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Clarivate Analytics

Review Article

The year's new drugs & biologics 2019

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Summary

Highlights of our annual review of new approvals and launches on global drug markets include the approval and launch of Trikafta, the most widely applicable treatment to date for cystic fibrosis; approval of the first Ebola vaccine for general (rather than emergency) use; the pilot rollout in three African countries of the world's first malaria vaccine; approval of a new treatment option for multidrug-resistant bacterial infections; and the approval and launch in China of the first new drug to treat Alzheimer's disease in more than a decade. Several new immune checkpoint inhibitors and antibody–drug conjugates were approved for cancer indications, confirming continued industry enthusiasm for cancer immunotherapy. The most notable trend of 2019 was the granting by the Food and Drug Administration (FDA) of a record number of accelerated approvals, many of which were issued several months ahead of the expected action date.

Key words: New drug launches – New drug approvals – Line extensions – New formulations – New indications – New combinations – Orphan drugs – First-in-class drugs – Accelerated approval

Introduction

Inaugurated 32 years ago, this annual review article provides the opportunity to present from both a historical and a research perspective those molecular entities and biological drugs that were launched or approved in various countries for the first time during the year just ended.

Fifty-six new molecular entities and biologics were introduced in their first markets worldwide in 2019 (see Table I). In addition, 24 significant new line extensions—a label used in this publication to refer to new combinations, new formulations and new indications for previously marketed drugs—were rolled out worldwide during the year. Another

Table I. *New drugs & biologics by therapeutic category, launched in 2009-2019*.*

Therapeutics	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019
Central nervous system	7	4	5	2	4	3	4	7	6	6	8
Respiratory	2	1	1	2	1	5	3	1	1	2	1
Cardiovascular	1	1	1	1	2	1	1	2	0	1	3
Renal–urologic	2	0	2	1	0	2	1	1	0	1	1
Hematologic	3	1	3	2	1	7	7	4	2	7	6
Gastrointestinal	1	1	0	1	4	1	4	1	4	2	1
Endocrine drugs	3	2	1	4	4	6	3	1	3	4	5
Dermatologic	1	0	1	2	1	1	2	4	3	3	5
Anti-infective	1	2	6	0	5	11	5	5	6	10	3
Musculoskeletal	3	0	1	2	0	1	1	1	3	1	3
Immunologic	17	5	4	5	11	2	5	10	8	5	4
Cancer	6	7	7	10	12	10	14	5	18	18	13
Ophthalmic	1	1	2	0	1	2	0	1	2	3	1
Metabolic drugs	3	4	2	2	7	3	5	4	4	5	2
Poisoning & drug abuse	0	0	0	1	1	0	0	1	0	0	0
Mouth & dental	0	0	0	0	1	0	0	0	0	0	0
Diagnostic agents	0	0	0	1	1	3	0	2	1	1	0
Total	**51**	**29**	**36**	**36**	**56**	**58**	**55**	**50**	**61**	**69**	**56**

*Does not include line extensions.

26 new products, including both novel drugs and biologics and new line extensions, were approved, although we were unable to verify that they had been launched before December 31, 2019.

The most active therapeutic group was again oncolytic agents, with 13 new products introduced, followed by central nervous system (CNS) agents with 8.

Nine first-in-class agents were launched for the first time in 2019, among them new treatments for Alzheimer's disease (AD), hemophilia and hypoactive sexual desire disorder, as well as several first-in-class cancer therapeutics.

Again in 2019, the U.S. was the most active market for new drugs, accounting for 56% of global new launches (Fig. 1). The U.S. Food and Drug Administration (FDA) has been aggressively accelerating the process for approving new drugs. In 2017, U.S. researchers found that FDA review times (2011–2015) were on average 60 days shorter than at the European Medicines Agency (EMA) (1); since then, the U.S. regulatory body has picked up its pace even further. The agency is fast tracking and accelerating the approval of more drugs and rejecting fewer, leading some to accuse it of being a partner to the industry that it is tasked with regulating. Also notable is the consistent increase in new drugs and biologics emerging from China's domestic pharma industry. Seven of last year's first launches were reported in that country, accounting for 12% of the global total.

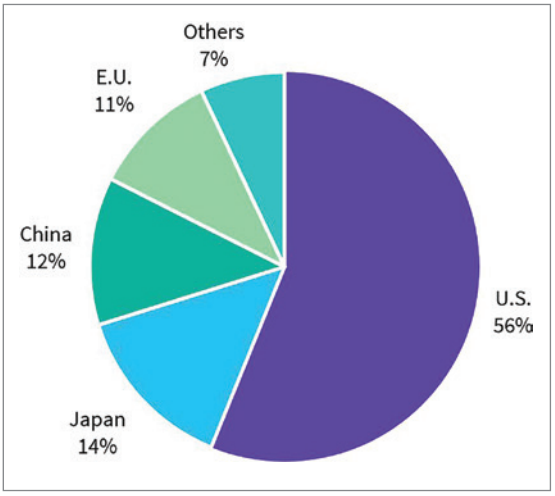

Figure 1. Distribution of new drug launches by country, 2019.

Regulatory agencies—primarily the FDA, although programs are also being established in other markets—can expedite the development and review processes and provide incentives to drug companies via a growing number of special designations. The first such program authorized by the U.S. Congress was the 1983 Orphan Drug Act, conceived and introduced to spur investigation into treatments for rare diseases. This was followed in 1988 by "fast track" designation, designed to facilitate the development and expedite the review of drugs to treat serious conditions and fill unmet medical needs. This was followed in 1992 by the Prescription Drug User Fee Act (PDUFA), which included "accelerated approval" and "priority review" programs (and, not incidentally, first required drug companies to pay fees to the regulatory agency). In 1997, the PDUFA goal for review times was lowered from a year to 10 months. In 2012, Congress added the "breakthrough therapy," designation, which enabled the FDA to waive normal procedures and requirements for drugs deemed to demonstrate a substantial improvement over available treatments. Approximately three-quarters of new drugs in the U.S. receive some type of expedited review at this time (2). In the European Union, the priority medicines (PRIME) program, now in its third year, focuses on medicines that may offer a major therapeutic advantage over existing treatments or benefit patients without treatment options. Between March 2014 and August 2016, the EMA ran a pilot project to assess the Adaptive Pathways approach, a scientific concept for drug development and data generation which allows for early and progressive patient access to new medicines in areas of high medical need. The EMA has also implemented an "accelerated assessment" program, which provides for faster review (150 vs. 210 days) of drugs that are able to address unmet medical needs. In Japan, the Sakigake designation system was established in 2015 to promote access to innovative drugs, devices and regenerative medicines. Modeling the success of the U.S.'s pioneering orphan drug program, many other countries have set up similar programs over the years.

The two categories of disease that have benefitted most from these programs are cancer and rare diseases. A study by *The Wall Street Journal* found that the majority of cancer drugs approved from 2015-2018

Table II. *Drug development in an age of exceptionality: special regulatory status/designations granted to 2019 newly launched products*.*

Drug name	Indication	Orphan drug	Breakthrough therapy	Accelerated approval	Fast track	Priority review	Real-time oncology	QIDP	Rare pediatric disease	Sakigake
Alpelisib	$HR^+/HER2^-$, *PIK3CA*-mutated, advanced or metastatic breast cancer					X	X			
Apremilast	Behçet's disease	X								
Beperminogene perplasmid	Chronic arterial occlusion (arteriosclerosis obliterans and Buerger's disease)				X					
Brexanolone	Postpartum depression		X			X				
Dupilumab	Chronic rhinosinusitis with nasal polyposis					X				
Eculizumab	Neuromyelitis optica spectrum disorder	X								
Elexacaftor/tezacaftor/ivacaftor	Cystic fibrosis	X				X				
Emapalumab	Primary hemophagocytic lymphohistiocytosis	X	X			X			X	
Entrectinib	Solid tumors with *NTRK* gene fusion	X	X							
	ROS1 fusion-positive non-small cell lung cancer	X								
Erdafitinib	Urothelial carcinoma		X							
Esketamine hydrochloride	Treatment-resistant depression		X							
Evocalcet	Hypercalcemia in patients with parathyroid carcinoma or primary hyperparathyroidism	X								
Fedratinib	Myelofibrosis	X								
Golodirsen	Duchenne muscular dystrophy	X		X	X	X				
Lefamulin	Community-acquired bacterial pneumonia				X	X		X		
Luspatercept	β-Thalassemia	X			X	X				
Nintedanib	Systemic sclerosis-associated interstitial lung disease	X	X			X				

(Continued)

Table II. *Drug development in an age of exceptionality: special regulatory status/designations granted to 2019 newly launched products*. (Cont.)*

Drug name	Indication	Orphan drug	Breakthrough therapy	Accelerated approval	Fast track	Priority review	Real-time oncology	QIDP	Rare pediatric disease	Sakigake
Omadacycline	Community-acquired bacterial pneumonia and acute skin and skin structure infections				X			X		
Onasemnogene abeparvovec	Spinal muscular atrophy	X	X							
Pexidartinib hydrochloride	Tenosynovial giant cell tumor	X	X							
Polatuzumab vedotin	Diffuse large B-cell lymphoma	X		X						
Pretomanid	Extensively drug-resistant and multidrug-resistant tuberculosis	X			X			X		
Quizartinib	Acute myeloid leukemia	X								
Ravulizumab	Paroxysmal nocturnal hemoglobinuria	X				X				
	Atypical hemolytic uremic syndrome	X								
Rifamycin	Travelers' diarrhea				X			X		
Ropeginterferon alfa-2b	Polycythemia vera	X								
Ruxolitinib phosphate	Graft-versus-host disease	X	X			X				
Selinexor	Multiple myeloma	X		X	X					
Solriamfetol hydrochloride	Narcolepsy	X								
Stemirac	Spinal cord injury									X
Tagraxofusp	Blastic plasmacytoid dendritic cell neoplasm	X								
Treosulfan	Conditioning treatment prior to allogeneic hematopoietic stem cell transplantation	X								
Volanesorsen	Familial chylomicronemia syndrome	X								
Voxelotor	Sickle cell disease	X	X	X	X	X			X	
Zanubrutinib	Mantle cell lymphoma		X	X						

QIDP, Qualified Infectious Disease Product.
*Designations apply only to the indication and country of launch. This table includes line extensions.

were fast tracked, and that just 19% had proof upon approval that their use translated into significant increases in overall survival (2). Postmarketing studies, which are required by the agency in order for a drug to be granted full approval, do not always confirm the results of smaller studies using surrogate endpoints upon which accelerated approval was based (3).

All told, roughly half of all new drugs, biologics and line extensions introduced worldwide in 2019 had been granted at least one special designation in the country of launch, as shown in Table II.

Agents for Analgesia & Anesthesia

Neuropathic pain encompasses a heterogeneous group of chronic conditions that cannot be explained by a single etiology or anatomical lesion. It evolves in the wake of a variety of causative etiologies and underlying mechanisms; representative neuropathic pain syndromes include postherpetic neuralgia, diabetic neuropathy, trigeminal neuralgia, central pain syndromes, phantom limb pain and Guillain–Barré syndrome. All neuropathic pain states are characterized by hyperexcitability that may vary in type and degree, depending upon a combination of factors derived from the patient and the underlying neurological condition. In 2019, the voltage-dependent calcium channel subunit α-2/δ-1 ligand **mirogabalin besylate** (Tarlige; Daiichi Sankyo) was approved and launched in Japan for the treatment of peripheral neuropathic pain (PNP), including diabetic PNP and postherpetic neuralgia.

Lasmiditan hydrochloride (Reyvow; Lilly), an oral 5-HT_{1F} receptor agonist, belongs to a new class known as neurally acting antimigraine agents (NAAMAs). NAAMAs were designed to deliver efficacy in migraine without the vasoconstrictor activity associated with previous generations of antimigraine drugs. Lasmiditan selectively targets 5-HT_{1F} receptors expressed in the trigeminal nerve pathway. In October 2019, it was approved by the U.S. FDA for the acute treatment of migraine, with or without aura, in adults. Following Drug Enforcement Administration (DEA) review, Lilly anticipates launching the drug in early 2020.

As highlighted in last year's edition of this publication (4), calcitonin gene-related peptide (CGRP) is a promising new target for antimigraine drugs. The 37-amino acid vasodilatory neuropeptide is distributed widely throughout the central and peripheral nervous systems and the cardiovascular system, where it exerts a range of biological effects and physiological functions that are critical in the pathophysiology of migraine, including both neuromodulation and vasodilation. Three anti-CGRP receptor monoclonal antibodies (MAbs) were introduced in 2018, all indicated for migraine prophylaxis and administered via injection. In 2019, the FDA approved the first orally active small-molecule drug acting on CGRP: **ubrogepant** (Ubrelvy), indicated for the acute treatment of migraine, with or without aura, in adults. Ubrogepant was discovered by Merck & Co. and licensed in 2015 to Allergan for development and commercialization worldwide. Launch is planned for the first half of 2020.

Jiangsu Hengrui's **remimazolam tosylate**, a benzodiazepine and γ-aminobutyric acid ($GABA_A$) BZ site receptor agonist, was approved in late December in China, where it is indicated for sedation in patients undergoing diagnostic upper gastrointestinal endoscopy.

Psychopharmacologic Drugs

According to the World Health Organization (WHO), depression affects more than 300 million people of all ages worldwide, equivalent to 4.4% of the global population. In spite of this prevalence, treatment is often ineffective or only partially effective, or is associated with intolerable side effects. For decades, depression has been treated with tricyclic antidepressants, monoamine oxidase inhibitors or neurotransmitter reuptake inhibitors. Last year saw the introduction of two new antidepressants with novel mechanisms of action (5). Both were granted breakthrough therapy designation, and both are approved for medically supervised administration only.

