among people with diabetes are 2.3 times higher than among those without diabetes.
- A significant portion of the U.S. health care dollar goes to treating people with diabetes. More than $1 in $10 is spent directly on diabetes and associated complications, and $1 in $5 is spent on caring for people with diabetes.

Sources:

1. *National Diabetes Fact Sheet, 2011,* U.S. Centers for Disease Control and Prevention (CDC), *www.cdc.gov*
2. *Diabetes Report Card 2012,* CDC, *www.cdc.gov*
3. *Economic Costs of Diabetes in the U.S. in 2012,* American Diabetes Association (ADA), *www.diabetes.org*

Diabetes, Type 1 Diabetes and Type 2 Diabetes

Product Name	Sponsor	Indication	Development Phase*
Afrezza® insulin inhalation	MannKind *Valencia, CA*	type 1 diabetes, type 2 diabetes	application submitted www.mannkindcorp.com
albiglutide (GLP-1 agonist)	GlaxoSmithKline *Research Triangle Park, NC*	type 2 diabetes	application submitted www.gsk.com
alpha-1 antitrypsin (AAT) (serine proteinase inhibitor)	Omni Bio Pharmaceutical *Greenwood Village, CO*	type 1 diabetes	Phase I/II www.omnibiopharma.com
AMG 876 (fusion protein)	Amgen *Thousand Oaks, CA*	type 2 diabetes	Phase I www.amgen.com
analog insulin-PH20	Halozyme Therapeutics *San Diego, CA*	type 1 diabetes , type 2 diabetes	Phase II www.halozyme.com
ARI-2243 (DPP-4 inhibitor)	Arisaph Pharmaceuticals *Boston, MA*	type 2 diabetes	Phase I www.arisaph.com
BI-187004 CL	Boehringer Ingelheim Pharmaceuticals *Ridgefield, CT*	type 2 diabetes	Phase I www.boehringer-ingleheim.com
BIOD-123 (RHI-based ultra-rapid-acting insulin)	Biodel *Danbury, CT*	type 1 diabetes	Phase II www.biodel.com
BIOD-531 (RHI-based concentrated ultra-rapid-acting insulin)	Biodel *Danbury, CT*	type 2 diabetes	Phase I www.biodel.com
Bydureon® exenatide weekly suspension	AstraZeneca *Wilmington, DE* Bristol-Myers Squibb *Princeton, NJ*	type 2 diabetes	Phase III www.astrazeneca.com www.bms.com
Bydureon® Dual Chamber Pen exenatide extended release	AstraZeneca *Wilmington, DE* Bristol-Myers Squibb *Princeton, NJ*	type 2 diabetes	application submitted www.astrazeneca.com www.bms.com

*For more information about a specific medicine or company in the report, please use the website provided.

Diabetes, Type 1 Diabetes and Type 2 Diabetes

Product Name	Sponsor	Indication	Development Phase
Byetta® exenatide	Bristol-Myers Squibb *Princeton, NJ* Eli Lilly *Indianapolis, IN*	type 2 diabetes (adolescents)	Phase III www.bms.com www.lilly.com
canagliflozin/metformin extended-release fixed-dose combination	Janssen Research & Development *Raritan, NJ*	type 2 diabetes	Phase III www.janssenrnd.com
canagliflozin/metformin immediate-release fixed-dose combination	Janssen Research & Development *Raritan, NJ*	type 2 diabetes	application submitted www.janssenrnd.com
CJC-1134-PC (GLP-1 stimulant)	ConjuChem *Los Angeles, CA*	type 2 diabetes	Phase II www.conjuchem.com
dapagliflozin/metformin fixed-dose combination	AstraZeneca *Wilmington, DE* Bristol-Myers Squibb *Princeton, NJ*	type 2 diabetes	application submitted www.astrazeneca.com www.bms.com
dapagliflozin/saxagliptin fixed-dose combination	AstraZeneca *Wilmington, DE* Bristol-Myers Squibb *Princeton, NJ*	diabetes	Phase III www.astrazeneca.com www.bms.com
diabetes biologic	Eli Lilly *Indianapolis, IN*	diabetes	Phase I www.lilly.com
diabetes biologic	Eli Lilly *Indianapolis, IN*	diabetes	Phase I www.lilly.com
diabetes NCE	Eli Lilly *Indianapolis, IN*	diabetes	Phase I www.lilly.com
diabetes NCE	Eli Lilly *Indianapolis, IN*	diabetes	Phase I www.lilly.com
diabetes NCE	Eli Lilly *Indianapolis, IN*	diabetes	Phase I www.lilly.com
diabetes NCE	Eli Lilly *Indianapolis, IN*	diabetes	Phase I www.lilly.com
DS-1150b (GLUT4 stimulant)	Daiichi Sankyo *Parsippany, NJ*	type 2 diabetes	Phase I completed www.daiichisankyo.com
DS-7309 (glucokinase activator)	Daiichi Sankyo *Parsippany, NJ*	type 2 diabetes	Phase I www.daiichisankyo.com

