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Sample Report

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FDA APPROVED

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6 **Fast-track Designations** designations were awarded, including for **PR001**, an adeno-associated virus–based gene therapy sponsored by Prevail Therapeutics for the treatment of **GBA1 mutation–positive Parkinson disease**.

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IN THE PIPELINE

25 **Late-phase** clinical trial announcements.

- **AstraZeneca's Lokelma** is the first-ever randomized, placebo-controlled trial to evaluate a potassium binder in patients on stable hemodialysis.
- New data suggest that **tirzepatide treatment** may be effective not only in lowering hemoglobin A1C and body weight in people with type 2 diabetes but also in treating other metabolic conditions.
- New trial results from an evaluation of **Lynparza (olaparib)** have shown that this drug is the first and only poly adenosine diphosphate–ribose polymerase inhibitor to demonstrate efficacy over chemotherapy for the treatment of advanced ovarian cancer.

WHAT TO EXPECT

13 **Drugs** with goal dates in **July** and **August.**

Introduction

The FDA approved 17 new drugs in June, including the first-ever treatments for hypoactive sexual desire disorder (Vyleesi [bremelanotide]) and neuromyelitis optica spectrum disorder (Soliris [eculizumab]) as well as a new drug to treat type 2 diabetes in pediatric patients (Victoza [liraglutide]).

By this time last year, the FDA had approved 20 new molecular entities as opposed to the 14 approved so far this year, prompting analysts to speculate about the pace of drug approvals under the new FDA commissioner.[1,2] Janet Woodcock, director of the FDA's Center for Drug Evaluation and Research, emphasized that the agency is still committed to accelerating drug development and approvals. Woodcock, speaking at the Silicon Valley Bank Leerink Therapeutics Day in Boston, said that the pace of new approvals would stay steady or even increase. She explained that the **FDA has been adapting to the pharmaceutical industry's shift toward developing therapies for serious, difficult-to-treat diseases and that the industry is just beginning to see the fruits of human genome sequencing, which will result in more drug approvals in the future .**[1,2]

The results of 25 late-phase clinical trials were announced in June, and additional strides were made in the field of diabetes, as recent clinical trial results indicated that a single course of the immunotherapy drug teplizumab may delay the onset of type 1 diabetes by nearly 50% in individuals at risk of developing the disease. In addition, a trial of the sodium glucose cotransporter 2 (SGLT2) inhibitor Invokana (canagliflozin) showed that for the first time, a medicine to treat type 2 diabetes had a cardiovascular benefit in patients who did not have preexisting cardiovascular disease.

This report, which has been drawn from industry news, FDA updates, and company press releases, provides a concise, high-level overview of the drug development pipeline in June 2019. It compiles the most current list of nongeneric drugs approved by the FDA during this period, regulatory designations that indicate upcoming approvals, and phase 3 clinical trial announcements. Finally, this report provides a preview of drugs that are currently under review by the FDA, with approval decisions expected in July and August.

*Approvals include new drug applications (NDAs), supplemental new drug applications (sNDAs), biologics license applications (BLAs), and supplemental biologics license applications (sBLAs). New formulations of existing drugs are not included in this report, nor are generic drugs and biosimilars.

FDA Drug and Biologic Approvals and Rejections: June 2019

The FDA approved 17 new drugs† in June, which included 2 new molecular entities and 15 supplemental approvals. June's drug approvals include a number of firsts: the first-ever approved treatment for hypoactive sexual desire disorder (AMAG Pharmaceuticals' Vyleesi), the first approved treatment for neuromyelitis optica spectrum disorder (Alexion Pharmaceuticals' Soliris), and the first noninsulin drug approved to treat type 2 diabetes in pediatric patients since metformin was approved for pediatric use in 2000 (Novo Nordisk's Victoza). The FDA granted accelerated approval to 2 drugs: Merck's Keytruda (pembrolizumab) for the treatment of metastatic small cell lung cancer and Genentech's Polivy (polatuzumab vedotin-piiq) for the treatment of relapsed or refractory diffuse large B-cell lymphoma.

June's approvals also included a new indication for the previously FDA-approved drug Zerbaxa (ceftolozane and tazobactam) for the treatment of hospital-acquired bacterial pneumonia (HABP) and ventilator-associated bacterial pneumonia (VABP). According to data from the Centers for Disease Control and Prevention, HABP and VABP are together the second most common type of hospital-acquired infection in the United States and are a common problem in the intensive care unit setting.

Details of June's drug approvals are provided in Table 1 below.

† Approvals include new drug applications (NDAs), supplemental new drug applications (sNDAs), biologics license applications (BLAs), and supplemental biologics license applications (sBLAs). New formulations of existing drugs are not included in this report, nor are generic drugs and biosimilars.