A new intranasal spray formulation of the *N*-methyl-D-aspartate (NMDA) receptor antagonist **esketamine hydrochloride** (Spravato; Janssen) was approved by the FDA and introduced last year in the U.S. for use, in conjunction with an oral antidepressant, for the treatment of adults with treatment-resistant depression (defined as failure to respond to any two antidepressants). This is a new indication for

esketamine, which has been marketed since 1997 as an intravenous general anesthetic. In clinical trials enrolling more than 1,700 patients with treatment-resistant depression, esketamine administered by the intranasal route at subanesthetic doses, given in combination with a newly initiated oral antidepressant, was associated with reduction of depressive symptoms and delayed time to relapse of symptoms. Of note, at least one member of the Psychiatric Drugs Advisory Committee, who was not present at the meeting due to a U.S. government shutdown, argued that this treatment effect was not significant (6). Moreover, esketamine can cause serious side effects, including sedation, dissociation, and suicidal ideation and behavior (5). In late December, the European Commission (EC) issued its own approval for esketamine, administered in combination with a selective serotonin reuptake inhibitor or serotonin and norepinephrine reuptake inhibitor, for adults living with treatment-resistant major depressive disorder.

Allopregnanolone is a positive allosteric modulator of synaptic and extrasynaptic $GABA_A$ receptors that has been studied as a potential antidepressant. **Brexanolone** (Zulresso; Sage Therapeutics), an intravenous formulation of allopregnanolone, was approved and launched last year in the U.S. as the first and only treatment specifically indicated for postpartum depression. The most common medical complication of childbirth, postpartum depression affects approximately 400,000 women each year in the U.S. Brexanolone is formulated using Ligand's Captisol, a chemically modified cyclodextrin with a structure designed to optimize the solubility and stability of drugs. The drug is administered by continuous intravenous infusion for 2.5 days under the supervision of healthcare providers in sites of care that have been certified under the Zulresso Risk Evaluation and Mitigation Strategy (REMS) program.

A great deal has been achieved in the treatment of schizophrenia in recent decades, especially with respect to the treatment of positive symptoms by targeting dopamine D_2 receptors. However, the disease has a range of other symptoms which severely affect quality of life and which require other strategies or additional targets. Last year saw the first approval of a new drug designed to fill this gap: Intra-Cellular Therapies' **lumateperone tosylate** (Caplyta). Lumateperone acts synergistically via multiple systems, thus representing a unique approach for the therapeutic management of a range of neuropsychiatric disorders. It possesses a potent antagonistic activity at serotonin 5-HT_{2A} receptors and also binds to dopamine (D_1 as well as D_2) receptors, with partial agonism at presynaptic D_2 receptors and postsynaptic antagonism. Further, preclinical data demonstrated that lumateperone uniquely acts as an indirect modulator of glutamatergic phosphoprotein, with D_1-dependent augmentation of both NMDA and AMPA activity via the mammalian target of rapamycin (mTOR) pathway, mechanisms thought to predict potent and rapid antidepressant effects (7). The efficacy of lumateperone was demonstrated in two placebo-controlled trials, which confirmed a statistically significant separation from placebo on the primary endpoint, the Positive and Negative Syndrome Scale total score. The drug will be launched in 2020.

In March, the FDA approved Jazz Pharmaceuticals' dual-acting dopamine and norepinephrine reuptake inhibitor **solriamfetol hydrochloride** (Sunosi) to improve wakefulness in adult patients with excessive daytime sleepiness associated with narcolepsy or obstructive sleep apnea (OSA). Approval was based on data from the TONES (Treatment of Obstructive sleep apnea and Narcolepsy Excessive Sleepiness) phase III program, which included four randomized, placebo-controlled studies that demonstrated the superiority of solriamfetol relative to placebo. In 12-week studies, approximately 68-74% of people taking solriamfetol at 75 mg and 78-90% of those taking the drug at 150 mg reported improvement in their overall clinical condition, as assessed by the Patient Global Impression of Change scale. At week 12, 150 mg of solriamfetol for narcolepsy patients and all doses for OSA patients demonstrated improvements in wakefulness compared with placebo as assessed in test sessions 1 (approximately 1 hour after dosing) through 5 (approximately 9 hours after dosing) of the maintenance of wakefulness test. The most common adverse reactions (incidence ≥ 5% and higher than placebo) reported in both the narcolepsy and OSA study populations were headache, nausea, decreased appetite and anxiety. The drug was launched in July, following a final scheduling decision by the U.S. DEA. Solriamfetol was also

approved in Europe in January 2020 for the same indication.

In December, the FDA approved a second new treatment for a sleep disorder: the dual orexin receptor antagonist **lemborexant** (Dayvigo; Eisai), indicated for the treatment of adults with insomnia characterized by difficulties with sleep onset and/or sleep maintenance. The orexin neuropeptide signaling system plays a role in wakefulness. Blocking the binding of wake-promoting neuropeptides orexin A and orexin B to orexin receptors OX_1 and OX_2 is thought to suppress the wake drive. Lemborexant binds to OX_1 and OX_2 receptors and acts as a competitive antagonist with stronger inhibition effect toward OX_2. Lemborexant is only the second orexin antagonist to emerge from the pipeline, following the 2014 introduction of suvorexant. It will be available in the U.S. following DEA scheduling, which was expected to occur within 90 days of approval.

Neurologic Drugs

The pivotal role of the intestinal microbiome in human health and disease has become increasingly apparent in recent years. The microbiome—defined as the genetic material of all commensal microorganisms residing in the gut, respiratory tract, skin and elsewhere in the human organism—has been known for some time to function as a signaling hub, integrating environmental stimuli with host genetic and immune signals to regulate the host's metabolic and immune functions, as well as orchestrating its response to infection. More recently, alterations to the gut microbiome have also been implicated in neurological disorders such as AD through a multiplicity of interactions (8). In November 2019, China's National Medical Products Administration (NMPA) granted conditional approval for **GV-971** (Oligomannate), a first-in-class treatment for AD thought to act by reconditioning dysbiosis of the gut microbiome (Fig. 2). The product is a mixture of acidic linear oligosaccharides isolated from brown algae. It was developed by Shanghai Green Valley Pharmaceuticals and is indicated for the treatment of mild to moderate AD and for improving cognitive function. In a phase III trial in Chinese patients with mild to moderate AD, GV-971 was shown to statistically improve cognitive function as early as 4 weeks after treatment initiation, with sustained benefits at each follow-up visit throughout the 36-week study. The mean difference between the active and placebo groups in Alzheimer's Disease Assessment Scale-Cognitive subscale (ADAS-Cog12) scores was 2.54. GV-971 was safe and well tolerated. The conditional approval in China requires further evaluation of the mechanism of action, safety and efficacy of GV-971. A multicenter global phase III clinical trial with sites in the U.S., Europe and Asia is planned to begin in early 2020 to support global regulatory filing of the product, expected within 5 years. GV-971 was launched in China in late December.

Acorda Therapeutics' Inbrija, a new inhalation formulation of the standard antiparkinsonian drug **levodopa**, was introduced in the U.S. last year for the intermittent treatment of "off" episodes in people with Parkinson's disease treated with carbidopa/levodopa. "Off" episodes are characterized by the return of motor and nonmotor symptoms between regular doses of antiparkinsonian drugs; these typically become progressively worse as the disease progresses. Later in the year, Inbrija was also approved in the European Union.

Cenobamate (Xcopri), a novel anticonvulsant discovered and developed by Korean company SK Biopharmaceuticals, was approved in November by the U.S. FDA, indicated for the treatment of partial-onset seizures in adults. While the precise mechanism by which cenobamate exerts its therapeutic effect is unknown, the drug is believed to reduce repetitive neuronal firing by inhibiting voltage-gated sodium currents. It is also a positive allosteric modulator of $GABA_A$ receptors. Launch of cenobamate is expected in the second quarter of 2020, following scheduling review by the DEA.

The second-generation sphingosine-1-phosphate (S1P) receptor modulator **siponimod fumarate** (Mayzent; Novartis) was approved and launched last spring in the U.S. for the treatment of adults with relapsing forms of multiple sclerosis, including clinically isolated syndrome, relapsing–remitting disease and active secondary progressive multiple sclerosis (SPMS). Later in the year, the EMA's Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion for siponimod

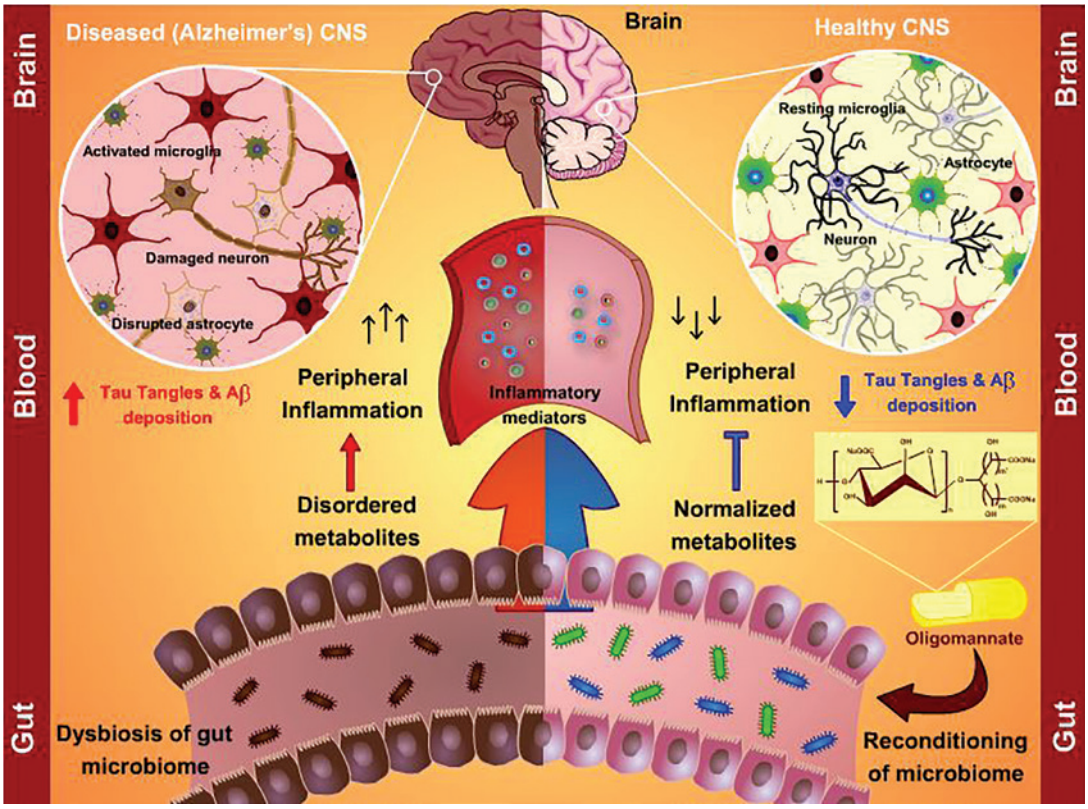

Figure 2. Oligomannate (GV-971), a first-in-class agent, is a seaweed-based drug intended to treat Alzheimer's disease. This drug is administered orally and has the ability to restore the gut microbiome to a state of symbiosis, thereby reducing peripheral and central inflammation. This in turn regulates the central nervous system (CNS), decreases deposition of amyloid protein and tau hyperphosphorylation, and improves cognitive function.

for the treatment of adult patients with SPMS with active disease evidenced by relapses or imaging features of inflammatory activity (i.e., gadolinium-enhancing T1 lesions or active, new or enlarging, T2 lesions). Approval in Europe for this indication took place in January 2020.

Stemirac (STR-01), a novel cell therapy discovered at Sapporo Medical University and developed by Nipro, was approved and launched last year in Japan for the treatment of spinal cord injury. Stemirac consists of autologous human bone marrow-derived mesenchymal stem cells expanded in autologous human serum. The cell therapy was designated as a target product under the country's 2015 Sakigake designation system.

Spinal muscular atrophy (SMA) is a rare, autosomal recessive neurodegenerative disorder, predominantly with onset in childhood, that affects motor neurons in the spinal cord and brainstem. SMA is found worldwide, with an estimated incidence of 1 in 11,000 live births and a carrier frequency of 1 in 50. Approximately 95% of SMA subtypes involve mutations in the survival motor neuron 1 gene (*SMN1*). Until just 2 years ago, supportive care was the only treatment available for SMA; in 2017, the disease-modifying therapy nusinersen was introduced, radically improving the treatment landscape for type I SMA. In 2019, prospects for patients improved further with the U.S. approval and launch of **onasemnogene abeparvovec** (Zolgensma), an

adeno-associated virus vector-based gene therapy developed by the Novartis subsidiary AveXis. Zolgensma is indicated for the treatment of pediatric patients less than 2 years of age with SMA with biallelic mutations in the *SMN1* gene. It is designed to address the genetic root cause of SMA by providing a functional copy of the human *SMN* gene, potentially halting disease progression through sustained SMN protein expression following a single, one-time intravenous infusion. The potentially curative nature of the therapy was used to justify its record-breaking price tag of USD 2.1 million. The product has orphan drug status and breakthrough therapy designation in the U.S.