Diabetes, Type 1 Diabetes and Type 2 Diabetes

Product Name	Sponsor	Indication	Development Phase
DS-8500 (GPR119 agonist)	Daiichi Sankyo *Parsippany, NJ*	diabetes	Phase I www.daiichisankyo.com
dulaglutide (GLP-1 agonist)	Eli Lilly *Indianapolis, IN*	type 2 diabetes	application submitted www.lilly.com
DV-0100 (dendritic cell vaccine) ORPHAN DRUG	DiaVacs *Edgewater, NJ*	type 1 diabetes	Phase II www.diavacs.us.com
EGT 0001442 (SGLT2 inhibitor)	Theracos *Marlborough, MA*	type 2 diabetes	Phase II www.theracos.com
empagliflozin (SGLT2 inhibitor)	Boehringer Ingelheim Pharmaceuticals *Ridgefield, CT* Eli Lilly *Indianapolis, IN*	type 2 diabetes	application submitted www.boehringer-ingelheim.com www.lilly.com
empagliflozin/linagliptin fixed-dose combination	Boehringer Ingelheim Pharmaceuticals *Ridgefield, CT* Eli Lilly *Indianapolis, IN*	type 2 diabetes	Phase III www.boehringer-ingelheim.com www.lilly.com
empagliflozin/metformin fixed-dose combination	Boehringer Ingelheim Pharmaceuticals *Ridgefield, CT* Eli Lilly *Indianapolis, IN*	type 2 diabetes	Phase I www.boehringer-ingelheim.com www.lilly.com
ertugliflozin (SGLT2 inhibitor)	Merck *Whitehouse Station, NJ* Pfizer *New York, NY*	type 2 diabetes	Phase III www.merck.com www.pfizer.com
Farxiga™ dapagliflozin	AstraZeneca *Wilmington, DE* Bristol-Myers Squibb *Princeton, NJ*	type 2 diabetes (adolescents and children)	Phase I www.astrazeneca.com www.bms.com
gevokizumab (XOMA 052)	XOMA *Berkeley, CA*	type 1 diabetes	Phase II www.xoma.com
glucagon-R antagonist (LY2409021)	Eli Lilly *Indianapolis, IN*	type 2 diabetes	Phase II www.lilly.com
GSK1070806 (IL-18 mAb)	GlaxoSmithKline *Research Triangle Park, NC*	type 2 diabetes	Phase II www.gsk.com

Diabetes, Type 1 Diabetes and Type 2 Diabetes

Product Name	Sponsor	Indication	Development Phase
GSK1614235/GSK2330672 (SGLT1 inhibitor/iBAT inhibitor)	GlaxoSmithKline *Research Triangle Park, NC*	type 2 diabetes	Phase I www.gsk.com
GSK 2330672 (iBAT inhibitor)	GlaxoSmithKline *Research Triangle Park, NC*	type 2 diabetes	Phase II www.gsk.com
HE3286	Harbor Biosciences *San Diego, CA*	type 2 diabetes	Phase II www.harbortx.com
HIP-2B (human pro-islet peptide)	CureDm *Wilmington, DE*	type 1 diabetes, type 2 diabetes	Phase I www.curedm.com
HM11260C (exenatide long-acting)	Hanmi Pharmaceutical *Seoul, South Korea*	type 2 diabetes	Phase II www.hanmipharm.com
HM12460A (long-acting insulin)	Hanmi Pharmaceutical *Seoul, South Korea*	type 1 diabetes, type 2 diabetes	Phase I www.hanmipharm.com
IDegLira insulin degludec/liraglutide (NN9068)	Novo Nordisk *Plainsboro, NJ*	type 2 diabetes	Phase III www.novonordisk.com
insulin aspart faster-acting (NN1218)	Novo Nordisk *Plainsboro, NJ*	type 1 diabetes, type 2 diabetes	Phase III www.novonordisk.com
insulin B-chain vaccine	Orban Biotech *Brookline, MA*	type 1 diabetes	Phase I completed www.orbanbiotech.com
insulin biosimilar	Harvest Moon Pharmaceuticals *Falls Church, VA*	diabetes	Phase III www.harvestmoonpharma.com
insulin biosimilar	Sanofi US *Bridgewater, NJ*	diabetes	Phase I www.sanofi.com
insulin glargine biosimilar	Harvest Moon Pharmaceuticals *Falls Church, VA*	diabetes	in clinical trials www.harvestmoonpharma.com
insulin glargine biosimilar	Wockhardt *Mumbai, India*	type 1 diabetes	Phase I completed www.wockhardt.com
insulin inhalation (Dance-01)	Dance Biopharm *San Francisco, CA*	type 1 diabetes	Phase I/II www.dancebiopharm.com
insulin lispro (LY275585)	Eli Lilly *Indianapolis, IN*	type 1 diabetes, type 2 diabetes	in clinical trials www.lilly.com
insulin peglispro (LY2605541)	Eli Lilly *Indianapolis, IN*	type 1 diabetes, type 2 diabetes	Phase III www.lilly.com

Diabetes, Type 1 Diabetes and Type 2 Diabetes

Product Name	Sponsor	Indication	Development Phase
ISIS-GCCRRx (antisense oligonucleotide)	Isis Pharmaceuticals *Carlsbad, CA*	type 2 diabetes	Phase II www.isispharm.com
ISIS-GCGRRx (antisense oligonucleotide)	Isis Pharmaceuticals *Carlsbad, CA*	type 2 diabetes	Phase II www.isispharm.com
ISIS-PTP1BRx (antisense oligonucleotide)	Isis Pharmaceuticals *Carlsbad, CA*	type 2 diabetes	Phase II www.isispharm.com
ITCA 650 (exenatide subcutaneous implant)	Intarcia Therapeutics *Boston, MA*	type 2 diabetes	Phase III www.intarcia.com
Janumet® sitagliptin/metformin	Merck *Whitehouse Station, NJ*	type 2 diabetes (adolescents and children)	Phase III www.merck.com
Janumet® XR sitagliptin/metformin extended release	Merck *Whitehouse Station, NJ*	type 2 diabetes (adolescents and children)	Phase III www.merck.com
JTT-851 (G protein-coupled receptor 40 agonist)	Akros Pharma *Princeton, NJ*	type 2 diabetes	Phase II www.akrospharma.com
KD026 (MTP inhibitor)	Kadmon Pharmaceuticals *New York, NY*	type 2 diabetes	Phase II www.kadmon.com
Kombiglyze™ XR saxagliptin/metformin extended release	AstraZeneca *Wilmington, DE* Bristol-Myers Squibb *Princeton, NJ*	type 2 diabetes (adolescents and children)	Phase I www.astrazeneca.com www.bms.com
LAI287 (NN1436)	Novo Nordisk *Plainsboro, NJ*	type 1 diabetes, type 2 diabetes	Phase I www.novonordisk.com
LEZ763	Novartis Pharmaceuticals *East Hanover, NJ*	type 2 diabetes	Phase II completed www.novartis.com
LGD-6972 (glucagon receptor antagonist)	Ligand Pharmaceuticals *La Jolla, CA*	type 2 diabetes	Phase I www.ligand.com
LIK066 (SGLT 1/2 inhibitor)	Novartis Pharmaceuticals *East Hanover, NJ*	type 2 diabetes	Phase II www.novartis.com
linagliptin/pioglitazone fixed-dose combination	Boehringer Ingelheim Pharmaceuticals *Ridgefield, CT* Eli Lilly *Indianapolis, IN*	type 2 diabetes	Phase III completed www.boehringer-ingelheim.com www.lilly.com