Table 1. Drug Approvals, June 2019

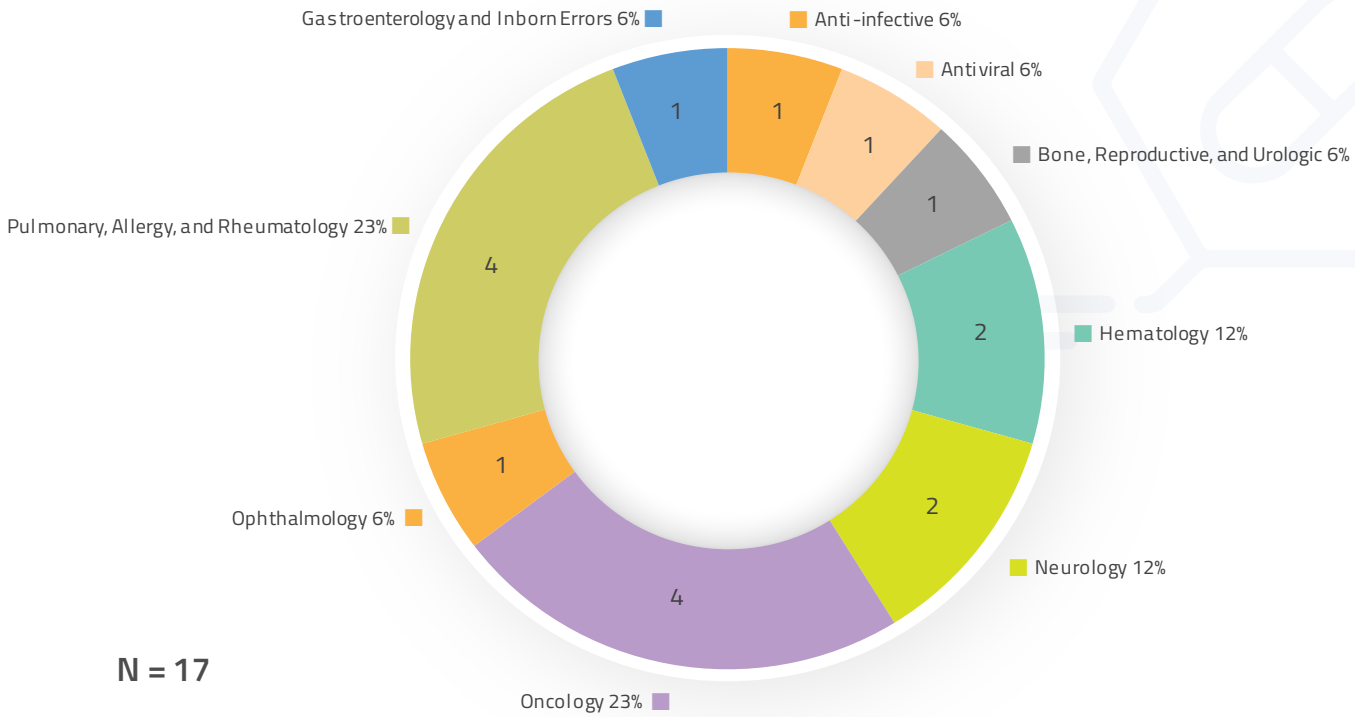
Date of Approval	Company	Trade Name (Generic Name)	New or Expanded Indication
Anti-infective			
6/3/19	Merck Sharp & Dohme Corp	Zerbaxa (ceftolozane and tazobactam)	For the treatment of nosocomial pneumonia, including ventilator-associated pneumonia caused by certain susceptible gram-negative microorganisms, in adults
Antiviral			
6/18/19	Gilead Sciences, Inc	Biktarvy (bictegravir, emtricitabine, and tenofovir alafenamide)	As a complete regimen for the treatment of human immunodeficiency virus type 1 infection in pediatric patients weighing at least 25 kg who have no antiretroviral treatment history or to replace the current antiretroviral regimen
Bone, Reproductive, and Urologic			
6/21/19	AMAG Pharmaceuticals, Inc	Vyleesi (bremelanotide)	For premenopausal women with acquired, generalized hypoactive sexual desire disorder, as characterized by low sexual desire that causes marked distress or interpersonal difficulty and is not due to a coexisting medical or psychiatric condition, problems with the relationship, or the effects of a medication or drug substance
Gastroenterology and Inborn Errors			
6/17/19	Novo Nordisk Inc	Victoza (liraglutide)	As an adjunct to diet and exercise to improve glycemic control in patients aged 10 years and older with type 2 diabetes

Date of Approval	Company	Trade Name (Generic Name)	New or Expanded Indication
Hematology			
6/27/19	Dova Pharmaceuticals, Inc	Doptelet (avatrombopag)	For the treatment of chronic immune thrombocytopenia in adults
Neurology			
6/4/19	Eli Lilly and Co	Emgality (galcanezumab-gnlm)	For the treatment of episodic cluster headaches in adults
6/7/19	PTC Therapeutics, Inc	Emflaza (deflazacort)	For the treatment of Duchenne muscular dystrophy in patients aged 2 years and older
Oncology			
6/10/19	Genentech, Inc	Polivy (polatuzumab vedotin-piiq)	Given in combination with bendamustine and a rituximab product for the treatment of relapsed or refractory diffuse large B-cell lymphoma in adults
6/10/19	Merck Sharp & Dohme Corp	Keytruda (pembrolizumab)	Given in combination with platinum and fluorouracil for the first-line treatment of metastatic or unresectable recurrent head and neck squamous cell carcinoma
6/17/19	Merck Sharp & Dohme Corp	Keytruda (pembrolizumab)	For the treatment of metastatic small cell lung cancer in patients with disease progression on or after platinum-based chemotherapy and at least one other prior line of therapy
6/27/19	Janssen Pharmaceuticals, Inc	Darzalex (daratumumab)	Given in combination with lenalidomide and dexamethasone for the treatment of newly diagnosed multiple myeloma in patients who are ineligible for autologous stem cell transplantation and in patients with relapsed or refractory multiple myeloma who have received at least one prior therapy
Ophthalmology			
6/27/19	Alexion Pharmaceuticals Inc	Soliris (eculizumab)	For the treatment of neuromyelitis optica spectrum disorder in adults who are anti–aquaporin-4 antibody positive
Pulmonary, Allergy, and Rheumatology			
6/6/19	GlaxoSmithKline plc	Anoro Ellipta (umeclidinium bromide and vilanterol)	For the maintenance treatment of chronic obstructive pulmonary disease
6/6/19	GlaxoSmithKline plc	Incruse Ellipta (umeclidinium bromide)	For the maintenance treatment of chronic obstructive pulmonary disease
6/21/19	Vertex Pharmaceuticals, Inc	Symdeko (tezacaftor/ivacaftor and ivacaftor)	For patients aged 6 years and older with cystic fibrosis who are homozygous for the F508del mutation or who have at least one mutation in the cystic fibrosis transmembrane conductance regulator gene
6/27/19	Regeneron Pharmaceuticals, Inc	Dupixent (dupilumab)	As an add-on maintenance treatment for adults with inadequately controlled chronic rhinosinusitis with nasal polyposis