In 2016, in spite of a negative recommendation from the Peripheral and Central Nervous System Advisory Committee, the FDA granted accelerated approval of Sarepta Therapeutics' first-in-class exon-skipping agent eteplirsen for the treatment of Duchenne muscular dystrophy (DMD) in patients with a specific mutation (9). Three years later, again in spite of a negative opinion (complete response letter) issued by the agency itself just months earlier, the FDA approved Sarepta's second exon-skipping antisense agent, **golodirsen** (Vyondys 53), indicated for the treatment of DMD in patients with a confirmed mutation amenable to exon 53 skipping. According to the FDA, only about 8% of DMD patients have this mutation; as such, golodirsen has orphan drug status. The exon-skipping strategy is based on the discovery that internally deleted dystrophins may retain part of their functionality; hence, if the disrupted open-reading frame could be restored, the production of at least partially functioning dystrophin could be resumed. Echoing the case of eteplirsen, accelerated approval of golodirsen was based on the surrogate endpoint of an increase in dystrophin production in the skeletal muscle observed in some patients treated with the drug. The agency concluded that the data submitted by Sarepta demonstrated an increase in dystrophin production "that is reasonably likely to predict clinical benefit in patients with DMD who have a confirmed mutation of the dystrophin gene amenable to exon 53 skipping" (10), although clinical benefit of the drug, including improved motor function, has not been established. In making this decision, the FDA said it had also considered the potential risks associated with the drug (infections and renal toxicity), as well as the life-threatening and debilitating nature of the disease and the lack of available therapy. Sarepta announced that commercial distribution of golodirsen would begin immediately. Continued approval of the drug may be contingent upon verification of a clinical benefit in confirmatory trials.

Neuromyelitis optica spectrum disorder (NMOSD), also known as Devic disease, is a chronic, relapsing autoimmune inflammatory disorder affecting the brain and spinal cord, and characterized by unilateral or bilateral attacks of optic neuritis and/or myelitis. NMOSD is a rare disorder, with a prevalence of 1-10 per 100,000 population worldwide, according to the U.S. National Organization for Rare Disorders (NORD) (11). Its etiology is unknown, but in approximately two-third of cases, patients have antibodies to aquaporin-4 (AQP4-IgG) as well as complement-mediated damage to the CNS. It is typically treated with immunosuppressants or prednisone. Last summer, the FDA approved a new treatment option for patients with NMOSD: Alexion's complement inhibitor **eculizumab** (Soliris). This is a new indication for the anti-C5 MAb, which was previously launched for paroxysmal nocturnal hemoglobinuria (PNH), atypical hemolytic uremic syndrome (aHUS) and myasthenia gravis. It was immediately made available for the new indication, for which it has orphan drug status, in the U.S. Eculizumab is under regulatory review for NMOSD in Japan.

Respiratory Drugs

Allergen-specific immunotherapy is an increasingly popular option for the treatment of patients with confirmed sensitivity to one or a few allergens. Itulazax, a novel **tree pollen sublingual immunotherapy** (SLIT) from ALK-Abelló, was approved last year in the E.U. (17 countries) and launched for the first time in Germany. The sublingual tablet vaccine is indicated for the treatment of adult patients with moderate to severe allergic rhinitis and/or conjunctivitis induced by pollen from the birch homologous family of trees—which includes birch, alder, beech, hazel, hornbeam and oak—and whose symptoms cannot be adequately controlled with symptom-relieving medication. In contrast with subcutaneous immunotherapy, which can cause adverse reactions

and must be administered by a doctor, SLIT is well tolerated and can be taken by the patient at home.

In December, Glenmark Pharmaceuticals announced receipt of marketing authorization from Australia's Therapeutic Goods Administration (TGA) for the fixed-dose combination product Ryaltris (**olopatadine hydrochloride/mometasone furoate**), indicated for the treatment of allergic rhinitis and rhinoconjunctivitis in patients over age 12. The fixed-dose nasal spray delivers the antihistamine olopatadine and the corticosteroid mometasone furoate in a single administration. It will be marketed in Australia, which has one of the world's highest indices of allergic rhinitis—nearly 20%—, by Seqirus.

The anti-interleukin-4 (IL-4) receptor MAb **dupilumab** (Dupixent; Regeneron/Sanofi), marketed since 2017 for atopic dermatitis and since 2018 for asthma, was approved and launched in 2019 for a third indication: treatment, in combination with other agents, of chronic rhinosinusitis with nasal polyposis (CRSwNP) in adults whose disease is not controlled. Prior to the introduction of dupilumab, the only treatment option for CRSwNP was intranasal or short-course systemic corticosteroids. Following a priority review, the U.S. FDA approved the new indication for dupilumab on the basis of two pivotal trials—the 24-week SINUS-24 and 52-week SINUS-52 studies—that evaluated dupilumab 300 mg every 2 weeks plus standard-of-care mometasone furoate nasal spray (MFNS) compared to placebo injection plus MFNS (ClinicalTrials.gov Identifiers NCT02912468 and NCT02898454). In these trials, dupilumab significantly improved key disease measures and met all primary and secondary endpoints: the treatment reduced polyp size, sinus opacification and severity of symptoms, and was well tolerated. This new indication was also approved later in the year by the EMA.

Breztri Aerosphere (**budesonide/glycopyrronium bromide/formoterol fumarate**), a triple combination therapy developed by AstraZeneca subsidiary Pearl Therapeutics, was approved and launched last year in Japan for the relief of symptoms of chronic obstructive pulmonary disease (COPD). A single inhalation of Breztri delivers the inhaled corticosteroid budesonide, the long-acting muscarinic agonist glycopyrronium bromide and the long-acting β_2-agonist formoterol fumarate via a pressurized metered-dose inhaler that uses Aerosphere delivery technology. Triple combination therapy is increasingly used to treat COPD, which affects more than 5 million people in Japan; Breztri Aerosphere is the first such product to be approved in that country. Applications for approval are under review in the E.U. and China; in the U.S., the FDA issued a complete response letter in October.

The cystic fibrosis transmembrane regulator (CFTR) protein is embedded in the membranes of several cell types in the body and plays a pivotal role in the pathogenesis of cystic fibrosis (CF). CFTR levels are highest in the epithelial cells lining the internal surfaces of the pancreas, sweat glands, salivary glands, intestines and reproductive organs, as well as in the submucosal glands of the airways—precisely the organs and tissues that are most affected in patients with CF. The most straightforward role of CFTR involves its function as a cAMP-regulated chloride channel, facilitating the flow of chloride ions in both directions. In addition to serving as a chloride channel itself, CFTR also acts as a channel regulator, influencing the function of other chloride channels and of sodium channels located nearby on the cell membrane. The discovery of a new class of drugs targeting the defective CFTR protein marked a new era in the treatment of CF. The first drug in this class, ivacaftor (Kalydeco), was launched in 2012 and transformed the outlook for a subset of CF patients with certain specific *CFTR* mutations. Ivacaftor-containing two-drug combinations (Orkambi and Symdeko) provided additional options for a wider population of CF patients. The first ivacaftor-containing three-drug combination, Trikafta (**elexacaftor/ivacaftor/tezacaftor**), was approved by the FDA in October 2019 (just 3 months after the new drug application [NDA] was filed), and was launched almost immediately. Trikafta is indicated for the treatment of patients aged 12 years and older who have at least one copy of the F508del mutation in the *CFTR* gene, regardless of their second mutation. This means that approximately 90% of all CF patients are eligible for treatment with the combination.

In September, the FDA approved the triple kinase (vascular endothelial growth factor receptor [VEGFR], fibroblast growth factor receptor [FGFR]

and platelet-derived growth factor receptor [PDGFR]) inhibitor **nintedanib** (Ofev; Boehringer Ingelheim) for a new indication: to slow the rate of decline in pulmonary function in patients with systemic sclerosis-associated interstitial lung disease. It is the first FDA-approved treatment for this rare lung condition, and has both orphan drug status and breakthrough therapy designation in the U.S. Approval, which followed a priority review, was supported by a randomized, double-blind, placebo-controlled trial of 576 patients aged 20-79 years with the disease (NCT02597933). Patients received treatment for 52 weeks, with some patients treated for up to 100 weeks. The primary test for efficacy measured the forced vital capacity and showed that those patients who took nintedanib had less lung function decline than those on placebo (12). The overall safety profile observed in the active treatment group was consistent with the known safety profile of the therapy. The most frequent serious adverse event reported in patients treated with nintedanib was pneumonia (2.8% vs. 0.3% placebo). Adverse reactions leading to permanent dose reduction were reported in 34% of nintedanib-treated patients compared to 4% of placebo-treated patients; diarrhea was the most frequent such adverse reaction in the active treatment group. Nintedanib was approved in 2014 for adult patients with idiopathic pulmonary fibrosis and in 2015 for non-small cell lung cancer.

Cardiovascular Drugs

Azurity's Katerzia (**amlodipine benzoate**) was approved and launched last year in the U.S. This novel salt of the established calcium channel blocker is the first and only amlodipine oral suspension. It can be used alone or in combination with other antihypertensive and antianginal agents, and is indicated for the treatment of hypertension in adults and pediatric patients and for coronary artery disease in adults. Katerzia offers a safe and effective, ready-to-use oral suspension for children 6 years of age and older who require or prefer an oral liquid option of amlodipine.

Daiichi Sankyo's **esaxerenone** (Minnebro), a nonsteroidal, selective mineralocorticoid receptor blocker identified during a research collaboration with Exelixis, was launched last year in Japan. It is indicated for the treatment of essential hypertension, and is only the third drug in this class. Mineralocorticoids are involved in the regulation of electrolyte and water balance. They affect ion transport in epithelial cells and renal tubules, causing retention of sodium and loss of potassium.

In March, AnGes obtained conditional approval from the Japanese Ministry of Health, Labour and Welfare (MHLW) for **beperminogene perplasmid** (DNA plasmid encoding the hepatocyte growth factor gene [*HGF*]) to treat patients with critical limb ischemia (CLI). Beperminogene perplasmid, the first gene therapy product to be approved in Japan, is indicated for the improvement of ulcers in patients suffering from chronic arterial occlusion (arteriosclerosis obliterans and Buerger's disease) who have had an inadequate response to standard pharmacotherapy and who experience difficulty in undergoing revascularization. Approval was sought based on results from a randomized, placebo-controlled phase III trial and investigator-led study conducted in Japan. Under the conditions of the approval, AnGes will conduct a confirmatory study for all patients who receive the treatment under this conditional approval and will submit an application to lift the conditions within 5 years. AnGes has granted to Mitsubishi Tanabe Pharma the marketing rights to beperminogene perplasmid in Japan and the U.S. for treating peripheral arterial diseases, including CLI. Mitsubishi Tanabe launched the product under the brand name Collategene in September.

Renal–Urologic Drugs

Following approval in the E.U. almost a year earlier, AstraZeneca's phosphate-binding agent **sodium zirconium cyclosilicate** (Lokelma) was launched for the first time in the Scandinavian countries in early 2019. The drug is indicated for the treatment of hyperkalemia, a serious condition characterized by elevated potassium levels in the blood associated with cardiovascular, renal and metabolic diseases. The risk of hyperkalemia increases significantly for patients with chronic kidney disease (CKD) and for those who take common medications for heart failure, such as renin–angiotensin–aldosterone system (RAAS) inhibitors. To help prevent the recurrence of hyperkalemia, RAAS-inhibitor therapy is often modified or discontinued, which

can compromise cardio-renal outcomes and increase the risk of death. Regulatory approval was supported by data from three double-blind, placebo-controlled trials and one open-label trial, in which patients with hyperkalemia were treated for up to 12 months. In these trials, the median time to achieving normal potassium levels in the blood for patients receiving Lokelma was 2.2 hours, with 98% achieving normal levels within 48 hours from baseline. Lokelma demonstrated sustained potassium control for up to 1 year.