Diabetes, Type 1 Diabetes and Type 2 Diabetes

Product Name	Sponsor	Indication	Development Phase
LixiLan lixisenatide/insulin glargine fixed-ratio	Sanofi US *Bridgewater, NJ*	type 2 diabetes	Phase II www.sanofi.com
luseogliflozin (TS-071)	Taisho Pharmaceutical *Tokyo, Japan*	type 2 diabetes	Phase I www.taisho.co.jp
LX4211 (SGLT1/SGLT2 inhibitor)	Lexicon Pharmaceuticals *The Woodlands, TX*	type 1 diabetes, type 2 diabetes	Phase II www.lexgen.com
Lyxumia® lixisenatide	Sanofi US *Bridgewater, NJ*	type 2 diabetes	Phase III www.sanofi.com
MABp1 (T2-18C3)	Xbiotech *Austin, TX*	type 2 diabetes	Phase II completed www.xbiotech.com
MBX 2982	CymaBay Therapeutics *Hayward, CA*	type 2 diabetes	Phase II www.cymabay.com
mesenchymal precursor cells (MPC)	Mesoblast *Melbourne, Australia*	type 2 diabetes	Phase I/II www.mesoblast.com
metreleptin (leptin analogue)	AstraZeneca *Wilmington, DE* Bristol-Myers Squibb *Princeton, NJ*	diabetes and lipodystrophy (Fast Track)	application submitted www.astrazeneca.com www.bms.com
MK-8521	Merck *Whitehouse Station, NJ*	type 2 diabetes	Phase I www.merck.com
MK-8655	Merck *Whitehouse Station, NJ*	type 2 diabetes	Phase I www.merck.com
MSDC-0602 (mTOT modulator)	Metabolic Solutions Development *Kalamazoo, MI*	type 2 diabetes	Phase II www.msdrx.com
Nesina® alogliptin	Takeda Pharmaceuticals *Deerfield, IL*	type 2 diabetes (adolescents and children)	Phase I www.takeda.com
new insulin glargine biosimilar (LY2963016)	Boehringer Ingelheim Pharmaceuticals *Ridgefield, CT* Eli Lilly *Indianapolis, IN*	type 1 diabetes, type 2 diabetes	application submitted www.boehringer-ingelheim.com www.lilly.com
NewMet™ metformin delayed release	Elcelyx Therapeutics *San Diego, CA*	type 2 diabetes	Phase II www.elcelyx.com

Diabetes, Type 1 Diabetes and Type 2 Diabetes

Product Name	Sponsor	Indication	Development Phase
NGM 282	NGM Biopharmaceuticals *South San Francisco, CA*	type 2 diabetes	Phase II www.ngmbio.com
NM504 (microbiome modulator)	MicroBiome Therapeutics *Broomfield, CO*	metformin-intolerant type 2 diabetes --- prediabetes	Phase 0 www.mbiome.com --- Phase 0 www.mbiome.com
NN1953 (oral insulin)	Novo Nordisk *Plainsboro, NJ*	type 1 diabetes, type 2 diabetes	Phase I www.novonordisk.com
NN1954 (oral insulin)	Novo Nordisk *Plainsboro, NJ*	type 1 diabetes, type 2 diabetes	Phase I www.novonordisk.com
NN1956 (long-acting basal insulin analogue)	Novo Nordisk *Plainsboro, NJ*	type 1 diabetes, type 2 diabetes	Phase I www.novonordisk.com
NN9924	Novo Nordisk *Plainsboro, NJ*	type 2 diabetes	Phase II www.novonordisk.com
NN9926	Novo Nordisk *Plainsboro, NJ*	type 2 diabetes	Phase I www.novonordisk.com
NN9927	Novo Nordisk *Plainsboro, NJ*	type 2 diabetes	Phase I www.novonordisk.com
NN9928	Novo Nordisk *Plainsboro, NJ*	type 2 diabetes	Phase I www.novonordisk.com
omarigliptin (DPP-4 inhibitor)	Merck *Whitehouse Station, NJ*	type 2 diabetes	Phase III www.merck.com
Onglyza® saxagliptin	AstraZeneca *Wilmington, DE* Bristol-Myers Squibb *Princeton, NJ*	type 2 diabetes (adolescents and children)	Phase III www.astrazeneca.com www.bms.com
Oral-Lyn® oral insulin	Generex Biotechnology *Toronto, Canada*	type 1 diabetes	Phase III www.generex.com
ORMD 0801 (oral insulin capsule)	Oramed *Jerusalem, Israel*	type 2 diabetes	Phase II www.oramed.com
oxyntomodulin	Merck *Whitehouse Station, NJ*	type 2 diabetes	Phase I completed www.merck.com