Source: Drugs@FDA: FDA approved drug products. US Food & Drug Administration website. http://www.accessdata.fda.gov/scripts/cder/drugsatfda/.

A breakdown of June's drug approvals, categorized by therapeutic area, is shown in Figure 1.

Figure 1. Drug Approvals by Therapeutic Area, June 2019



The FDA issued 3 **complete response letters (CRLs)** in June. Glenmark Pharmaceuticals received a CRL for Ryaltris (olopatadine hydrochloride and mometasone furoate), currently under review for the treatment of seasonal allergic rhinitis.[3] Acer Therapeutics received a CRL citing the need for additional clinical data for Edsivo (celiprolol) for the treatment of vascular Ehlers-Danlos syndrome, a rare disease that affects the skin, joints, and blood vessels.[4] AstraZeneca received a CRL for Farxiga (dapagliflozin), an SGLT2 inhibitor under review as an adjunct to insulin to improve glycemic control in adults with type 1 diabetes. This CRL came just 3 months after the FDA rejected Sanofi's Zynquista (sotagliflozin), a dual SGLT1/2 inhibitor.[5]

Drug Approval Highlights

Drug Development in Women's Health

On June 21, the FDA approved AMAG Pharmaceuticals' Vyleesi to treat acquired, generalized hypoactive sexual desire disorder in premenopausal women. Hypoactive sexual desire disorder is characterized by low sexual desire that causes marked distress or interpersonal difficulty and is not due to a coexisting medical or psychiatric condition, problems within the relationship, or the effects of a medication or other drug substance.

The approval of Vyleesi marks another milestone in the rapidly expanding area of women's health. Both the FDA and pharmaceutical industry have identified advancements in women's health as a key priority.[6,7] In 2012, the FDA identified female sexual dysfunction as 1 of 20 disease areas needing focused attention, and in 2014, the agency held a public meeting to advance its understanding of female sexual dysfunction, during which it solicited perspectives directly from patients about their condition and its impact on daily life.[6]

This year, the FDA has approved Duchesnay's Osphena (ospemifene), indicated for the treatment of dyspareunia (pain during sexual intercourse), Sage Therapeutics' Zulresso (brexanolone), the first-ever treatment for postpartum depression, Amgen's Evenity (romosozumab), a treatment for osteoporosis in women, and several drugs for cancers affecting women.

Focus: Upcoming Therapies With Special Designations

The FDA grants **expedited regulatory designations** to hasten the approval of drugs that have the potential to treat serious, life-threatening, or underserved conditions. These designations include **priority review**, **fast track**, **breakthrough therapy**, and **accelerated approval**.‡ The FDA also has a **rare pediatric disease priority review voucher program**, which allows a sponsor who receives an approval for a drug or biologic for a rare pediatric disease to qualify for a voucher that can be redeemed to receive a priority review of a subsequent marketing application for a different product. Companies may announce the award of such designations, and this serves as an indicator of a drug's progress toward approval, although the timeline for approval varies based on the current status of the drug's individual development program.

In June 2019, the FDA awarded 1 breakthrough therapy designation and 6 fast-track designations, and it granted priority reviews to 6 new drugs.

Breakthrough therapy designations designations are awarded to drugs that have the potential for a significant positive clinical impact. The following drug was granted a breakthrough therapy designation in June:

- **Avexitide**, sponsored by Eiger BioPharmaceuticals, under investigation for the treatment of community-acquired bacterial pneumonia in adults

Fast-track designations were awarded to the following drugs in June:

- **PR001**, an adeno-associated virus–based gene therapy sponsored by Prevail Therapeutics for the treatment of *GBA1* mutation–positive Parkinson disease
- **Momelotinib**, sponsored by Sierra Oncology for the treatment of intermediate- or high-risk myelofibrosis
- **ARO-AAT**, a novel RNA interference therapeutic sponsored by Arrowhead Pharmaceuticals for the treatment of a rare genetic liver disease associated with alpha-1 antitrypsin deficiency
- **Jardiance** (empagliflozin), sponsored by Eli Lilly to reduce the risk of cardiovascular death and hospitalization for heart failure in patients with chronic heart failure
- **CLR 131**, sponsored by GlaxoSmithKline for the treatment of advanced ovarian, fallopian tube, or primary peritoneal cancer in patients who have had at least 3 prior chemotherapy regimens
- **Zejula** (niraparib), being developed by Imara for the treatment of sickle cell disease

Priority review designations were granted to the following drugs in June:

- **Baxdela** (delafloxacin), sponsored by Melinta Therapeutics for the treatment of community-acquired bacterial pneumonia in adults
- **Ultomiris** (ravulizumab-cwvz), sponsored by Alexion Pharmaceuticals for the treatment of atypical hemolytic uremic syndrome
- **Zejula**, sponsored by GlaxoSmithKline for the treatment of advanced ovarian, fallopian tube, or primary peritoneal cancer in patients who have had at least 3 prior chemotherapy regimens
- **Talicia** (rifabutin, amoxicillin, and omeprazole), sponsored by RedHill Biopharma for the treatment of *Helicobacter pylori* infection
- **Rituxan** (rituximab), sponsored by Genentech for the treatment of granulomatosis with polyangiitis and microscopic polyangiitis in children aged 2 years and older
- **Upadacitinib** sponsored by AbbVie for the treatment of moderate to severe rheumatoid arthritis in adults

‡ In addition to the regulatory designations listed here, the FDA awards orphan drug designations. These are not included in this report, however, because they do not necessarily expedite the FDA's review process.

Phase 3 and 4 Clinical Trial Updates

The results of 25 late-phase clinical trials were announced in June. The announcement of positive trial results does not necessarily indicate trial completion, but a company may submit a **new drug application (NDA)**, **supplemental new drug application (sNDA)**, new biologics license application (BLA), or supplemental biologics license application (sBLA) soon after or, in some instances, before obtaining phase 3 trial results, so clinical trial announcements are another indicator of drugs coming to the market. In addition, clinical trial announcements provide insight into the areas in which individual pharmaceutical companies are focusing their drug development efforts and whether the areas of active development are succeeding or not. The details of the clinical trial announcements from June are provided in Table 2 below.

Table 2. June 2019 Clinical Trial Announcements[a]

Company	Drug Name (Generic Name)	Trial Name and Indication	Noteworthy
Antiviral			
Shionogi & Co, Ltd (with Genentech, Inc)	Xofluza (baloxavir marboxil)	BLOCKSTONE; for the prophylaxis treatment of influenza infection	Xofluza treatment significantly reduced the likelihood of people developing the flu after exposure to an infected household member. An application has been submitted to the FDA, with a decision expected in November.
Cardiovascular and Renal			
AstraZeneca plc	Lokelma (sodium zirconium silicate)	DIALIZE; for the treatment of hyperkaliemia in patients with end-stage renal disease on hemodialysis	Results from DIALIZE showed that 41% of patients treated with Lokelma maintained normal predialysis potassium levels compared with 1% of patients treated with placebo. Lokelma was approved for the treatment of hyperkalemia last year; however, patients on dialysis were excluded from earlier studies. This is the first-ever randomized, placebo-controlled trial to evaluate a potassium binder in patients on stable hemodialysis.
Dermatology and Dental			
AbbVie Inc	Skyrizi (risankizumab-rzaa)	IMMhance; for the treatment of plaque psoriasis	After continuous treatment for 2 years, 72% of patients treated with Skyrizi saw a 100% improvement in their Psoriasis Area and Severity Index score.
Genentech, Inc	Rituxan (rituximab)	PEMPHIX; for the treatment of moderate to severe pemphigus vulgaris in adults	PEMPHIX results suggest that Rituxan may provide complete remission rates and successful tapering of corticosteroid therapy in patients with pemphigus vulgaris, making it superior to mycophenolate mofetil, an unapproved treatment for this condition that is accepted as the standard of care.
Gastroenterology and Inborn Errors			
AstraZeneca plc	Farxiga (dapagliflozin)	DECLARE-TIMI 58; to reduce the risk of kidney function decline, end-stage renal disease, and renal death in patients with type 2 diabetes	Farxiga treatment was associated with a 47% reduction in the combined risk of kidney function decline, end-stage renal disease, and renal death in patients with type 2 diabetes. Despite these findings, the FDA rejected approval of Farxiga this month.