Hematologic Agents

The first-in-class hypoxia-inducible factor prolyl hydroxylase (HIF-PH) inhibitor **roxadustat** (Airuizhuo) was launched for the first time last year in China (Fig. 3). HIF-PH inhibitors are a novel category of orally active erythropoietic agents that work by stabilizing the HIF complex and stimulating endogenous production of erythropoietin. Roxadustat is indicated for the treatment of anemia in patients with CKD who are dialysis-dependent, whether they use hemodialysis or peritoneal dialysis. The drug was developed

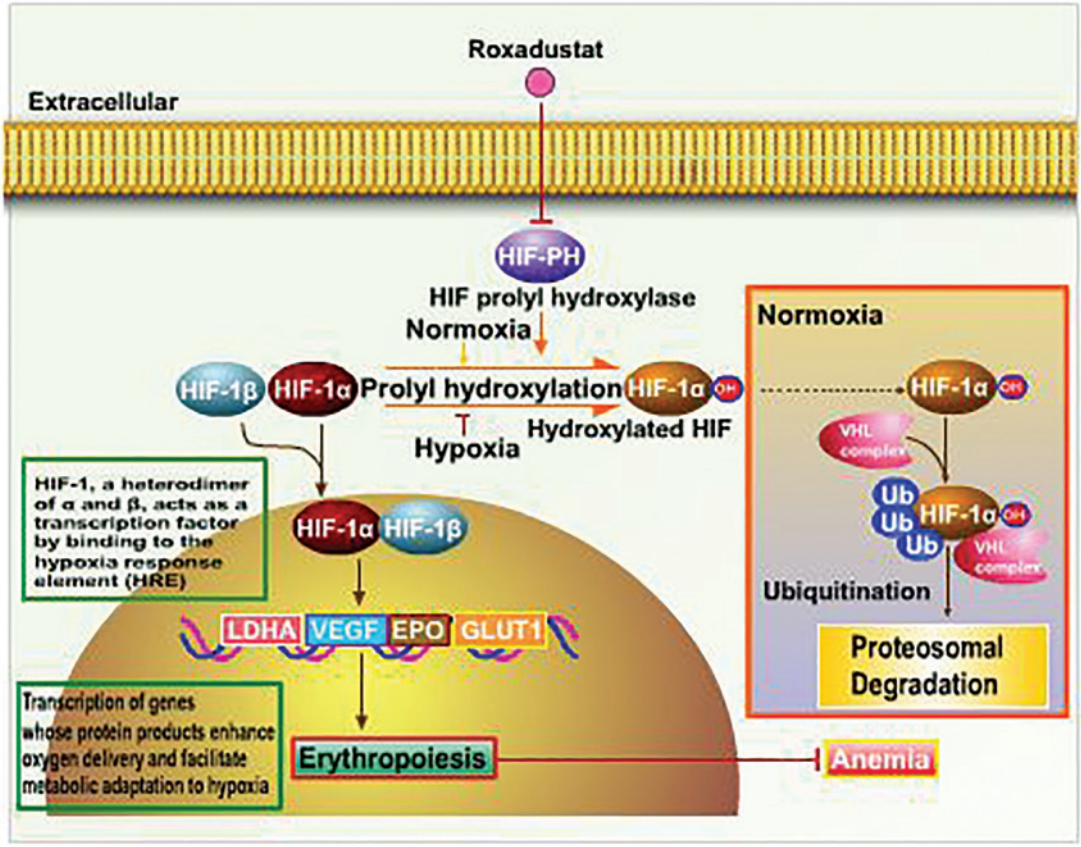

Figure 3. Hypoxia-inducible factor (HIF) regulates expression of the erythropoietin gene (*EPO*) in the kidney and liver. Oxygen-dependent degradation of HIF-1α is mediated by prolyl hydroxylation, and this process in turn suppresses *EPO* expression in liver and kidneys. The HIF stabilizer roxadustat, which acts by inhibiting HIF prolyl hydroxylases (PHs), is designed to stabilize and upregulate *EPO* gene transcription, thereby stimulating endogenous erythropoiesis and reversing anemia.

by FibroGen and is licensed to AstraZeneca for the Chinese market.

In June 2019, the EC granted conditional marketing authorization for bluebird bio's **betibeglogene darolentivec** (Zynteglo), a gene therapy for patients age 12 years and older with transfusion-dependent β-thalassemia (TDT) who do not have a β^0/β^0 genotype, for whom hematopoietic stem cell (HSC) transplantation is appropriate but a human leukocyte antigen (HLA)-matched related HSC donor is not available. The one-time gene therapy is based on autologous $CD34^+$ cells encoding $\beta^{A\text{-}T87Q}$-globin gene, and addresses the underlying genetic cause of TDT, offering eligible patients the potential to achieve lifelong independence from transfusion. Betibeglogene darolentivec was developed under the EMA's PRIME program; it was also selected for the agency's Adaptive Pathways pilot program. In late October, the EMA approved a refined manufacturing process for Zynteglo, paving the way for the company to begin treating patients in early 2020.

In November, the FDA approved **luspatercept** (Reblozyl; Acceleron Pharma/Celgene) for the treatment of anemia in adult patients with β-thalassemia who require regular red blood cell (RBC) transfusions. Luspatercept is a first-in-class transforming growth factor β (TGF-β)-inhibiting erythroid maturation agent, representing a new class of therapy which works by regulating late-stage RBC maturation to help patients reduce their RBC transfusion burden (Fig. 4). Following a priority review, approval was based on results from the pivotal, randomized,

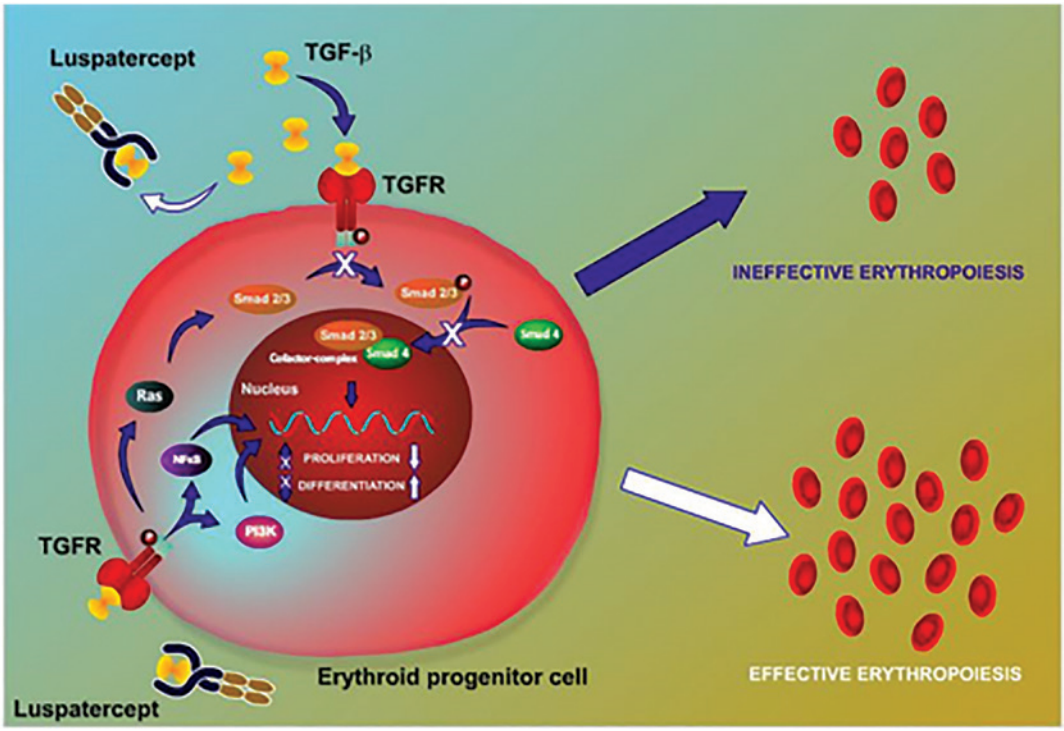

Figure 4. Luspatercept is a first-in-class erythroid maturation agent in development for serious blood disorders associated with ineffective erythropoiesis. The drug binds several transforming growth factor β (TGF-β) superfamily ligands, thereby diminishing Smad2/3 signaling. This, in turn, decreases proliferation and promotes differentiation of late-stage erythroid precursors and restores the production of red blood cells.

double-blind, placebo-controlled, multicenter phase III BELIEVE study (NCT02604433), which evaluated luspatercept for the treatment of anemia in adult patients with β-thalassemia who require regular RBC transfusions (defined as 6-20 RBC units per 24 weeks, with no transfusion-free period greater than 35 days during that period). The trial achieved a clinically meaningful and statistically significant improvement on the primary endpoint. In the luspatercept arm, 21.4% of patients achieved a 33% or greater reduction from baseline in RBC transfusion burden (with a reduction of at least 2 units) during weeks 13-24 after randomization, compared with 4.5% in the placebo arm. The study also met key secondary endpoints, including transfusion burden reduction of at least 33% (with a reduction of at least 2 units), during weeks 37-48, which was achieved in 19.6% of patients in the luspatercept arm and 3.6% in the placebo arm. Other efficacy endpoints included transfusion burden reduction of at least 50% (with a reduction of at least 2 units) during weeks 13-24 and weeks 37-48. A 50% or greater reduction in transfusion burden was observed in 7.6% of patients receiving luspatercept versus 1.8% of patients in the placebo arm at weeks 13-24, and 10.3% of patients versus 0.9% of patients at weeks 37-48, respectively. The drug, which has orphan drug status, was launched in the U.S. within a week of approval.

Coagulation factor replacement therapy with recombinant factor VIII (rFVIII), administered on demand to stop bleeds or prophylactically to prevent bleeding episodes, is the backbone of therapy for patients with congenital hemophilia A. One major drawback to existing coagulation factor concentrate formulations is the need for frequent (often daily) administration, so that many patients eventually require placement of a central venous access device. These devices may lead to significant adverse events such as infection and thrombosis, representing a serious limitation, particularly in the treatment of pediatric patients. The development of longer-acting rFVIII formulations has thus become an important objective. Last year one such biologic was approved in several countries, including the U.S., E.U, Canada and Japan: Novo Nordisk's glycopegylated rFVIII, **turoctocog alfa pegol** (Esperoct). It was launched in its first markets, Germany and Switzerland, in the third quarter, indicated for the treatment and prophylaxis of bleeding in patients 12 years and above with hemophilia A (congenital FVIII deficiency). Although the product had been granted orphan drug status in the E.U. in 2012, this designation was withdrawn in May 2019 by request of Novo Nordisk at the time of granting of marketing authorization.

Polycythemia vera (PV) is a rare blood disease in which the body makes too many RBCs. This causes the blood to be thicker and form blood clots more easily than normal, and increases the risk of stroke and myocardial infarction. In February, the EC approved PharmaEssentia's **ropeginterferon alfa-2b** (Besremi) as monotherapy for the treatment of adults with PV without symptomatic splenomegaly. Besremi is the first and only approved therapy that can be used in PV patients regardless of previous hydroxyurea exposure. The approval is applicable to all 28 European Union member states plus Iceland, Norway and Liechtenstein, and the marketing authorization holder for Besremi in Europe is AOP Orphan Pharmaceuticals. The first product launches took place in Austria and Germany.

Sickle cell disease (SCD) is a chronic, lifelong inherited hematologic disorder affecting RBCs. Because of a genetic mutation, people with SCD have RBCs containing an abnormal type of hemoglobin known as hemoglobin S (HbS). Under conditions of low oxygen tension, these RBCs polymerize and become sickle- or crescent-shaped, making it difficult for them to pass through small blood vessels. The sickle cells also show an increased propensity to stick to one another and to vascular endothelial cells. Patients with SCD suffer from debilitating episodes of vaso-occlusive crises (VOCs), which occur when the rigid, adhesive and inflexible RBCs block blood vessels, resulting in excruciating pain. Sickle cell crises can lead to organ damage, stroke, pulmonary complications and other adverse outcomes, including acute chest syndrome, which may be potentially fatal and is the leading cause of death in this patient population. As reported here last year (4), 2018 saw the introduction of the first new SCD treatment in 50 years. In 2019, two additional new treatment options were approved.

SCD is associated with chronic inflammation, causing higher levels of cell adhesion proteins, including P-selectin; these also contribute to make blood

vessels and blood cells stickier and more prone to multicellular interactions in the bloodstream. This environment can lead to painful and potentially life-threatening VOCs. Novartis' **crizanlizumab** (Adakveo), a novel targeted therapy for SCD, was approved by the FDA in November, 2 months ahead of its PDUFA date. Crizanlizumab is a MAb that binds to P-selectin. The approval was supported by results of the 52-week, randomized, placebo-controlled SUSTAIN trial, which showed that crizanlizumab significantly lowered the median annual rate of VOCs by 45% compared with placebo (1.63 vs. 2.98). Furthermore, it reduced the median number of hospitalization days per year by 42% (4 vs. 6.87 days, respectively) (13).

Later in the same month, and also well ahead of the PDUFA date, the FDA granted accelerated approval to another first-in-class agent for SCD: the antisickling agent **voxelotor** (Oxbryta; Global Blood Therapeutics [GBT]). Voxelotor, a hemoglobin polymerization inhibitor, is a direct antisickling agent (Fig. 5) with demonstrated benefit in animal

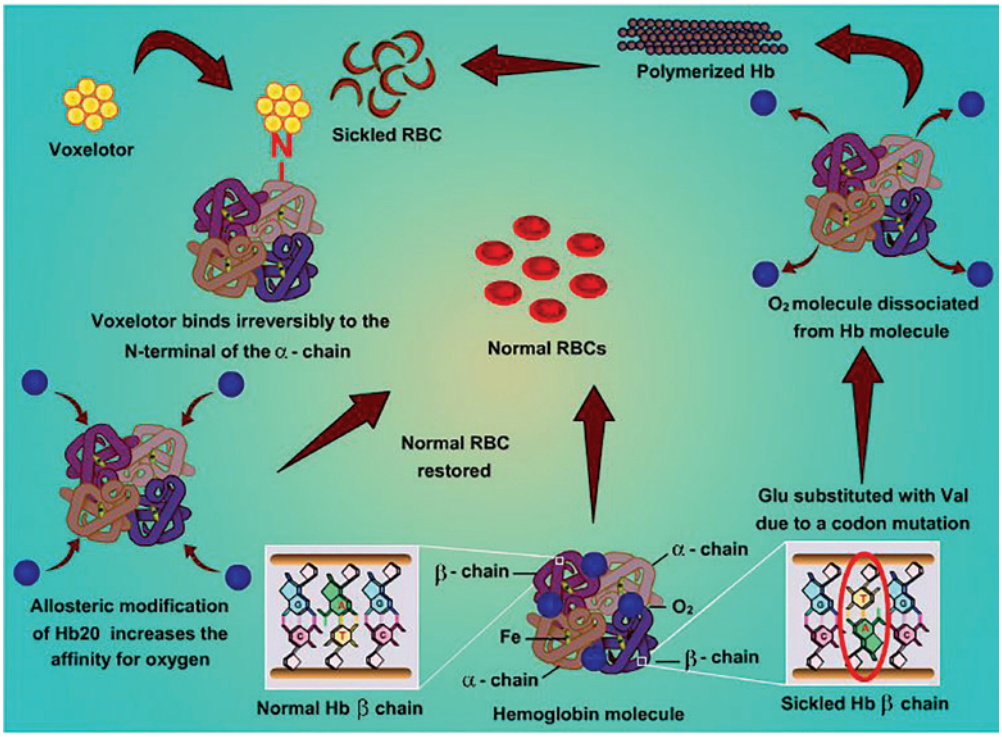

Figure 5. Sickle hemoglobin (HbS) polymerization is the causal factor for sickle cell disease. The substitution of glutamate (Glu) with valine (Val), associated with a codon mutation in the β-chain of the Hb molecule reduces the affinity for the O_2 molecule leading to its dissociation. This, in turn, causes the formation of abnormal, sickle-shaped red blood cells (RBCs) that aggregate and block blood vessels throughout the body. Voxelotor, a first-in-class novel molecule, binds irreversibly with the N-terminal Val of the α-chain of Hb, leading to an allosteric modification of Hb20, which increases the affinity for oxygen. Oxygenated HbS does not polymerize. By directly blocking HbS polymerization, voxelotor reverses the affinity of HbS for the O_2 molecule thereby restoring normal blood flow.