Diabetes, Type 1 Diabetes and Type 2 Diabetes

Product Name	Sponsor	Indication	Development Phase
oxyntomodulin peptide	Eli Lilly *Indianapolis, IN*	diabetes	Phase I www.lilly.com
P7435	Piramal Enterprises *Mumbai, India*	diabetes	Phase I www.piramal.com
P11187	Piramal Enterprises *Mumbai, India*	type 2 diabetes	Phase I www.piramal.com
PAZ320	Boston Therapeutics *Manchester, NH*	type 2 diabetes	Phase II www.bostonti.com
PB1023 (weekly GLP-1R agonist)	PhaseBio Pharmaceuticals *Malvern, PA*	type 2 diabetes	Phase II www.phasebio.com
PE0139 (basal native insulin)	PhaseBio Pharmaceuticals *Malvern, PA*	type 2 diabetes	Phase I www.phasebio.com
PEG-FGF21 (pegylated-fibroblast growth factor-21)	Ambrx *San Diego, CA* Bristol-Myers Squibb *Princeton, NJ*	type 2 diabetes	Phase I www.ambrx.com www.bms.com
Peptide p277 ORPHAN DRUG	Andromeda Biotech *Yavne, Israel*	type 1 diabetes	Phase III www.andromedabio.com
PF-04937319 (partial glucokinase activator)	Pfizer *New York, NY*	type 2 diabetes	Phase II www.pfizer.com
PF-05175157	Pfizer *New York, NY*	type 2 diabetes	Phase I www.pfizer.com
PF-05231023	Pfizer *New York, NY*	type 2 diabetes	Phase I www.pfizer.com
PF-06291874	Pfizer *New York, NY*	type 2 diabetes	Phase I www.pfizer.com
PF-06342674	Pfizer *New York, NY*	type 1 diabetes	Phase I www.pfizer.com
ranolazine extended-release	Gilead Sciences *Foster City, CA*	type 2 diabetes	Phase III www.gilead.com

Diabetes, Type 1 Diabetes and Type 2 Diabetes

Product Name	Sponsor	Indication	Development Phase
RG7697 (dual agonist [GLP and GIP] peptide analogue)	Roche *Nutley, NJ*	type 2 diabetes	Phase I www.roche.com
RM 493 (MC4R peptide therapeutic)	Rhythm Pharmaceuticals *Boston, MA*	diabetes	Phase II www.rhythmtx.com
Ryzodeq® insulin degludec/insulin aspart	Novo Nordisk *Plainsboro, NJ*	type 1 diabetes, type 2 diabetes	application submitted www.novonordisk.com
S-707106 (insulin sensitizer)	Shionogi *Osaka, Japan*	type 2 diabetes	Phase II www.shionogi.co.jp
semaglutide (NN9535)	Novo Nordisk *Plainsboro, NJ*	type 2 diabetes	Phase III www.novonordisk.com
teneligliptin (DPP-4 inhibitor)	Mitsubishi Tanabe Pharma America *Jersey City, NJ*	type 2 diabetes	Phase I www.mt-pharma-america.com
teplizumab (anti-CD3 mAb) ORPHAN DRUG	Macrogenics *Rockville, MD*	type 1 diabetes	Phase III www.macrogenics.com
TOL-3021 (antigen-specific immunotherapeutic vaccine)	Tolerion *Portola Valley, CA*	type 1 diabetes	Phase II www.tolerioninc.com
trelagliptin (DPP-4 inhibitor)	Takeda Pharmaceuticals *Deerfield, IL*	type 2 diabetes	Phase II www.takeda.com
Tresiba® insulin degludec	Novo Nordisk *Plainsboro, NJ*	type 1 diabetes, type 2 diabetes --- type 1 diabetes (adolescents)	application submitted www.novonordisk.com --- Phase III completed www.novonordisk.com
TTP054 (GLP-1 receptor agonist)	TransTech Pharma *High Point, NC*	type 2 diabetes	Phase II www.ttpharma.com
TTP399 (glucokinase inhibitor)	TransTech Pharma *High Point, NC*	type 2 diabetes	Phase I/II www.ttpharma.com
TTP814 (PTP-1B inhibitor)	TransTech Pharma *High Point, NC*	type 2 diabetes	Phase I/II www.ttpharma.com
U300	Sanofi US *Bridgewater, NJ*	type 1 diabetes, type 2 diabetes	Phase III www.sanofi.com

Diabetes, Type 1 Diabetes and Type 2 Diabetes

Product Name	Sponsor	Indication	Development Phase
U-Strip™ insulin transdermal ultrasonic patch	Transdermal Specialties *Norwalk, CT*	type 1 diabetes, type 2 diabetes	Phase I www.transdermalspecialties.com
Victoza® liraglutide	Novo Nordisk *Plainsboro, NJ*	type 1 diabetes	Phase III www.novonordisk.com
VRS-859 (exenatide-XTEN)	Diartis Pharmaceuticals *Redwood City, CA*	type 2 diabetes	Phase I www.diartispharma.com
ZP2929 (glucagon and GLP-1 receptor agonists)	Zealand Pharma *Copenhagen, Denmark*	type 2 diabetes	Phase I www.zealandpharma.com

Diabetes-Related Conditions

Product Name	Sponsor	Indication	Development Phase
AKB-9778 (Tie-2 activator)	Aerpio Therapeutics *Cincinnati, OH*	diabetic macular edema	Phase II www.aerpio.com
ALG-1001 (oligopeptide therapy)	Allegro Ophthalmics *San Juan Capistrano, CA*	diabetic macular edema	Phase I/II www.allegroeye.com
AppliGel-G gentamicin topical	Royer Biomedical *Frederick, MD*	diabetic foot ulcers	Phase I/II www.royerbiomedical.com
ARA 290	Araim Pharmaceuticals *Yorktown, NY*	diabetic neuropathy	Phase I/II www.araim.org
AS-3201 (ranirestat)	Eisai *Woodcliff Lake, NJ*	diabetic neuropathy	Phase II/III www.eisai.com
atrasentan	AbbVie *North Chicago, IL*	diabetic nephropathy (adjunctive therapy)	Phase III www.abbvie.com
AVP-923 (dextromethorphan/quinidine fixed-dose combination)	Avanir Pharmaceuticals *Aliso Viejo, CA*	diabetic neuropathy	Phase III www.avanir.com
AZD1722/RDX5791 (NHE3 inhibitor)	Ardelyx *Fremont, CA* AstraZeneca *Wilmington, DE*	management of fluid retention in patients with chronic kidney disease and type 2 diabetes	Phase II www.ardelyx.com www.astrazeneca.com