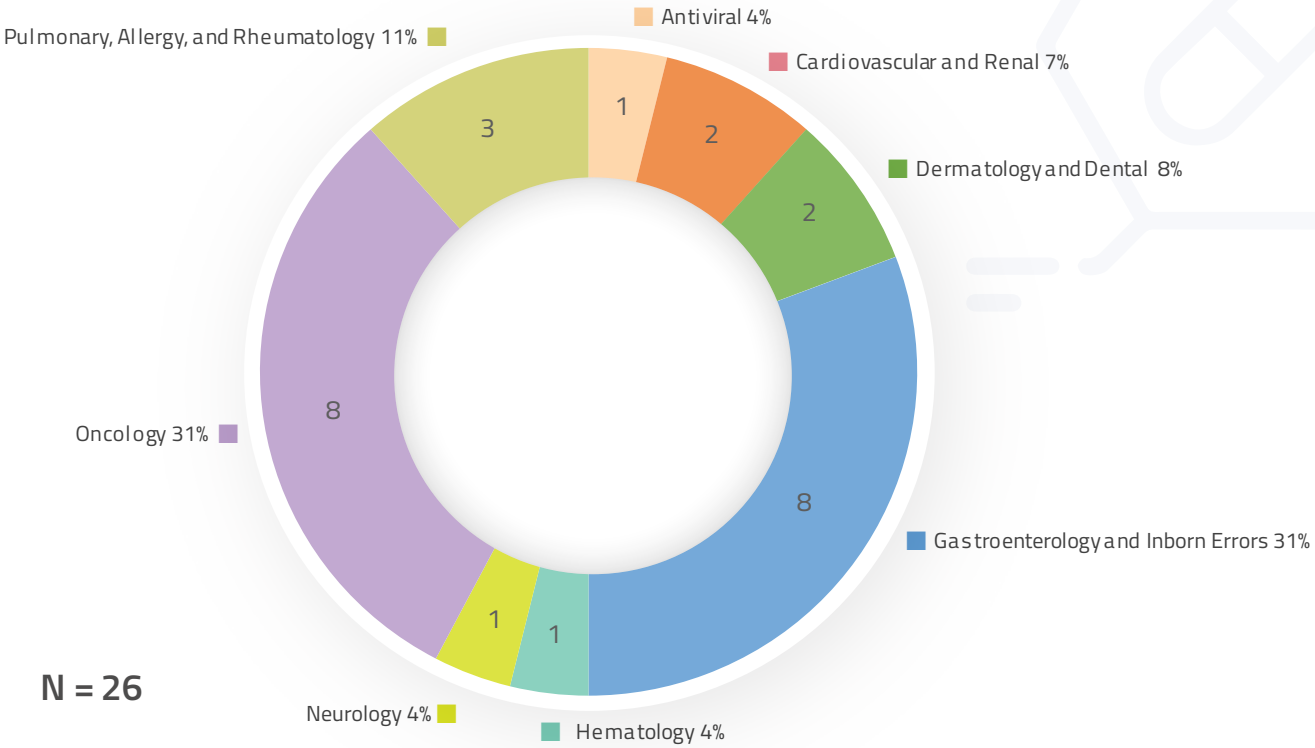
Boehringer Ingelheim and Eli Lilly and Co	Tradjenta (linagliptin)	CAROLINA; to reduce the cardiovascular risk in patients with type 2 diabetes	Results from the CAROLINA trial show that there is not an increased cardiovascular risk associated with Tradjenta treatment compared with treatment with a generic, glimepiride, in the only active-comparator cardiovascular outcome trial for a dipeptidyl peptidase 4 inhibitor.
Cancer Prevention Pharmaceuticals, Inc	CPP-1X/sul (eflornithine and sulindac)	For the treatment of familial adenomatous polyposis in adults	Treatment with eflornithine and sulindac was not superior to treatment with either eflornithine or sulindac alone in the overall population, but the combination showed significant improvements in delaying surgical events in the lower gastrointestinal tract.
Eli Lilly and Co	Tirzepatide	To lower hemoglobin A1C and body weight in people with type 2 diabetes	New data suggest tirzepatide treatment may be effective not only in lowering hemoglobin A1C levels and body weight in people with type 2 diabetes but also in treating other metabolic conditions.
Eli Lilly and Co	Trulicity (dulaglutide)	REWIND; to reduce major cardiovascular events in a broad range of patients with type 2 diabetes	Results from REWIND showed that treatment with Trulicity resulted in a 12% reduction in major cardiovascular events in people with and without established cardiovascular disease. REWIND is the longest cardiovascular outcome trial in the glucagon-like peptide 1 receptor agonist class. The 12% risk reduction, however, looks similar to the 13% achieved by Victoza in Novo Nordisk's LEADER trial.
Johnson & Johnson	Invokana (canagliflozin)	CREDENCE; to reduce the risk of major cardiovascular events and kidney failure in patients with type 2 diabetes and chronic kidney disease	Invokana exhibited benefit in patients both with and without known cardiovascular disease. This is the first time a medicine for type 2 diabetes has shown a cardiovascular benefit in patients who did not have preexisting cardiovascular disease.
Novo Nordisk A/S	Victoza (liraglutide)	NewLira; for the treatment of type 1 diabetes	Victoza, when taken every day, preserved postprandial insulin secretion for 1 year after patients' type 1 diabetes diagnosis. Victoza was approved by the FDA this month as an adjunct to diet and exercise to improve glycemic control in patients aged 10 years and older with type 2 diabetes.
Novo Nordisk A/S	Ozempic (semaglutide)	PIONEER 6; as an adjunct to diet and exercise to improve blood sugar in adults with type 2 diabetes	New data showed that Ozempic met the noninferiority criteria for a reduction in major adverse cardiovascular events compared with placebo and compared with the standard of care. This drug is under priority review by the FDA, with a goal date in September.
Hematology			
Global Blood Therapeutics, Inc	Voxelotor	HOPE; for the treatment of sickle cell disease	While patients treated with voxelotor in the HOPE trial experienced a statistically significant "hemoglobin response," the drug failed to demonstrate a significant effect on a secondary end point, vaso-occlusive crisis, a type of acute pain episode experienced by patients with sickle cell disease. Despite this, the company plans to file for accelerated approval this year.
Neurology			
Alnylam Pharmaceuticals, Inc	Onpattro (patisiran)	APOLLO; for the treatment of polyneuropathy of hereditary transthyretin amyloidosis	A new analysis of the phase 3 APOLLO study showed that patients who were previously treated with Pfizer's tafamidis and who received patisiran for 18 months showed significant improvements in polyneuropathy and quality-of-life measures.