models as well as in patients with SCD. By increasing the oxygen affinity of hemoglobin, voxelotor prevents HbS polymerization and the sickling of RBCs. Approval was based on data from the phase III study HOPE (NCT03036813), which enrolled 274 patients aged 12 years and older with SCD. The study showed that after 24 weeks of treatment, 51% of patients receiving voxelotor achieved a > 1 g/dL increase in hemoglobin (a surrogate endpoint) compared with 6.5% receiving placebo (14). The study did not, however, show a decrease in the rate of VOCs. The most common adverse reactions occurring in 10% or more of patients treated with voxelotor with a difference of > 3% compared with placebo were headache (26% vs. 22%), diarrhea (20% vs. 10%), abdominal pain (19% vs. 13%), nausea (17% vs. 10%), fatigue (14% vs. 10%), rash (14% vs. 10%) and pyrexia (12% vs. 7%). As a condition of accelerated approval, GBT will continue to study voxelotor in the HOPE-KIDS 2 study, a postapproval confirmatory study using transcranial doppler flow velocity to demonstrate a decrease in stroke risk in children aged 2-15 years. The drug was launched in December.

In the early days of 2019, the anti-complement 5 (C5) MAb **ravulizumab** (Ultomiris; Alexion) was launched in the U.S. for the treatment of adult patients with PNH. This ultra-rare, debilitating blood disorder is characterized by hemolysis, the destruction of RBCs by the complement system. PNH affects men and women of all races, backgrounds and ages, with an average age of onset in the early 30s. Symptoms include fatigue, difficulty swallowing, shortness of breath, abdominal pain, erectile dysfunction, dark-colored urine and anemia. The most serious consequence of chronic hemolysis is thrombosis, which can occur in blood vessels throughout the body, damaging vital organs and potentially causing premature death. The FDA granted this application priority review designation, and ravulizumab also received orphan drug status. Later in the year, ravulizumab was approved for PNH in the European Union and Japan.

In October, the FDA approved a second indication for **ravulizumab**: for the treatment of adults and pediatric patients 1 month of age and older with aHUS, to inhibit complement-mediated thrombotic microangiopathy. aHUS is a rare disease that causes abnormal blood clots to form in small blood vessels in the kidneys. These clots, if they block or restrict blood flow, can cause serious medical problems including hemolytic anemia, thrombocytopenia and kidney failure. aHUS can occur at any age and is often caused by a combination of environmental and genetic factors (15). Ravulizumab also has orphan drug status for this second indication, and was rolled out immediately to the aHUS community.

Gastrointestinal Drugs

Proton pump (H^+/K^+-ATPase) inhibitors (PPIs) are widely used for the treatment of gastric ulcer and gastroesophageal reflux disease (GERD). They are generally considered to be safe, although long-term usage can lead to an increased risk of bone fracture as these agents can interfere with calcium absorption. In an effort to overcome the shortcomings of existing PPIs, a newer-generation class of compounds known as potassium-competitive acid blockers (P-CABs) has been developed and evaluated in clinical trials. P-CABs inhibit H^+/K^+-ATPase in a potassium-competitive and reversible manner, with higher pKa values and improved stability at low pH. These properties endow the P-CABs with improved pharmacokinetic properties, as manifested by a less variable onset of action, reduced acid liability, prolonged efficacy over the 24-hour period and more consistent efficacy across a wide range of patient profiles. Last year, CJ HealthCare launched the P-CAB **tegoprazan** (K-CAB) in the Republic of Korea. The drug is indicated for the treatment of GERD, including both erosive esophagitis and nonerosive reflux disease.

In November, the FDA approved RedHill Biopharma's triple combination Talicia (**omeprazole magnesium/amoxicillin/rifabutin**) for the treatment of *Helicobacter pylori* infection in adults. Talicia is the only rifabutin-based therapy approved for the treatment of *H. pylori* infection and is designed to address the high resistance of *H. pylori* bacteria to current clarithromycin-based standard-of-care therapies. RedHill expects to launch Talicia in the U.S. in the first quarter of 2020.

Aemcolo, a novel formulation of **rifamycin** developed by Cosmo Pharmaceuticals and licensed to RedHill Biopharma for sale and marketing, was launched in the U.S. for the new indication of travelers' diarrhea

in adults. Aemcolo is a delayed-release tablet formulation of the minimally absorbed antibiotic that is delivered to the colon. It is specifically indicated for travelers' diarrhea caused by noninvasive strains of *Escherichia coli*; in order to avoid the development of drug-resistant bacteria, Aemcolo should only be used to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. The FDA granted qualified infectious disease product (QIDP) and fast track designations for Aemcolo.

Ardelyx's **tenapanor** (Ibsrela) was approved in September for the treatment of irritable bowel syndrome with constipation in adults. Tenapanor is a minimally absorbed small molecule that acts locally in the gastrointestinal tract by inhibiting the sodium/hydrogen exchanger 3 (NHE-3). The apical membrane protein NHE-3 is highly expressed in the intestine and colon, where it regulates salt and water absorption in the gut. Abnormally high intestinal absorption of sodium is one mechanism that contributes to constipation via reduced water content in feces. NHE-3 inhibitors help normalize or augment the intestinal fluid content by decreasing sodium absorption throughout the gastrointestinal tract, thereby restoring normal hydration of the intestinal contents, accelerating stool transit and relieving pain. Ardelyx is currently in discussions with potential strategic partners to market Ibsrela in the United States.

Endocrine Drugs

Among the insulin secretagogue class of antidiabetic drugs, incretin mimetics represent an important and growing treatment option. Last year, Hansoh Pharma launched the long-acting glucagon-like peptide 1 (GLP-1) receptor agonist **polyethylene glycol loxenatide** (Fulaimei) in China, a country where nearly 10% of the population suffers diabetes. The drug is indicated as monotherapy or in combination with metformin, in addition to diet and exercise, to improve the blood glucose control in adult patients with type 2 diabetes (T2D).

Another GLP-1 agonist, Novo Nordisk's **semaglutide**, was introduced in the U.S. last year in a new tablet formulation called Rybelsus; the active ingredient had previously been approved in an injectable formulation (Ozempic). Rybelsus is the first GLP-1 receptor agonist that can be taken orally, and is indicated as an adjunct to diet and exercise to improve glycemic control in adults with T2D. FDA approval was based on the results from 10 PIONEER trials, which included 9,543 adults with T2D. Rybelsus lowered blood sugar more effectively than sitagliptin and empagliflozin. Treatment with Rybelsus resulted in up to a 4.4-kg reduction in body weight. Rybelsus demonstrated a safe and well-tolerated profile across the PIONEER program, with the most common adverse event being mild to moderate nausea that diminished over time.

Although they have been on the market for less than a decade, sodium/glucose cotransporter (SGLT) inhibitors have become well established as oral antidiabetic agents for the treatment of T2D. SGLT inhibitors continued to make the news in 2019, with the approval and launch in India of Remo (**remogliflozin etabonate**) and the approval of the combination product Remo-M (**remogliflozin etabonate/metformin**), both from Glenmark Pharmaceuticals, as well as the approval in the E.U. of **sotagliflozin** (Zynquista; Lexicon).

AstraZeneca's Qternmet XR, a triple combination incorporating the SGLT inhibitor **dapagliflozin**, the dipeptidyl peptidase 4 (DPP IV) inhibitor **saxagliptin** and the insulin sensitizer **metformin**, was approved by the FDA last May for the treatment of adults with T2D. The combination was approved in November in the E.U., where it will be marketed under the name Qtrilmet; it is indicated to improve glycemic control in adults with T2D when metformin with or without a sulfonylurea and either saxagliptin or dapagliflozin does not provide adequate glycemic control, or when T2D patients are already being treated with metformin, saxagliptin and dapagliflozin.

In related news, and on the basis of its favorable effect on cardiovascular disease in diabetes patients, the FDA approved a new indication for the marketed SGLT inhibitor **canagliflozin** (Invokana; Mitsubishi Tanabe/Janssen): to reduce the risk of end-stage kidney disease, doubling of serum creatinine, cardiovascular death and hospitalization for heart failure in adults with T2D mellitus and diabetic nephropathy with albuminuria. The new indication is based on results from the phase III CREDENCE study in patients with T2D and diabetic kidney disease, which was stopped early when it met the prespecified criteria for efficacy (NCT02065791). In the randomized,

double-blind, event-driven, placebo-controlled, parallel-group, two-arm, multicenter study, the SGLT inhibitor demonstrated a 30% reduction in the risk of the primary composite endpoint (end-stage kidney disease, doubling of serum creatinine and renal or cardiovascular death). Results also showed canagliflozin reduced the risk of secondary cardiovascular endpoints, including a 39% reduction in the risk of hospitalization for heart failure. Overall, adverse events and serious adverse events were similar but numerically lower in the canagliflozin group compared with placebo. The rates of diabetic ketoacidosis and genital mycotic infections were numerically higher with the study drug, as observed in other clinical trials. Additionally, there was no imbalance in lower limb amputation or bone fracture in this trial and no new safety signals were identified (16).

Hypoglycemia, defined as blood sugar level of less than 54 mg/dL, is a potentially dangerous consequence of exercise, alcohol consumption or prolonged fasting, as well as of poor or overly intensive glucose control, and is most common in diabetes patients treated with insulin. Symptoms range from dizziness, anxiety and confusion to coordination problems, blurred vision, loss of consciousness and seizures. Chronic hypoglycemia can have severe negative effects on cognitive ability and brain microanatomy, particularly in children with type 1 diabetes, and severe hypoglycemia can be life-threatening. Mild episodes of hypoglycemia may be reversed by intake of oral carbohydrates (candy, fruit juice, soda or glucose tablets), while more severe episodes may require the administration of glucagon by intramuscular injection. The year 2019 saw the introduction of two new glucagon formulations for the treatment of hypoglycemia, greatly facilitating the treatment of hypoglycemia. In July, the FDA approved Lilly's **Baqsimi**, a single-dose intranasal device delivering glucagon dry powder. It is indicated for the treatment of severe hypoglycemia in patients with diabetes aged 4 years and older, and was launched in August. The following month, the FDA approved Xeris Pharmaceuticals' **Gvoke**, a single-dose prefilled syringe or HypoPen autoinjector device for the treatment of patients aged 2 and older. Gvoke was launched in November.

In April 2019, TherapeuticsMD announced the commercial launch of Bijuva (**17β-estradiol/progesterone**), the first and only FDA-approved bio-identical combination hormone therapy delivering estradiol and progesterone in a single, oral capsule. The product is indicated for the treatment of moderate to severe vasomotor symptoms due to menopause in women with a uterus. Approval was based on the Bijuva clinical development program that included the pivotal phase III Replenish Trial (NCT01942668), which evaluated the safety and efficacy of Bijuva in generally healthy, postmenopausal women with a uterus for the treatment of moderate to severe hot flashes (17). Bijuva resulted in a statistically significant reduction from baseline in both the frequency and severity of hot flashes compared with placebo, while reducing the risks to the endometrium. The most common adverse reactions reported were breast tenderness, headache, vaginal bleeding, vaginal discharge and pelvic pain. There were no clinically significant changes in lipid, coagulation or glucose parameters as compared to placebo, and no unexpected safety signals were seen.

Drospirenone (Slynd; Exeltis USA), the first progestin-only oral contraceptive agent, was approved by the FDA in May for pregnancy prevention. The novel estrogen-free contraceptive is supplied as a 24-active plus 4-inactive tablet dosing regimen. Significantly, it allows a 24-hour missed pill window. This not only can mean favorable safety and efficacy, but an improved bleeding profile and contraceptive efficacy for up to 24 hours in the event of a delayed or missed dose. Slynd was launched in the U.S. in September.

The Population Council's Annovera (**segesterone acetate/ethinyl estradiol vaginal system**) was launched last year in the U.S., where it is the first long-acting prescription birth control that is patient-controlled, procedure-free and reversible. Annovera is a small, soft flexible ring that prevents ovulation for an entire year (13 cycles) and can be inserted and removed by a woman at her discretion in repeated 4-week cycles. This technology combines low doses of a novel progestin, segesterone acetate, with the widely used estrogen ethinyl estradiol. The approval was based in part on data from 17 clinical trials, including two pivotal phase III safety and efficacy trials. The phase III program enrolled a total of 2,308 women across 27 study sites in the U.S., Latin America, Europe and Australia. Women in

the trials were between 18 and 40 years of age and were instructed to use the system over 13 menstrual cycles, or 1 full year. The data show that Annovera is 97.3% effective in preventing pregnancy when used as directed. Annovera offers a similar risk profile to those of other combined hormonal contraceptives, and carries a boxed warning related to increased cardiovascular risk when used while smoking. Annovera is licensed to TherapeuticsMD for marketing in the U.S.