Diabetes-Related Conditions

Product Name	Sponsor	Indication	Development Phase
AZD5213 (histamine-3 receptor antagonist)	AstraZeneca *Wilmington, DE*	diabetic neuropathy	Phase II www.astrazeneca.com
baricitinib (JAK1/JAK2 inhibitor)	Eli Lilly *Indianapolis, IN* Incyte *Wilmington, DE*	diabetic nephropathy	Phase II www.lilly.com www.incyte.com
BMS-813160 (CCR2/CCR5 chemokine receptor antagonist)	Bristol-Myers Squibb *Princeton, NJ*	diabetic nephropathy	Phase II www.bms.com
camicinal (GSK962040)	GlaxoSmithKline *Research Triangle Park, NC*	diabetic gastroparesis	Phase II www.gsk.com
CBX129801 (long-acting C-peptide)	Cebix *San Diego, CA*	diabetic neuropathy (Fast Track)	Phase II www.cebix.com
CCX 140 (CCR2 receptor antagonist)	ChemoCentryx *Mountain View, CA*	diabetic nephropathy	Phase II www.chemocentryx.com
Cogenzia™ gentamicin implant	Innocoll *County Westmeath, Ireland*	diabetic foot ulcers	Phase III www.innocollinc.com
CTP-499 (PDE inhibitor)	Concert Pharmaceuticals *Lexington, MA*	diabetic nephropathy (adjunctive therapy)	Phase II www.concertpharma.com
CureXcell™ leukocyte cell therapy	Macrocure *Petach Tikva, Israel*	diabetic foot ulcers (adjunctive therapy)	Phase III www.macrocure.com
darapladib (Lp-PLA2 inhibitor)	GlaxoSmithKline *Research Triangle Park, NC*	diabetic macular edema	Phase II www.gsk.com
dexamethasone palmitate (intravetrious)	Santen *Emeryville, CA*	diabetic macular edema	Phase I/II www.santeninc.com
d-methadone	Relmada Therapeutics *New York, NY*	diabetic neuropathy	Phase I/II www.relmada.com
DSC127 (angiotensin receptor agonist)	Derma Sciences *Princeton, NJ*	diabetic foot ulcers	Phase III www.dermasciences.com
EVK-001 (metoclopramide intranasal)	Evoke Pharma *Solana Beach, CA*	diabetic gastroparesis	Phase II www.evokepharma.com

Diabetes-Related Conditions

Product Name	Sponsor	Indication	Development Phase
Eylea® aflibercept	Bayer HealthCare Pharmaceuticals *Whippany, NJ* Regeneron Pharmaceuticals *Tarrytown, NY*	diabetic macular edema	application submitted www.bayerpharma.com www.regeneron.com
finerenone	Bayer HealthCare Pharmaceuticals *Whippany, NJ*	diabetic nephropathy	Phase II www.bayerpharma.com
GKT137831	Genkyotex Innovation *Geneva, Switzerland*	diabetic nephropathy	Phase II www.genkyotex.com
GSK1278863 (prolyl hydroxylase inhibitor)	GlaxoSmithKline *Research Triangle Park, NC*	diabetic foot ulcers	Phase I www.gsk.com
HO/03/03 (protein kinase C-modulating inhibitors and stimulant)	HealOr *Ness Ziona, Israel*	diabetic foot ulcers	Phase II/III www.healor.com
H.P. Acthar® Gel repository corticotropin injection	Questcor Pharmaceuticals *Anaheim Hills, CA*	diabetic nephropathy	Phase II www.questcor.com
iCO-007 (antisense oligonucleotide)	iCo Therapeutics *Vancouver, Canada*	diabetic macular edema	Phase II www.icotherapeutics.com
Iluvien® fluocinolone acetonide micro-insert intravitreous implant	Alimera Sciences *Alpharetta, GA*	diabetic macular edema (Fast Track)	application submitted www.alimerasciences.com
Lucentis® ranibizumab (sustained delivery implant)	Genentech *South San Francisco, CA*	diabetic macular edema	Phase I www.gene.com
nepafenac	Alcon Laboratories *Fort Worth, TX*	diabetic retinopathy	Phase III www.alcon.com
Nexagon® antisense oligonucleotide	CoDa Therapeutics *San Diego, CA*	diabetic foot ulcers	Phase II www.codatherapeutics.com
NP-1998	Acorda Therapeutics *Ardsley, NY*	diabetic neuropathy	Phase II www.acorda.com
OC-10X	OcuCure Therapeutics *Roanoke, VA*	diabetic retinopathy	Phase I www.ocucure.com
Optina™ danazol low-dose	Ampio Pharmaceuticals *Greenwood Village, CA*	diabetic macular edema	Phase II www.ampiopharma.com