Oncology			
Astex Pharmaceuticals Inc and Otsuka Pharmaceutical Co, Ltd	ASTX727 (cedazuridine and decitabine)	ASCERTAIN; for the treatment of intermediate- and high-risk myelodysplastic syndromes or chronic myelomonocytic leukemia	Results showed that the fixed-dose combination delivers a pharmacokinetically equivalent exposure to decitabine. Astex plans to file an NDA with the FDA by the end of 2019.
AstraZeneca plc	Calquence (acalabrutinib)	ASCEND; for the treatment of previously treated chronic lymphocytic leukemia	An encouraging 88% of patients on Calquence remained free of disease progression after 12 months compared with 68% of patients on rituximab combined with idelalisib or bendamustine.
AstraZeneca plc	Calquence (acalabrutinib)	ASCEND; for the treatment of relapsed or refractory chronic lymphocytic leukemia	Calquence significantly delayed disease progression in relapsed or refractory chronic lymphocytic leukemia compared with both idelalisib and bendamustine.
AstraZeneca plc	Calquence (acalabrutinib)	ELEVATE-TN; for the treatment of chronic lymphocytic leukemia in treatment-naïve patients	Calquence in combination with obinutuzumab demonstrated a statistically significant and clinically meaningful improvement in progression-free survival compared with the chemotherapy-based combination of chlorambucil and obinutuzumab.
AstraZeneca plc	Imfinzi (durvalumab)	CASPIAN; for the first-line treatment of small cell lung cancer	Imfinzi plus chemotherapy resulted in a statistically significant and clinically meaningful improvement in overall survival at an interim analysis.
AstraZeneca plc and Merck Sharp & Dohme Corp	Lynparza (olaparib)	POLO; for the first-line maintenance treatment of germline BRCA-mutated metastatic pancreatic cancer that has not progressed following standard-of-care, platinum-based, first-line chemotherapy	In POLO, 22% of patients who received Lynparza remained free of disease progression after 2 years compared with 10% of patients who received placebo. Lynparza is now the first poly adenosine diphosphate–ribose polymerase inhibitor to demonstrate benefit in 3 different cancer types.
AstraZeneca plc and Merck Sharp & Dohme Corp	Lynparza (olaparib)	SOLO3; for the treatment of germline *BRCA1/2*-mutated advanced ovarian cancer in patients who have received 2 or more prior lines of chemotherapy	Treatment with Lynparza resulted in a statistically significant and clinically meaningful improvement in the objective response rate compared with chemotherapy. Lynparza is the first and only poly adenosine diphosphate–ribose polymerase inhibitor to demonstrate efficacy over chemotherapy in this indication.
Bristol-Myers Squibb Company and Pfizer Inc	Opdivo (nivolumab)	CheckMate-459; for the first-line treatment of unresectable hepatocellular carcinoma	The trial did not achieve statistical significance for its primary end point of overall survival; however, treatment with Opdivo resulted in a clear trend toward improvement in overall survival compared with treatment with sorafenib, a current standard of care.
Pulmonary, Allergy, and Rheumatology			
AbbVie Inc	ABT-494 (upadacitinib)	SELECT-EARLY and SELECT-COMPARE; given in combination with methotrexate for the treatment of moderate to severe rheumatoid arthritis	The trials showed that treatment with upadacitinib and methotrexate improved the signs and symptoms of rheumatoid arthritis. This drug is under FDA review, with a decision expected in the third quarter of 2019.
Genentech, Inc	Xolair (omalizumab)	POLYP 1 and POLYP 2; for the treatment of chronic rhinosinusitis with nasal polyps in adults who have not adequately responded to intranasal corticosteroids	Results demonstrated a statistically significant and clinically relevant improvement in both coprimary end points. The results from these pivotal studies provided further support that immunoglobulin E plays a role in inflammatory and respiratory conditions.
Savara Pharmaceuticals, Inc	Molgradex (molgramostim)	IMPALA; for the treatment of autoimmune alveolar pulmonary proteinosis	Patients treated with Molgradex did not experience a statistically significant benefit in lung function compared with patients who took placebo. Still, Savara executives expressed hope that the FDA would take a friendly view of Molgradex based on improvements in patient-reported quality-of-life scores.

[a] References available upon request.

A breakdown of all June clinical trial announcements by therapeutic area is shown in Figure 2 below.

Figure 2. June 2019 Clinical Trial Announcements by Therapeutic Area



Clinical Trial Highlights

Advances in Type 2 Diabetes: Cardiovascular Benefits and a Promising Immunotherapy

The American Diabetes Association annual meeting took place June 7 through June 11 in San Francisco, California. The meeting highlighted the industry's current focus on cardiovascular and renal outcomes in the prevention and management of type 2 diabetes. The CAROLINA trial, for example, is the first active-comparator cardiovascular outcome study to compare 2 commonly used antidiabetic medications, sulfonylurea glimepiride and the dipeptidyl peptidase 4 inhibitor Tradjenta (linagliptin).[8] The trial examined the 2 drugs in a cohort of more than 6000 adults with type 2 diabetes and found no differences for the incidences of nonfatal myocardial infarction, nonfatal stroke, and cardiovascular death during a median of 6 years.[8] Several other trials focused on drugs' effects on kidney disease and nonalcoholic steatohepatitis (NASH).[9]

"It's remarkable to see that a single course of two-week therapy cut the incidence of diabetes by almost 50% during this trial. These data clearly tell us short-term immunotherapy can significantly slow down clinical onset of diabetes. Developing immuno-modulatory drugs that don't require continuous treatment to impact autoimmune disease is a major paradigm shift."