In the summer of 2019, the U.S. FDA approved **bremelanotide** (Vyleesi; Palatin Technologies/AMAG Pharmaceuticals), a first-in-class melanocortin MC_3/MC_4 receptor agonist (Fig. 6), indicated to treat acquired, generalized hypoactive sexual desire disorder in premenopausal women. The

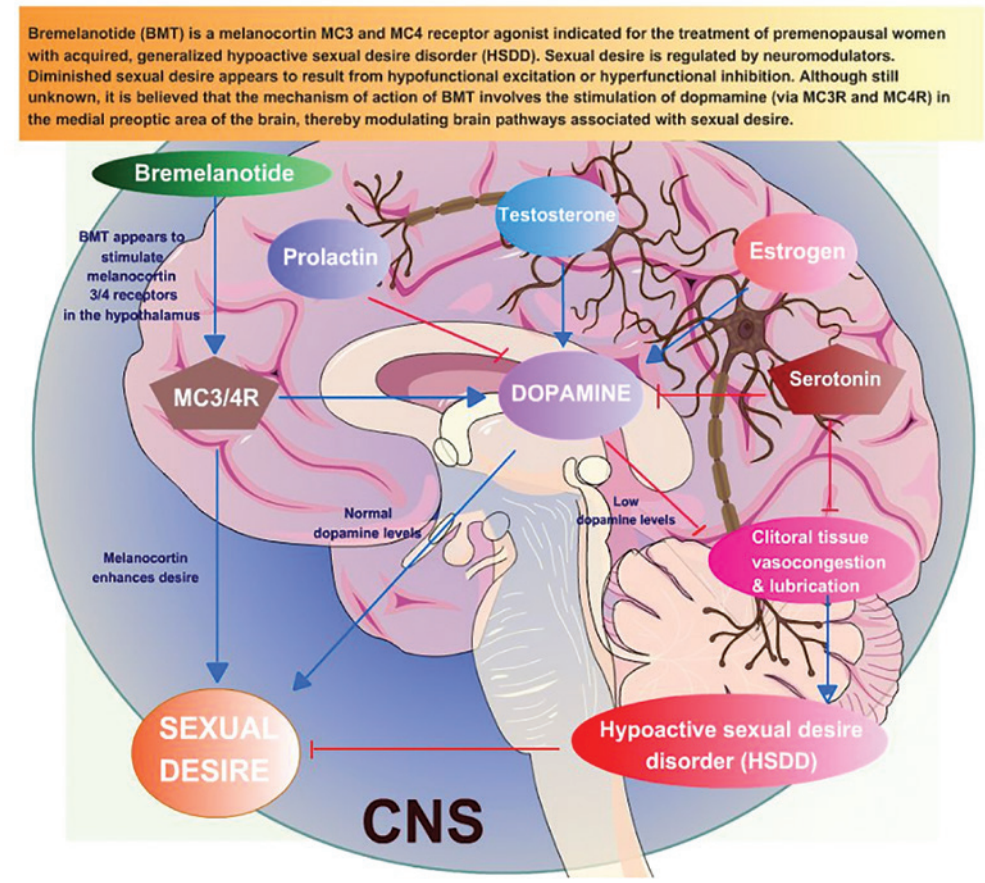

Figure 6. Bremelanotide (BMT) is a melanocortin MC_3 and MC_4 receptor agonist indicated for the treatment of premenopausal women with acquired, generalized hypoactive sexual desire disorder. Sexual desire is regulated by neuromodulators. Diminished sexual desire appears to result from hypofunctional excitation or hyperfunctional inhibition. Although still unknown, it is believed that the mechanism of action of bremelanotide involves the stimulation of dopamine (via MC_3 and MC_4) in the medial preoptic area of the brain, thereby modulating brain pathways associated with sexual desire.

drug is self-administered by autoinjector at least 45 minutes before anticipated sexual activity. The approval was based upon data from approximately 1,200 women in two pivotal, double-blind, placebo-controlled phase III trials (RECONNECT). In the two identical trials, bremelanotide met the prespecified coprimary efficacy endpoints of improvement in desire and reduction in distress as measured by validated patient-reported outcome instruments, with a favorable safety profile. Upon completion of the trials, women had the option to continue in a voluntary open-label safety extension study for an additional 12 months. Nearly 80% of patients who completed the phase III trials elected to remain in the open-label portion of the study, wherein all patients received the active drug. Bremelanotide was launched in late August.

Takeda's gonadotropin-releasing hormone (GnRH) receptor antagonist **relugolix** (Relumina) was approved and launched last year in Japan for the symptomatic relief of uterine fibroids. Takeda filed an application for approval in February 2018, based on the Japanese phase III clinical trials (TAK-385/CCT-002 study and 3008 study) in patients with uterine fibroids. In May 2018, the company licensed exclusive Japanese marketing rights for this indication to Aska.

Evocalcet (Orkedia; Kyowa Kirin), an oral calcium-sensing receptor (CaSR) agonist first approved in 2018 for the treatment of secondary hyperparathyroidism, was approved and launched in Japan in late 2019 for a new and related indication: treatment of hypercalcemia in patients with parathyroid carcinoma or primary hyperparathyroidism who are unable to undergo parathyroidectomy or relapse after parathyroidectomy. This action was labeled a "partial change approval" by Japan's MHLW, and was based on the results of a phase III trial. Evocalcet has orphan drug status in Japan for this new indication.

Dermatologic Drugs

In January 2019, Almirall launched the once-daily, oral, narrow-spectrum tetracycline-derived antibiotic **sarecycline hydrochloride** (Seysara) in the U.S., where it is indicated for the treatment of inflammatory lesions of non-nodular moderate to severe acne vulgaris in patients age 9 years and older. Sarecycline exhibits antibacterial activity against important skin/soft tissue pathogens with targeted activity against *Cutibacterium acnes*, an anaerobic Gram-positive bacterium linked with acne lesions (18). It also exerts anti-inflammatory effects, as do other tetracyclines used in the treatment of acne vulgaris. In contrast with broad-spectrum tetracyclines, sarecycline is less potent against aerobic Gram-negative bacilli and anaerobic bacteria associated with endogenous intestinal microbial flora. This provides it with a more specific antibacterial spectrum and lower chances of adverse off-target antibacterial effects, thus making it a promising choice of treatment over others in its class. It has demonstrated less propensity to resistance than other tetracyclines, and is active against tetracycline-resistant *Staphylococcus aureus* as well as erythromycin- and clindamycin-resistant *C. acnes* strains. Sarecycline was discovered by Paratek and licensed to Allergan, which subsequently divested its U.S. medical dermatology portfolio to Almirall.

Galderma's **trifarotene** (Aklief) was approved and launched last year in the U.S. for the topical treatment of acne in patients aged 9 years and older. Trifarotene is the only topical retinoid that selectively targets retinoic acid receptor γ (RAR-γ), the most common RAR found in the skin, and is the first new retinoid approved by the FDA for the treatment of acne in more than 20 years.

The IL-17 family has six known members (IL-17A-F); IL-17A is the principal T-helper 17 (Th17) cell effector cytokine. Activation of the Th17/IL-17 response has been implicated in various autoimmune disorders, including psoriasis, and several biologics targeting the cytokine are marketed as antipsoriatic agents. The most recent addition to the anti-IL-17A MAb family is **netakimab** (Efleira; Biocad), which was approved and launched for the first time last year in Russia for the treatment of moderate to severe plaque psoriasis.

IL-23 works upstream of IL-17, and its inhibition results in effective inhibition of the downstream cytokine, while requiring less frequent dosing. **Risankizumab** (Skyrizi), an IL-23-directed humanized MAb codeveloped by Boehringer Ingelheim and AbbVie, was launched by the latter in the U.S. and U.K. for the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy. Risankizumab was also launched in Japan,

where it is indicated for the treatment of psoriatic arthritis and plaque, pustular or erythrodermic psoriasis in adult patients who have an inadequate response to conventional therapies. The introduction of agents targeting the IL-17/IL-23 signaling pathway has revolutionized the treatment of psoriasis.

Duobrii, a fixed-dose combination of **halobetasol propionate and tazarotene** developed by Bausch Health (formerly Valeant), was launched in the U.S. in 2019 as a topical treatment for adults with plaque psoriasis. Duobrii is the first and only topical lotion that contains a unique combination of halobetasol propionate, a corticosteroid, and tazarotene, a retinoid. When used separately to treat plaque psoriasis, the duration of use of halobetasol propionate is limited by FDA labeling constraints to 2-4 weeks, and the use of tazarotene can be limited due to tolerability concerns. Duobrii, in contrast, has been used successfully for up to 52 weeks in safety studies.

Tapinarof is a naturally derived topical anti-inflammatory agent that acts as an aryl hydrocarbon receptor (AhR) agonist. In May 2019, the drug was approved in China for the treatment of moderate stable psoriasis vulgaris in adults. It was launched for this indication by Tianji Pharma, a subsidiary of Guanhao Biotech, in July.

Behçet's disease is a rare, chronic, relapsing, idiopathic autoimmune disorder that causes small blood vessels around the body to become inflamed, known as vasculitis. The symptoms—which vary depending on the body part affected—include recurrent oral and/or genital ulcerations, other skin lesions, uveitis and ocular lesions that may lead to blindness. The treatment of Behçet's disease is generally empiric, with a goal of controlling symptoms, suppressing the inflammatory process and preventing organ damage. Various anti-inflammatory and immunosuppressive agents have been used as the main therapeutic modalities, although none effectively controls all symptoms. On the basis of its anti-inflammatory activity in other indications, the small-molecule phosphodiesterase 4 (PDE4) inhibitor **apremilast** was evaluated for the treatment of oral ulcers in patients with Behçet's. By inhibiting PDE4, apremilast boosts levels of intracellular cyclic AMP, particularly in immune cells. This leads to decreases in levels of proinflammatory cytokines (tumor necrosis factor α [TNF-α], IL-23 and interferon γ [IFN-γ]), together with elevations in those of anti-inflammatory cytokines such as IL-10. Last year, on the basis of results obtained in the randomized, placebo-controlled, double-blind phase III RELIEF study, apremilast (Otezla; Celgene) was approved and launched in the U.S. for the treatment of oral ulcers in patients with Behçet's disease. The product has orphan drug status for this new indication. Apremilast has been marketed since 2014 for the treatment of psoriasis and psoriatic arthritis.

Anti-infective Therapy

For decades, experts have voiced concerns about the lack of new antibacterial agents with which to face the increasingly urgent threat of multidrug resistance. It was a promising development last year, therefore, when several new anti-infective drugs and drug combinations were approved by regulatory agencies around the world.

Pleuromutilin antibiotics interfere with bacterial protein synthesis via a specific interaction with the 23S rRNA of the 50S bacterial ribosome subunit. They have a distinct antibacterial profile and show no cross-resistance with any other class of antibiotics (19). In August 2019, the U.S. FDA approved oral and intravenous formulations of the pleuromutilin antibiotic **lefamulin** (Xenleta; Nabriva Therapeutics) for the treatment of community-acquired bacterial pneumonia (CABP) in adults. Lefamulin thus became the first intravenous and oral antibiotic with a novel mechanism of action to be approved by the FDA in nearly 2 decades. Both the intravenous and oral formulations of lefamulin had been granted QIDP and fast track designation by the FDA. As part of the former, lefamulin underwent priority review; the drug was launched in September.

In June, the FDA approved Merck & Co.'s new combination antibacterial Recarbrio (**imipenem/cilastatin sodium/relebactam**) for patients age 18 years and older who have limited or no alternative treatment options, for the treatment of complicated urinary tract infection (cUTI), including pyelonephritis, caused by the susceptible Gram-negative microorganisms *Enterobacter cloacae, E. coli, Klebsiella aerogenes, Klebsiella pneumoniae* and *Pseudomonas aeruginosa*. Recarbrio is also indicated in patients

age 18 years or older who have limited or no alternative treatment options, for the treatment of complicated intra-abdominal infections caused by the susceptible Gram-negative microorganisms *Bacteroides caccae, Bacteroides fragilis, Bacteroides ovatus, Bacteroides stercoris, Bacteroides thetaiotaomicron, Bacteroides uniformis, Bacteroides vulgatus, Citrobacter freundii, E. cloacae, E. coli, Fusobacterium nucleatum, K. aerogenes, Klebsiella oxytoca, K. pneumoniae, Parabacteroides distasonis* and *P. aeruginosa*. Approval of these indications, under priority review, is based on limited clinical safety and efficacy data for Recarbrio. To reduce the development of drug-resistant bacteria and maintain the effectiveness of Recarbrio and other antibacterial drugs, Recarbrio should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. In mid-December, the EMA's CHMP adopted a positive opinion recommending approval of Recarbrio for the treatment of infections due to aerobic Gram-negative organisms in adults with limited treatment options.