Diabetes-Related Conditions

Product Name	Sponsor	Indication	Development Phase
Ozurdex® dexamethasone ophthalmic (intravitreous)	Allergan *Irvine, CA*	diabetic macular edema	application submitted www.allergan.com
PDA002 (human placental-derived stem cell therapy)	Celgene *Summit, NJ*	diabetic foot ulcers	Phase I www.celgene.com
pexiganan	Dipexium Pharmaceuticals *White Plains, NY*	diabetic foot ulcers	Phase III www.dipexiumpharmaceuticals.com
PF-655 (RTP801i14)	Quark Pharmaceuticals *Fremont, CA*	diabetic macular edema	Phase II www.quarkpharma.com
PF-00489791	Pfizer *New York, NY*	diabetic nephropathy	Phase II www.pfizer.com
PF-04634817 (CCR2/5 antagonist)	Pfizer *New York, NY*	diabetic nephropathy	Phase II www.pfizer.com
pyridoxamine	NephroGenex *Research Triangle Park, NC*	diabetic nephropathy (Fast Track)	Phase II www.nephrogenex.com
RGN-259 eye drops (thymosin beta-4)	RegeneRx Biopharmaceuticals *Rockville, MD*	diabetic retinopathy	Phase II completed www.regenerx.com
RM-131 (ghrelin peptide agonist)	Rhythm Pharmaceuticals *Boston, MA*	diabetic gastroparesis	Phase II www.rhythmtx.com
SKL-NP	SK biopharmaceuticals *Fair Lawn, NJ*	diabetic neuropathy	Phase II www.skbp.com
sodium nitrite oral	TheraVasc *Cleveland, OH*	diabetic angiopathy	Phase II www.theravasc.com
TGF-α/epiregulin mAb (LY3016859)	Eli Lilly *Indianapolis, IN*	diabetic nephropathy	Phase I www.lilly.com
TGF-ß mAb (LY2382770)	Eli Lilly *Indianapolis, IN*	diabetic nephropathy	Phase II www.lilly.com
topical clonidine gel	BioDelivery Sciences International *Raleigh, NC*	diabetic neuropathy (Fast Track)	Phase II www.bdsi.com

Diabetes-Related Conditions

Product Name	Sponsor	Indication	Development Phase
Tradjenta® linagliptin	Boehringer Ingelheim Pharmaceuticals *Ridgefield, CT* Eli Lilly *Indianapolis, IN*	diabetic nephropathy	Phase III www.boehringer-ingelheim.com www.lilly.com
VM202 (modified hepatocyte growth factor gene therapy)	ViroMed *Seoul, South Korea* VM BioPharma *Atlanta, GA*	diabetic neuropathy	Phase II www.viromed.co.kr

The content of this report has been obtained through public, government and industry sources, and the Adis "R&D Insight" database based on the latest information. **Report current as of February 3, 2014.** *The medicines in this report include medicines being developed by U.S.-based companies conducting trials in the United States and abroad, PhRMA-member companies conducting trials in the United States and abroad, and foreign companies conducting clinical trials in the United States. The information in this report may not be comprehensive. For more specific information about a particular product, contact the individual company directly or go to* ***www.clinicaltrials.gov****. The entire series of Medicines in Development is available on PhRMA's website.*

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Glossary

application submitted—An application for marketing has been submitted by the company to the U.S. Food and Drug Administration (FDA).

diabetes—A chronic disease in which the body does not produce or properly use insulin, a hormone that is needed to convert sugar, starches and other food into energy needed for daily life. Symptoms may include excessive thirst, hunger, urination and weight loss. The cause of diabetes continues to be a mystery, although both genetics and environmental factors such as obesity and lack of exercise appear to play roles. **Type 1 diabetes**, the more severe form, results from the body's failure to produce insulin, which "unlocks" the cells of the body, allowing glucose to enter and fuel them. It is estimated that 5 percent to 10 percent of Americans who are diagnosed with diabetes have type 1, which requires insulin treatment. **Type 2 diabetes** results from insulin resistance (a condition in which the body fails to properly use insulin), combined with relative insulin deficiency. Most Americans who are diagnosed with diabetes have type 2, which in most cases can be controlled if treated properly by a combination of dietary measures, weight loss, and oral medication.

diabetic angiopathy—Similar to most complications brought about by diabetes, diabetic angiopathy is primarily due to hyperglycemia or the high levels of blood sugar known as glucose. Angiopathy can occur in any part of the body where the effect of high glucose levels result in the build-up of plaque in the inner walls of the vessels. There are two types of the disease—macroangiopathy or microangiopathy. In macroangiopathy, atherosclerosis and a resultant blood clot forms on the large blood vessels, sticks to the vessel walls, and blocks the flow of blood. Macroangiopathy may cause other complications, such as ischemic heart disease, stroke, and peripheral vascular disease, which contribute to the diabetic foot ulcers and the risk of amputation. In microangiopathy, the walls of the smaller blood vessels become so thick and weak that they bleed, leak protein, and slow the flow of blood through the body. The decrease of blood flow through clot formation impairs the flow of oxygen to cells and biological tissues (called ischemia) and leads to cellular death (necrosis and gangrene, which in turn may require amputation). Thus, tissues which are very sensitive to oxygen levels, such as the retina, develop microangiopathy and may cause blindness (so-called proliferative diabetic retinopathy). Damage to nerve cells may cause peripheral neuropathy, and to kidney cells, diabetic nephropathy.

diabetic gastroparesis—A disorder affecting people with both type 1 and type 2 diabetes in which the stomach takes too long to empty its contents (delayed gastric emptying). The vagus nerve controls the movement of food through the digestive tract. If the vagus nerve is damaged or stops working, the muscles of the stomach and intestines do not work normally, and the movement of food is slowed or stopped. Just as with other types of neuropathy (nerve damage), diabetes can damage the vagus nerve if blood glucose levels remain high over a long period of time. High blood glucose causes chemical changes in nerves and damages the blood vessels that carry oxygen and nutrients to the nerves. Gastroparesis can make diabetes worse by making it more difficult to manage blood glucose. When food that has been delayed in the stomach finally enters the small intestine and is absorbed, blood glucose levels rise. If food stays too long in the stomach, it can cause problems like bacterial overgrowth because the food has fermented. Also, the food can harden into solid masses, called bezoars, that may cause nausea, vomiting, and obstruction in the stomach. Bezoars can be dangerous if they block the passage of food into the small intestine.