Results from a midstage trial (sponsored by the National Institutes of Health and conducted in collaboration with

Provention Bio) showed that immunotherapy may delay the onset of type 1 diabetes in individuals at risk of developing the disease.10 The results showed that the anti-CD3 monoclonal antibody teplizumab significantly delayed the onset and diagnosis of clinical type 1 diabetes by a median of 2 years over placebo in children and adults considered to be at high risk. During the trial, 72% of patients in the placebo arm developed clinical diabetes compared with only 43% of patients in the teplizumab arm. "It's remarkable to see that a single course of two-week therapy cut the incidence of diabetes by almost 50% during this trial. These data clearly tell us short-term immunotherapy can significantly slow down clinical onset of diabetes. Developing immuno-modulatory drugs that don't require continuous treatment to impact autoimmune disease is a major paradigm shift," said Jeffrey Bluestone, PhD, A.W. and Mary Margaret Clausen distinguished professor of metabolism and endocrinology at the University of California San Francisco Diabetes Center, President and CEO of the Parker Institute for Cancer Immunotherapy, and director of Provention Bio.[10]

New Drugs for Nonalcoholic Steatohepatitis (NASH) Primed for Approval

NASH is a type of liver disease characterized by the accumulation of fat in the liver cells and inflammation that can lead to irreversible liver damage (cirrhosis) and, in some cases, hepatocellular carcinoma. It is a leading indication for liver transplantation in the United States.[11] The National Institutes of Health estimate that between 3% and 12% of adults in the United States (roughly 10 million to 30 million people) have NASH.[12] Despite uncertainty about the exact number of affected individuals (due to the disease being notoriously difficult to diagnose), the prevalence of NASH is increasing.[13] The main risk factors for fatty liver disease include a sedentary lifestyle, diabetes, obesity, high sugar intake, and old age, the rates of which are increasing across the United States, Europe, and Japan.[14] "Fatty liver disease and NASH are impending public health epidemics that have gone virtually unrecognized and untreated, leading to unnecessary patient and family suffering and death," said Donna Cryer, CEO of the Global Liver Institute.[15]

Despite the large unmet need, there are currently no FDA-approved drugs to treat NASH. That, however, could soon change, **as the first FDA-approved treatment for NASH may enter the market by the end of this year**. Intercept Pharmaceuticals announced earlier this year that it has successfully completed a phase 3 trial (the REGENERATE study) of Ocaliva (obeticholic acid) for the treatment for NASH.[14] The trial had 2 primary end points: improving fibrosis and preventing the worsening of NASH symptoms. The coprimary end points were achieved by 11.9% of patients on placebo compared with 17.6% of patients on the 10-mg dose of Ocaliva and 23.1% of patients on the 25-mg dose of Ocaliva. The company has said that it will soon file for marketing approval.

Additional candidates are working toward the marketplace. Allergan's cenicriviroc, GenFit's elafibranor, and Gilead Sciences' selonsertib are all in late-stage trials; however, selonsertib performed more poorly than placebo at reducing scarring in patients with stage 3 fibrosis in the STELLAR-3 trial, highlighting some of the challenges associated with treating NASH.[12] **There are currently more than 100 ongoing clinical trials (of all stages) investigating treatments for NASH.**

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Hot Topic, *continued*

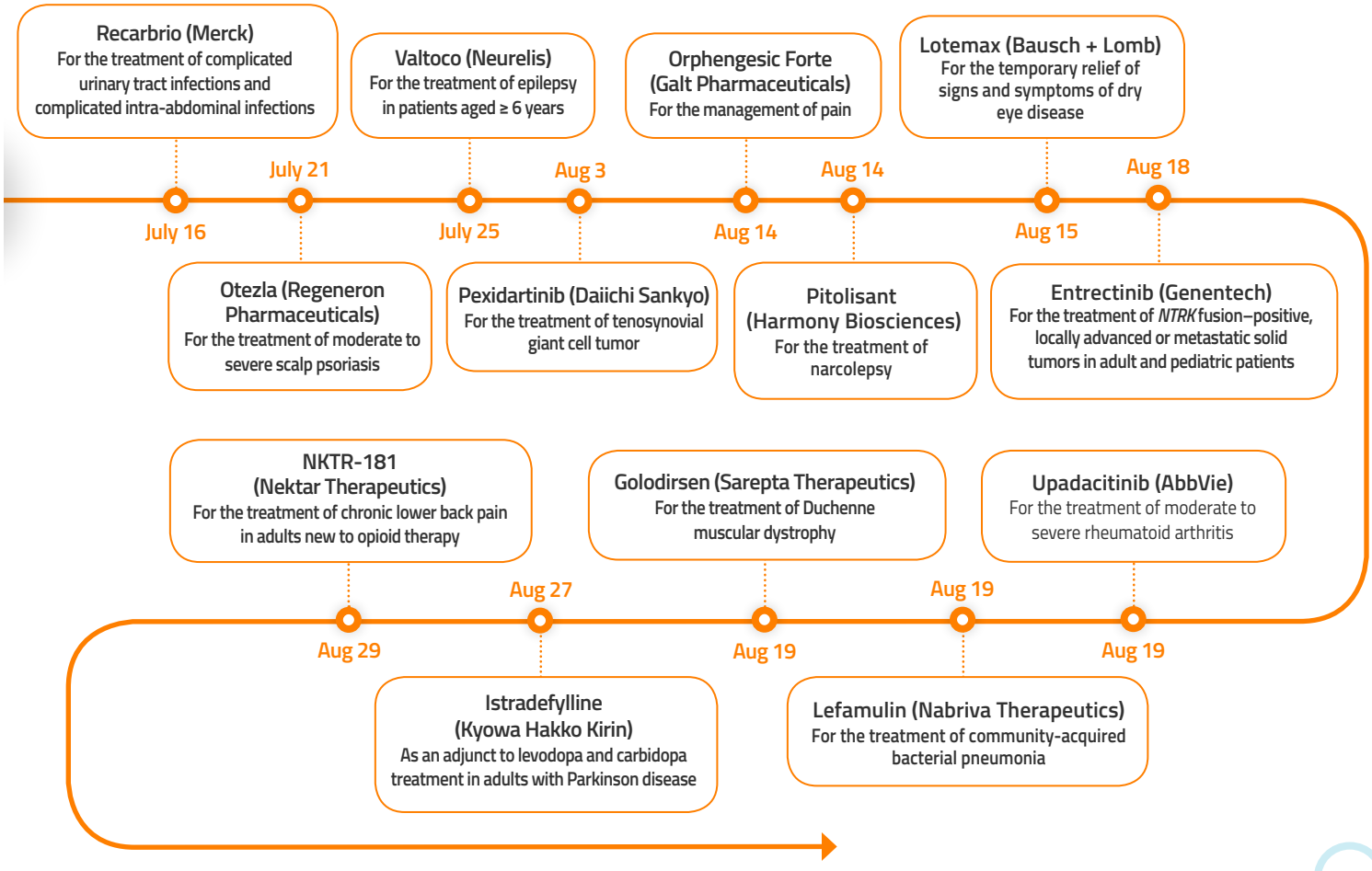
Drug developers have a significant hurdle to overcome when it comes to NASH; experts have said that without better diagnostic tools, many patients won't gain access to NASH drugs for years to come.[13-15] Liver biopsy is considered the gold standard for detecting NASH, but the procedure is invasive, expensive, and carries a small risk of infection and accidental damage to other organs.[13] The procedure can also be painful, which may deter patients since NASH is usually asymptomatic until its more advanced stages.