In mid-November, the FDA approved Shionogi's **cefiderocol** (Fetroja) for patients age 18 years and older who have limited or no alternative treatment options, for the treatment of cUTI, including pyelonephritis, caused by *E. coli*, *K. pneumoniae*, *Proteus mirabilis*, *P. aeruginosa* and *E. cloacae* complex. A member of the cephalosporin class, cefiderocol functions as a siderophore and binds to extracellular free ferric iron. In addition to passive diffusion via porin channels, cefiderocol is actively transported across the outer cell membrane of bacteria into the periplasmic space using a siderophore iron uptake mechanism. The drug exerts bactericidal action by inhibiting cell wall biosynthesis through binding to penicillin-binding proteins. Cefiderocol was designated a QIDP by the FDA, receiving fast track designation and priority review. Of note, an increase in all-cause mortality was observed in patients treated with cefiderocol as compared with best available therapy in a multinational, randomized, open-label trial in critically ill patients with carbapenem-resistant Gram-negative bacterial infections (NCT02714595); for this reason, the drug is reserved for use in patients with limited or no other treatment options. Shionogi anticipates making cefiderocol commercially available in early 2020.

Following a late 2018 approval, the novel tetracycline antibiotic **omadacycline** (Nuzyra; Paratek) was launched in the U.S. in early 2019, indicated for the treatment of adult patients with acute bacterial skin and skin structure infections and CABP caused by susceptible microorganisms. Omadacycline was granted fast track and QIDP designations in the U.S. for both of these indications. Paratek had also filed in the E.U. for approval of omadacycline for these indications; however, in October 2019, following an EMA request for an additional clinical study in patients with CABP, the company decided to withdraw both applications in order to later pursue a concurrent approval.

The quinolone antibacterial agent **lascufloxacin hydrochloride** (Lasvic; Kyorin) was approved by Japan's MHLW last year for the treatment of respiratory and ear, nose and throat infections. It is indicated for use in pharyngitis, stomatitis, tonsillitis, acute bronchitis, pneumonia, secondary infection of chronic respiratory disease, middle ear infection and sinusitis. It is suitable for treating infections caused by susceptible strains of *Staphylococcus, Streptococcus, Pneumococcus, Moraxella (Branhamella) catarrhalis, Klebsiella, Enterobacter, Haemophilus influenzae, Legionella pneumophila, Prevotella* and *Mycoplasma pneumoniae*.

Dovato, a fixed-dose combination of the HIV integrase inhibitor **dolutegravir** and the reverse transcriptase inhibitor **lamivudine**, was approved last year in the U.S., E.U. and Canada for the treatment of HIV-1 infection in treatment-naive adults with no known resistance to either agent. The combination product was developed by ViiV Healthcare with the aim of simplifying anti-HIV treatment regimens, and was introduced in the U.S., its first market, in April 2019.

African trypanosomiasis, commonly known as sleeping sickness, is caused by the parasite *Trypanosoma brucei gambiense*, which is transmitted to humans by the bite of infected tsetse flies. Without prompt diagnosis and treatment, sleeping sickness is usually fatal, as the parasites invade the CNS. In 2019, the antitrypanosomal medication **fexinidazole** (Fexinidazole Winthrop) was approved in the Democratic Republic of the Congo (DRC) and the European Union (in the latter case, for use outside the E.U.), becoming the first all-oral treatment

for this neglected tropical disease. In July, the WHO added fexinidazole to the Essential Medicines Lists for adults and children, for the treatment of the first and second stages (hemolymphatic and neurologic phases, respectively) of sleeping sickness. Fexinidazole development was driven by Drugs for Neglected Diseases initiative (DNDi) using a new model for drug development that ultimately involved 15 governmental, private industry and civil society partners, including Sanofi as the main pharma partner.

Pretomanid, a small-molecule inhibitor of cell wall biosynthesis, was approved last August by the FDA for use, as part of an oral combination regimen with bedaquiline and linezolid (BPaL regimen), for the treatment of adults with pulmonary, extensively drug-resistant tuberculosis (XDR-TB) and treatment-intolerant or nonresponsive multidrug-resistant tuberculosis (MDR-TB). Pretomanid was added to the Stop TB Partnership's Global Drug Facility product catalog in October, just 2 months after receiving approval, making the treatment available in 150 countries and territories. Pretomanid was first identified by Pathogenesis and was licensed to the Global Alliance for TB Drug Development (TB Alliance) for development, with a commitment to make it available royalty-free in endemic countries. In 2019, TB Alliance signed a license and collaboration agreement granting rights to Mylan to commercialize pretomanid, as part of the BPaL regimen, for the treatment of XDR-TB and MDR-TB. Pretomanid has been granted orphan drug, fast track and QIDP designations in the U.S.

Therapy of Musculoskeletal & Connective Tissue Diseases

The Janus kinases (JAK1, JAK2, JAK3 and Tyk2) are associated with different receptors for cytokines that are relevant in arthritis, including IL-6, IFN-γ, IL-12, IL-15 and IL-23. For this reason, JAK inhibitors have been investigated extensively as potential disease-modifying antirheumatic drugs, culminating in the first-in-class agent tofacitinib in 2012. Last year saw the introduction of two new JAK inhibitors for the treatment of rheumatoid arthritis: **peficitinib hydrobromide** (Smyraf; Astellas) in Japan and **upadacitinib tartrate** (Rinvoq; AbbVie) in the U.S.

The IL-23/IL-17 axis, described above (see Dermatologic Drugs section), regulates acquired immunity as well as proinflammatory and allergic responses, and has been identified as an important inflammatory pathway in ankylosing spondylitis (AS). In 2019, the anti-IL-17A MAb **ixekizumab** (Taltz; Lilly) was approved and launched for the treatment of adults with active AS, also known as radiographic axial spondylarthritis. This is a new indication for ixekizumab, which was previously launched for psoriasis, plaque psoriasis and psoriatic arthritis.

In August, Daiichi Sankyo announced that the FDA had approved **pexidartinib** (Turalio) as the first and only treatment for adult patients with symptomatic tenosynovial giant cell tumor (TGCT), a group of rare nonmalignant tumors that affect small and large joints. Researchers have determined that a minority of the cells that make up a TGCT carry a specific chromosomal translocation in specific regions on chromosomes 1 and 2. Cells containing this translocation overproduce colony-stimulating factor 1 (CSF-1) (20), and thus attract other cells expressing a CSF-1 receptor (CSF 1R), such as macrophages. These other cells make up the bulk of a TGCT, and most likely cause the inflammatory changes associated with these tumors. Pexidartinib, a small-molecule CSF-1R inhibitor, was discovered by Plexxicon, which was acquired by Daiichi in 2011, but continues to function as an independent unit. Pexidartinib is indicated for use in patients with TGCT that is associated with severe morbidity or functional limitations and is not amenable to improvement with surgery. Because of risk of hepatotoxicity, the drug will be available only through the Turalio REMS Program, and can only be prescribed by certified healthcare providers. Given the rarity of TGCT (incidence 1.8 people per 1 million population in the U.S.), pexidartinib has been awarded orphan drug and breakthrough therapy status.

Immunomodulators & Agents for Immunization

Hemophagocytic lymphohistiocytosis (HLH) is an ultra-rare, rapidly progressive and often fatal syndrome of hyperinflammation in which massive overexpression of IFN-γ is thought to drive immune system hyperactivation, ultimately leading to organ

failure. Both primary (familial) and secondary (acquired) forms exist. Primary HLH is a rare disease, with an incidence of approximately 1:50,000 births per year worldwide, according to the Immune Deficiency Foundation (21). In late 2018, the FDA approved **emapalumab** (Gamifant), a MAb that binds to and neutralizes IFN-γ, as the first new treatment for HLH in nearly a quarter of a century. Prior to this agent, standard therapy for HLH consisted of steroids, chemotherapy and hematopoietic stem cell transplant. Emapalumab was discovered and developed by NovImmune and is marketed by Sobi; the product was launched during the first quarter of 2019. Emapalumab has orphan drug status, breakthrough therapy designation and rare pediatric disease designation in the U.S., and was granted priority review by the FDA.

Asceniv (**immune globulin intravenous, human-slra**), is a plasma-derived, polyclonal, intravenous immune globulin from ADMA Biologics. The product, which was approved by the FDA in April 2019, is indicated for the treatment of primary humoral immunodeficiency (PI) or primary immune deficiency disease in adults and adolescents (12-17 years of age). PI includes but is not limited to the humoral immune defect in congenital agammaglobulinemia, common variable immunodeficiency (CVID), X-linked agammaglobulinemia, Wiskott–Aldrich syndrome and severe combined immunodeficiencies (SCID). Following optimization of the manufacturing process, Asceniv was launched in the U.S., its first market, in October.

Grifols obtained FDA approval last summer for Xembify (**immune globulin subcutaneous, human-klhw**), a subcutaneous immune globulin that is also indicated for the treatment of PI, including but not limited to congenital agammaglobulinemia, CVID, X-linked agammaglobulinemia, Wiskott–Aldrich syndrome and SCID. The product, which is indicated for use in patients 2 years of age and older, was launched in mid-December.

The JAK inhibitor **ruxolitinib phosphate** (Jakafi; Incyte) was approved and launched last year in the U.S. for a new indication: the treatment of steroid-refractory acute graft-versus-host disease (GvHD) in adult and pediatric patients aged 12 years and older. Approval, under priority review, was based on data from REACH1, an open-label, single-arm, multicenter study of ruxolitinib in combination with corticosteroids in patients with steroid-refractory grade II-IV acute GvHD (NCT02953678). Of the 71 patients recruited into REACH1, 49 patients were refractory to steroids alone, 12 patients had received two or more prior anti-GvHD therapies and 10 patients did not otherwise meet the FDA definition of steroid-refractory. Efficacy was evaluated on the basis of day 28 overall response rate (ORR), defined as a complete response (CR), very good partial response or partial response as per the Center for International Blood and Marrow Transplant Research (CIBMTR) criteria. The day 28 ORR in the 49 patients refractory to steroids alone was 57% with a CR rate of 31%. The most frequently reported adverse reactions among all 71 study participants were infections (55%) and edema (51%), and the most common laboratory abnormalities were anemia (75%), thrombocytopenia (75%) and neutropenia (58%). Ruxolitinib was previously launched for the treatment of myelofibrosis (2011) and PV (2014). It has orphan drug status and breakthrough therapy designation for the GvHD indication.

Medac's DNA alkylating agent **treosulfan**, long marketed for the treatment of ovarian cancer, was approved last year in the E.U. for a new indication: in combination with fludarabine, as part of conditioning treatment prior to allogeneic hematopoietic stem cell transplantation in adult patients with malignant and nonmalignant diseases, and in pediatric patients with malignant diseases. In comparison with other conditioning regimens, the treosulfan-based regimen is associated with reduced toxicity while maintaining a high level of intensity and antileukemic effect. Marketed for the new indication as Trecondi, the product was introduced in Germany in the third quarter. It has orphan drug status for this indication in the E.U. as well as the U.S.

In 2019, 4 years after receiving a positive scientific opinion from the CHMP, the WHO announced the rollout of the **RTS,S/AS01E malaria vaccine** Mosquirix in Malawi in a landmark pilot program, culminating 30 years of vaccine development. Malawi was the first of three African countries in which the vaccine was made available for administration to children up to 2 years of age; Ghana and Kenya introduced the vaccine shortly thereafter.

The pilot program will enroll approximately 360,000 children. Designed to generate evidence and experience to inform WHO policy recommendations on the broader use of Mosquirix (22), the program will look at reductions in child deaths; vaccine uptake, including whether parents bring their children on time for the four required doses; and vaccine safety in the context of routine use. The WHO-coordinated pilot program is a collaborative effort with ministries of health in Ghana, Kenya and Malawi and a range of in-country and international partners, including PATH and GlaxoSmithKline, the vaccine developer and manufacturer; the latter is donating up to 10 million vaccine doses for this pilot.

In another exciting development last year, the EC in November granted conditional approval for Merck & Co.'s **Ebola Zaire Vaccine** (Ervebo), the first Ebola vaccine to be approved by any regulatory agency following evaluation in large clinical trials; the FDA followed suit a month later. The vaccine was discovered at Canada's National Microbiology Laboratory with funding from the U.S. government's Biomedical Advanced Research and Development Authority (BARDA), and was developed through a public–private partnership with NewLink Genetics and Merck. It has been tested extensively in the last two major Ebola outbreaks in West Africa (2013-2016) and the DRC (2018-2019). Ervebo is indicated for active immunization of individuals age 18 years or older, to protect against Ebola virus disease caused by Zaire Ebola virus. The approval allows Merck to initiate manufacturing in Germany of licensed doses, which are expected to be available from Q3 2020. Merck is also working with the WHO, the U.S. government and Gavi, the Vaccine Alliance, to ensure uninterrupted access of its vaccine in support of international response efforts in the ongoing outbreak in the DRC. Two other Ebola vaccines had previously been approved, on the basis of phase I and phase II testing, albeit for emergency use only. Russia's Gamaleya Federal Research Centre for Epidemiology and Microbiology developed Gam Evac Combi, a combined vector vaccine against Ebola fever that was authorized for use in medical practice within the territory of the Russian Federation in 2015. In 2017, the China FDA approved Ad5-EBOV, a vaccine codeveloped by the Institute of Biomedical Engineering, Academy of Military Medical Sciences and Tianjin CanSino Biotechnology.

In September 2019, Bavarian Nordic received marketing approval from the FDA of its **MVA-BN orthopox vaccine** (Jynneos), indicated for the prevention of smallpox and monkeypox disease in adults 18 years of age and older determined to be at high risk for smallpox or monkeypox infection. The company was awarded a Priority Review Voucher along with the approval. Although the vaccine has been available in the E.U. since 2013 for prevention of smallpox, the additional indication of monkeypox in the U.S. is new and provides additional commercial opportunities: Jynneos is the world's first monkeypox vaccine. Jynneos is being supplied to the U.S. government for inclusion in the Strategic National Stockpile.