diabetic nephropathy—Kidney disease or damage that can occur in people with diabetes. The kidneys have many tiny blood vessels that filter waste from the blood. High blood sugar from diabetes can destroy those blood vessels. Over time, the kidney isn't able to do its job as well and may stop working completely, which is called kidney failure. Out of 100 people with diabetes, as many as 40 will develop kidney damage. Currently, diabetic nephropathy is the leading cause of chronic kidney disease in the United States and other Western societies. It is also one of the most significant long-term complications in terms of morbidity and mortality for individual patients with diabetes, which is responsible for up to 40 percent of all end-stage renal disease (ESRD) cases in the United States.

diabetic neuropathy—Nerve damage in the arms, hands, legs, and feet caused by diabetes. The condition develops slowly and worsens over time. Depending on the types of nerves involved, one or more signs and symptoms may be present in diabetic peripheral neuropathy. *Sensory neuropathy* results in numbness or tingling in the feet or pain or discomfort in the feet or legs, including prickly, sharp pain or burning feet. *Motor neuropathy* involves muscle weakness and loss of muscle tone in the feet and lower legs, loss of balance, or changes in foot shape that can lead to areas of increased

pressure. *Autonomic neuropathy* results in dry feet and cracked skin. The loss of sensation and other problems associated with nerve damage make a patient prone to developing skin ulcers (open sores) that can become infected and may not heal. This serious complication of diabetes can lead to the loss of a foot, a leg, or even a life.

diabetic retinopathy—The most common diabetic eye disease and a leading cause of blindness in American adults. It is caused by changes in the blood vessels of the retina, the light sensitive tissue at the back of the eye that is necessary for good vision. In some people with diabetic retinopathy, blood vessels may swell and leak fluid. In others, abnormal new blood vessels grow on the surface of the retina. Over time, diabetic retinopathy, which usually affects both eyes, can worsen and cause vision loss. The condition has four stages: 1) mild nonproliferative retinopathy, the earliest stage during which microaneurysms occur in the retina's tiny blood vessels; 2) moderate nonproliferative retinopathy, during which some blood vessels that nourish the retina are blocked; 3) severe nonproliferative retinopathy, when many more blood vessels are blocked and deprive several areas of the retina with their blood supply; and 4) proliferative retinopathy, the advanced stage when signals sent by the retina for nourishment trigger the growth of new blood vessels, which grow along the retina and the surface of the clear, vitreous gel that fills the inside of the eye. If those thin, fragile blood vessels leak blood, severe vision loss and even blindness can result. Up to 45 percent of Americans diagnosed with diabetes have some stage of diabetic retinopathy.

diabetic ulcers—The most common foot injuries leading to lower extremity amputation. The vast majority of diabetic foot complications resulting in amputation begin with the formation of skin ulcers. The three main causes of diabetic foot ulcers are: neuropathy, poor blood supply, and infection. Up to 15 percent of diabetics are likely to develop a foot ulcer at some stage in their lives. Early detection and appropriate treatment of those ulcers may prevent up to 85 percent of amputations. The risk of lower extremity amputation is 15 to 46 times higher in diabetics than in people who do not have the disease.

Fast Track—A process designed to facilitate the development and expedite the review of drugs to treat serious diseases and fill an unmet medical need. The status is assigned by the U.S. Food and Drug Administration. The purpose is to get important new drugs to the patient earlier. Fast Track addresses a broad range of serious diseases. Generally, determining factors include whether the drug will have an impact on such factors as survival, day-to-day functioning, or the likelihood that the disease, if left untreated, will progress from a less severe condition to a more serious one. Filling an unmet medical need is defined as providing a therapy where none exists, or providing a therapy which may be potentially superior to existing therapy. Once a drug receives Fast Track designation, early and frequent communication between the FDA and a drug company is encouraged throughout the entire drug development and review process. The frequency of communication assures that questions and issues are resolved quickly, often leading to earlier drug approval and access by patients.

macular edema—A condition in which fluid can leak into the center of the macula, the part of the eye where sharp, straight-ahead vision occurs. The fluid makes the macula swell, thus blurring vision. It can occur at any stage of **diabetic retinopathy**, although it is more likely to occur as the disease progresses. About half of the people with proliferative retinopathy also have macular edema.

metabolic syndrome—A group of metabolic risk factors that raise the risk of type 2 diabetes in one person, including: abdominal obesity (excessive fat tissue in and around the abdomen); atherogenic dyslipidemia (blood fat disorders—high triglycerides, low HDL cholesterol, and high

NCE—New chemical entity.

Orphan Drug—A drug to treat a disease that has a patient population of 200,000 or less in the United States, or a disease that has a patient population of more than 200,000 and a development cost that will not be recovered from sales in the United States.

Phase 0—First-in-human trials conducted in accordance with FDA's 2006 guidance on exploratory Investigational New Drug (IND) studies designed to speed up development of promising drugs by establishing very early whether the tested compound behaves in human subjects as was anticipated from preclinical studies.

Phase I—Researchers test the drug in a small group of people, usually between 20 and 80 healthy adult volunteers, to evaluate its initial safety and tolerability profile, determine a safe dosage range, and identify potential side effects.

Phase II—The drug is given to volunteer patients, usually between 100 and 300, to see if it is effective, identify an optimal dose, and to further evaluate its short-term safety.