Meanwhile, the FDA issued a draft guidance in June, *Nonalcoholic Steatohepatitis With Compensated Cirrhosis: Developing Drugs for Treatment*, to assist companies developing clinical trials for NASH with compensated cirrhosis. The agency has said that it will likely only evaluate drugs for NASH with compensated cirrhosis under the traditional approval pathway, not the accelerated approval pathway, without evidence that histological improvements (such as those from liver biopsy) reasonably predict clinical benefit.[16]

What to Expect

Companies may choose to announce the submission of a marketing application along with the FDA's goal date for completion of its review. A goal date is not a guarantee of approval, nor is it a guarantee that the drug will be reviewed on this timeline. The FDA's drug review timeline is dictated by the **Prescription Drug User Fee Act (PDUFA)**, which gives the FDA 10 months to review an application under a standard review and 6 months to review an application under a priority review. Table 3 shows applications currently under review and their expected review dates.

Table 3. Upcoming PDUFA Goal Dates



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The information provided in this report is true and complete to the best of our knowledge. This report is not meant to be used, nor should it be used, to diagnose or treat any medical condition. The publisher and author are not responsible for any damages or negative consequences for any treatment, action, application, or preparation to any person reading the information in this report. References are provided for informational purposes only and do not constitute endorsement of any websites or other sources.

Glossary of Terms

Complete response letter (CRL): A CRL indicates that the FDA has completed its review of a new or generic drug application and will not approve the application in its current form. The CRL describes issues that must be addressed before the FDA will review the application again.

Expedited regulatory designations:

- **Accelerated approval**: This is a mechanism that allows the FDA to approve a drug based on a surrogate end point. A surrogate end point is thought to predict clinical benefit but is not itself a measure of clinical benefit. Surrogate end points are used in clinical trials for which it may take a long time to measure a drug's intended clinical benefit. Sponsors of drugs approved with this designation are required to submit confirmatory long-term data in order for their drugs to maintain approval status.
- **Breakthrough therapy**: This designation is designed to expedite the development and review of drugs intended to treat serious conditions when preliminary clinical evidence indicates that these drugs may demonstrate substantial improvement over currently available therapies.
- **Priority review**: A priority review shortens the PDUFA timeline goal for the FDA's review from 10 months to 6 months.
- **Fast track**: This process is designed to facilitate the development and expedite the review of drugs to treat serious conditions and fill unmet medical needs.
- **Rare pediatric disease priority review voucher**: The rare pediatric disease priority review voucher program allows the FDA to award priority review vouchers to sponsors of rare pediatric disease product applications that meet certain criteria. Under this program, a sponsor who receives approval of a drug or biologic for a rare pediatric disease may qualify for a voucher that can be redeemed to receive a priority review of a subsequent marketing application for a different product.

New drug application (NDA) and supplemental new drug application (sNDA): An NDA is a vehicle through which pharmaceutical companies formally propose that the FDA approve a new drug for sale and marketing in the United States. An sNDA allows a company to make changes to a product that already has an approved NDA.

Prescription Drug User Fee Act (PDUFA): PDUFA authorizes the FDA to collect fees from pharmaceutical companies to support the FDA in its review of applications with the goal of expediting the drug approval process. Since its inception in 1992, PDUFA has expedited the review process and made it more predictable and efficient. Under PDUFA, the FDA created 2 designations for application review: priority review and standard review. A priority review designation means the FDA's goal is to take action on an application within 6 months, whereas a standard review allows the FDA 10 months to take action.ke action on an application within 6 months, whereas a standard review allows the FDA 10 months to take action.

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