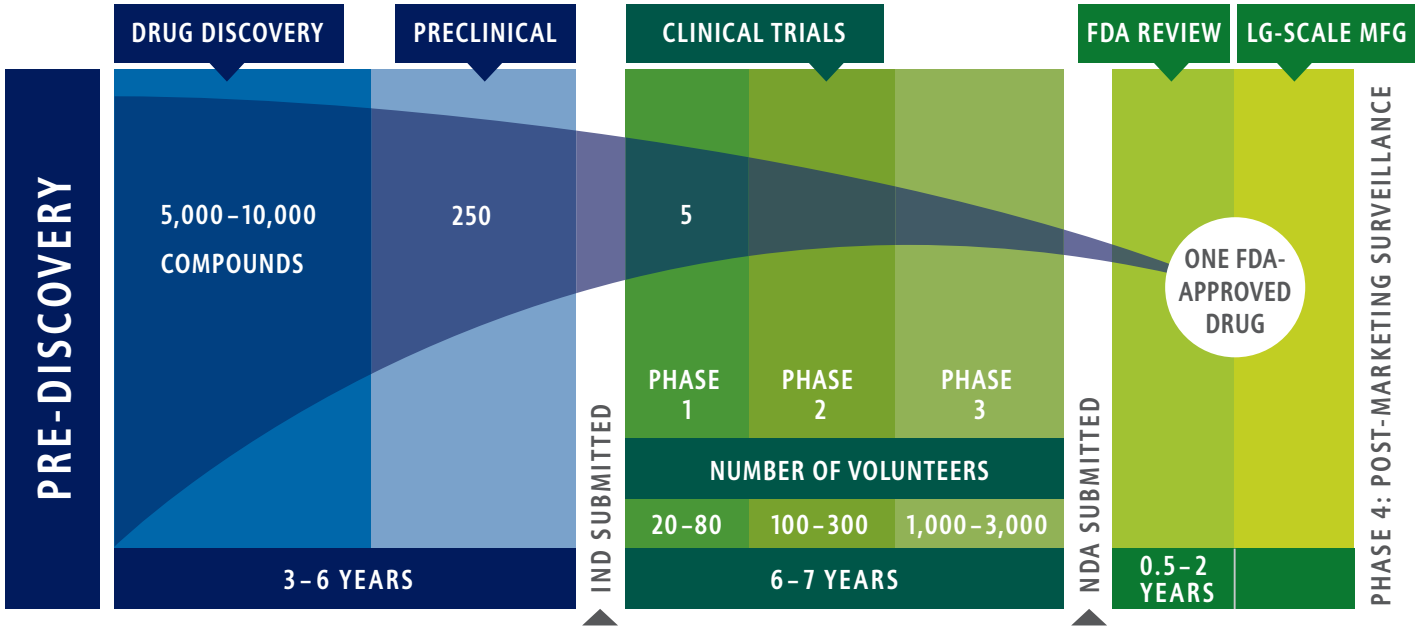
Phase III—The drug is given to a larger, more diverse patient population, often involving between 1,000 and 3,000 patients (but sometimes many more thousands), to generate statistically significant evidence to confirm its safety and effectiveness. They are the longest studies, and usually take place in multiple sites around the world.

Prediabetes—A condition characterized by higher than normal blood glucose levels but not yet high enough to be diagnosed as diabetes. Prediabetes puts people at a higher risk for developing type 2 diabetes and cardiovascular disease.

The Drug Discovery, Development and Approval Process

Developing a new medicine takes an average of 10-15 years;
For every 5,000-10,000 compounds in the pipeline, only 1 is approved.

Drug Discovery and Development: A LONG, RISKY ROAD



The Drug Development and Approval Process

The U.S. system of new drug approvals is perhaps the most rigorous in the world.

It takes 10-15 years, on average, for an experimental drug to travel from lab to U.S. patients, according to the Tufts Center for the Study of Drug Development. Only five in 5,000 compounds that enter preclinical testing make it to human testing. And only one of those five is approved for sale.

On average, it costs a company $1.2 billion, including the cost of failures, to get one new medicine from the laboratory to U.S. patients, according to a recent study by the Tufts Center for the Study of Drug Development.

Once a new compound has been identified in the laboratory, medicines are usually developed as follows:

Preclinical Testing. A pharmaceutical company conducts laboratory and animal studies to show biological activity of the compound against the targeted disease, and the compound is evaluated for safety.

Investigational New Drug Application (IND). After completing preclinical testing, a company files an IND with the U.S. Food and Drug Administration (FDA) to begin to test the drug in people. The IND shows results of previous experiments; how, where and by whom the new studies will be conducted; the chemical structure of the compound; how it is thought to work in the body; any toxic effects found in the animal studies; and how the compound is manufactured. All clinical trials must be reviewed and approved by the Institutional Review Board (IRB) where the trials will be conducted. Progress reports on clinical trials must be submitted at least annually to FDA and the IRB.

Clinical Trials, Phase I—Researchers test the drug in a small group of people, usually between 20 and 80 healthy adult volunteers, to evaluate its initial safety and tolerability profile, determine a safe dosage range, and identify potential side effects.

Clinical Trials, Phase II—The drug is given to volunteer patients, usually between 100 and 300, to see if it is effective, identify an optimal dose, and to further evaluate its short-term safety.

Clinical Trials, Phase III—The drug is given to a larger, more diverse patient population, often involving between 1,000 and 3,000 patients (but sometime many more thousands), to generate statistically significant evidence to confirm its safety and effectiveness. They are the longest studies, and usually take place in multiple sites around the world.

New Drug Application (NDA)/Biologic License Application (BLA). Following the completion of all three phases of clinical trials, a company analyzes all of the data and files an NDA or BLA with FDA if the data successfully demonstrate both safety and effectiveness. The applications contain all of the scientific information that the company has gathered. Applications typically run 100,000 pages or more.

Approval. Once FDA approves an NDA or BLA, the new medicine becomes available for physicians to prescribe. A company must continue to submit periodic reports to FDA, including any cases of adverse reactions and appropriate quality-control records. For some medicines, FDA requires additional trials (Phase IV) to evaluate long-term effects.

Discovering and developing safe and effective new medicines is a long, difficult, and expensive process. PhRMA member companies invested an estimated $48.5 billion in research and development in 2012.