Also in September, the Drug Controller General of India approved **Twinrab**, a cocktail of two MAbs developed by Zydus Cadila in partnership with the WHO. The product was approved for postexposure prophylaxis against rabies virus infection, in combination with a rabies vaccine.

Danish vaccine company AJ Vaccines, which took over the Statens Serum Institute vaccine business in 2017, obtained marketing approval in Denmark last year for the inactivated poliomyelitis vaccine Picovax (**IPV-AI-SSI**). The vaccine consists of inactivated poliovirus type 1, 2 and 3, and is based on a proprietary formulation technology that allows a lower dose of active substances. It is indicated for primary vaccination of infants from age 6 weeks and revaccination of infants, children, adolescents and adults. The Danish marketing approval paves the way for WHO prequalification, which will enable AJ Vaccines to deliver up to 100 million doses of Picovax to UN agencies from 2020-2024. Although polio has largely been eradicated in industrialized nations with effective national immunization programs, the disease remains endemic in three countries (Afghanistan, Nigeria and Pakistan); moreover, 13 others are considered "outbreak countries", i.e., those that have stopped indigenous wild poliovirus but are experiencing re-infection, either through the importation of wild or vaccine-derived poliovirus from another country, or the emergence and circulation of vaccine-derived poliovirus (23).

In late December, Sinovac announced that the China NMPA had approved and issued a product license for

the company's **live-attenuated varicella vaccine**, indicated to prevent varicella zoster virus (chickenpox) infection in children aged 1 to 12 years old. This is the first vaccine product approved by the Chinese government after the passage in June 2019 of the country's new vaccine management law. The law, which requires stricter management of the production, research and distribution of vaccines, was implemented in the wake of a series of safety scandals (24).

Human papillomavirus (HPV), a known carcinogen, is implicated in the development of virtually all cervical cancers; it is also an important risk factor for penile, vaginal/vulvar, anal and oropharyngeal cancers. HPV is responsible for more than 5% of the global cancer burden overall, including almost one-third of cancers attributable to an infectious agent. The first HPV vaccine (Merck & Co.'s Gardasil) was introduced in 2006, and two others soon followed. The inclusion of HPV vaccines in many national immunization programs has resulted in significant reductions in cervical cancer morbidity and mortality in those countries; however, HPV vaccination is still not widely practiced in developing countries such as China, where imported vaccines are too expensive for the general public (25). Thus the December 31 approval in China of Cecolin (Xiamen Innovax Biotech), a domestically developed **bivalent HPV virus-like particle (VLP) vaccine against HPV-16 and HPV-18 L1 capsid proteins**, is a significant development. The vaccine is indicated for use in girls and women aged 9-45 years. In a 2012 screening study conducted in 37 Chinese cities, the prevalence of HPV ranged from 18.4% in Nanchang to 31.9% in Haikou (26).

Treatment of Cancer

Most prostate cancers initially depend upon androgens for sustenance, and androgen deprivation therapy (ADT) is the first-line treatment of choice, consisting of GnRH agonists, antiandrogens or surgical castration. After a period of response to hormonal manipulation as described, tumors may progress to an androgen-independent (or castration-resistant) state, in which tumor growth and metastasis continue even in the absence of hormonal stimulation, necessitating modification of the treatment regimen. Last year saw the U.S. approval and launch of a next-generation androgen receptor inhibitor indicated for the treatment of patients with nonmetastatic castration-resistant prostate cancer: **darolutamide** (Nubeqa; Bayer/Orion). The FDA approval was based on the phase III ARAMIS trial evaluating darolutamide plus ADT, which demonstrated a highly significant improvement in the primary efficacy endpoint of metastasis-free survival, with a median of 40.4 months versus 18.4 months for placebo plus ADT (27).

In May, following a priority review, the FDA approved Novartis' phosphatidylinositol 3-kinase α (PI3Kα) inhibitor **alpelisib** (Piqray) in combination with fulvestrant for the treatment of postmenopausal women, and men, with hormone receptor-positive, HER2-negative ($HR^+/HER2^-$), *PIK3CA*-mutated, advanced or metastatic breast cancer, as detected by an FDA-approved test following progression on or after an endocrine-based regimen. Approval was based on results of the phase III trial SOLAR-1, which showed alpelisib plus fulvestrant nearly doubled median progression-free survival (PFS) compared with fulvestrant alone in $HR^+/HER2^-$ advanced breast cancer patients with a *PIK3CA* mutation (median PFS 11.0 vs. 5.7 months) (NCT02437318) (28). Alpelisib provided consistent PFS results across prespecified subgroups, including among patients previously treated with a cyclin-dependent kinase 4/6 (CDK4/6) inhibitor. The ORR was more than doubled when alpelisib was added to fulvestrant in patients with a *PIK3CA* mutation (ORR = 35.7% vs. 16.2% for fulvestrant alone). Approved together with its companion diagnostic test (Qiagen's therascreen PIK3CA RGQ PCR Kit), alpelisib was the first combination product approved under the FDA Oncology Center of Excellence's real-time oncology review (RTOR) pilot program (29). The U.S. launch of alpelisib took place shortly after approval.

The antibody–drug conjugate (ADC) **trastuzumab deruxtecan** (Enhertu), discovered by Daiichi Sankyo and licensed to AstraZeneca for codevelopment and commercialization, received accelerated approval from the FDA in the waning days of December 2019, 4 months ahead of the PDUFA date. The ADC is comprised of a humanized anti-HER2 antibody attached to a topoisomerase I inhibitor

payload by a tetrapeptide linker. It is indicated for the treatment of adult patients with unresectable or metastatic HER2-positive breast cancer who have received two or more prior anti-HER2-based regimens in the metastatic setting. In addition to the accelerated approval, which was based on efficacy results (tumor response rate and duration of response) in 184 patients in the DESTINY-Breast01 (NCT03248492) study, the FDA previously bestowed fast track and breakthrough therapy status to the product. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

The first-in-class pan-FGFR inhibitor **erdafitinib** (Balversa; Janssen) was approved and almost immediately launched last year in the U.S., where it is indicated for the treatment of adult patients with locally advanced or metastatic urothelial carcinoma that has susceptible *FGFR3* or *FGFR2* genetic alterations and that has progressed during or following at least one line of prior platinum-containing chemotherapy. Erdafitinib is the first FDA-approved oral pan-FGFR kinase inhibitor that binds to four FGFRs (FGFR-1 to -4), leading to decreased cell signaling and cellular apoptosis (Fig. 7). Erdafitinib also binds to RET, CSF-1 receptor (CSF-1R), PDGFR-α and PDGFR-β, Fms-related tyrosine kinase 4 (FLT4), KIT and VEGFR-2, exhibiting additional antitumor mechanisms that result in cell kill. Moreover, erdafitinib is the first oral treatment option for patients with urothelial carcinoma.

In late 2019, the FDA granted accelerated approval for a second new treatment option for urothelial carcinoma: **enfortumab vedotin** (Padcev; Astellas/Seattle Genetics), an ADC composed of a fully human MAb targeting the cell adhesion molecule nectin-4 conjugated to the microtubule-disrupting agent monomethyl auristatin E (MMAE) via a valine-citrulline cleavable linker. The ADC is designed to be stable in the bloodstream but to release MMAE upon internalization into nectin-4-expressing tumor cells, resulting in a targeted cell-killing effect. In an early clinical trial of enfortumab vedotin, 97% of bladder tumor samples tested were found to markedly express nectin-4, confirming the ubiquity of this target in bladder carcinoma. The FDA approved enfortumab vedotin for the treatment of adult patients with locally advanced or metastatic urothelial cancer who have previously received a programmed cell death protein 1/programmed cell death 1 ligand 1 (PD-1/PD-L1) inhibitor and a platinum-containing chemotherapy before or after surgery, or in a locally advanced or metastatic setting. Seattle Genetics estimates that of the 20,000 patients diagnosed with metastatic urothelial cancer each year in the U.S., between 2,000 and 3,000 would be eligible for treatment in this third-line setting. The ADC was approved under the FDA's Accelerated Approval Program on the basis of tumor response rate in the pivotal trial EV-201, a single-arm phase II multicenter trial that enrolled 125 patients (30). Continued approval may be contingent upon verification and description of clinical benefit in confirmatory trials.

In the summer of 2019, the FDA granted accelerated approval to another novel ADC: **polatuzumab vedotin** (Polivy; Genentech). The agent comprises an anti-CD79b MAb conjugated to MMAE via a protease-cleavable peptide linker. It is indicated for use in combination with bendamustine plus rituximab, for the treatment of adults with relapsed or refractory diffuse large B-cell lymphoma who have received at least two prior therapies, and has orphan drug status in the U.S. Polatuzumab vedotin is a first-in-class agent targeted to the CD79b protein, which is expressed specifically in the majority of B cells (Fig. 8). It binds to CD79b and destroys these B cells through the delivery of the anticancer agent MMAE, while having a minimal effect on normal cells. Polatuzumab vedotin was introduced in the U.S. shortly after approval. The ADC was also granted conditional approval last year in the E.U., where it has PRIME designation and orphan drug status, and where it is designated an Advanced Therapy Medicinal Product.

Myelofibrosis, considered a form of chronic leukemia, is an uncommon hematologic cancer in which the bone marrow is progressively replaced by fibrous scar tissue. It may exist as a primary disorder, or secondary to an autoimmune disease or other bone marrow cancer. Approximately 50% of patients with primary myelofibrosis have a mutation in the *JAK2* gene; the first specific treatment for myelofibrosis was ruxolitinib, a JAK2 inhibitor that was launched in 2011. Last year, the dual-acting JAK2/FLT3 inhibitor **fedratinib** (Inrebic; Celgene) was approved and launched in the U.S.,

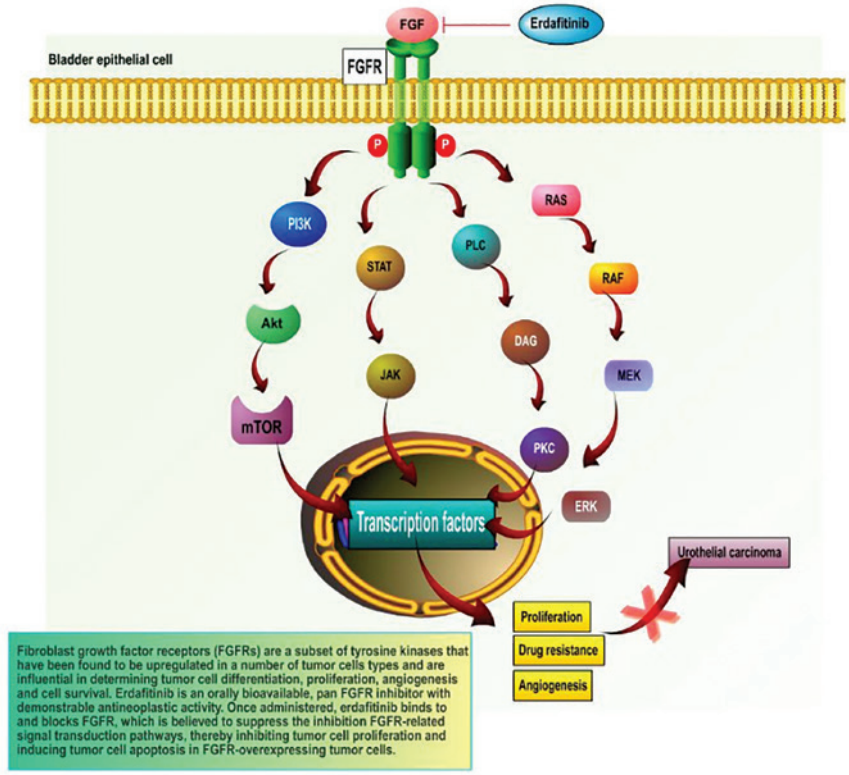

Figure 7. Fibroblast growth factor receptors (FGFRs) are a subset of tyrosine kinases that have been found to be upregulated in a number of tumor cell types and are influential in determining tumor cell differentiation, proliferation, angiogenesis and cell survival. Erdafitinib is an orally bioavailable, pan-FGFR inhibitor with demonstrable antineoplastic activity. Once administered, erdafitinib binds to and blocks FGFR, which is believed to suppress the inhibition of FGFR-related signal transduction pathways, thereby inhibiting tumor cell proliferation and inducing tumor cell apoptosis in FGFR-overexpressing tumor cells.

increasing the therapeutic options for this rare condition. Fedratinib is indicated for the treatment of adult patients with intermediate-2 or high-risk primary or secondary (post-PV or post-essential thrombocythemia) myelofibrosis. It has orphan drug status in the U.S. for this indication.

In June, Japan's MHLW approved the oral FLT3 inhibitor **quizartinib** (Vanflyta; Daiichi Sankyo) for the treatment of adult patients with relapsed/refractory FLT3-ITD acute myeloid leukemia (AML), as detected by an MHLW-approved test. The marketing authorization was based on the results from the global pivotal phase III QuANTUM-R study (NCT02039726) and a phase II study of quizartinib in Japan in patients with relapsed/refractory FLT3-ITD AML. QuANTUM-R was the first randomized phase III trial to demonstrate that an FLT3 inhibitor, given as an oral, single agent, prolonged overall survival compared with

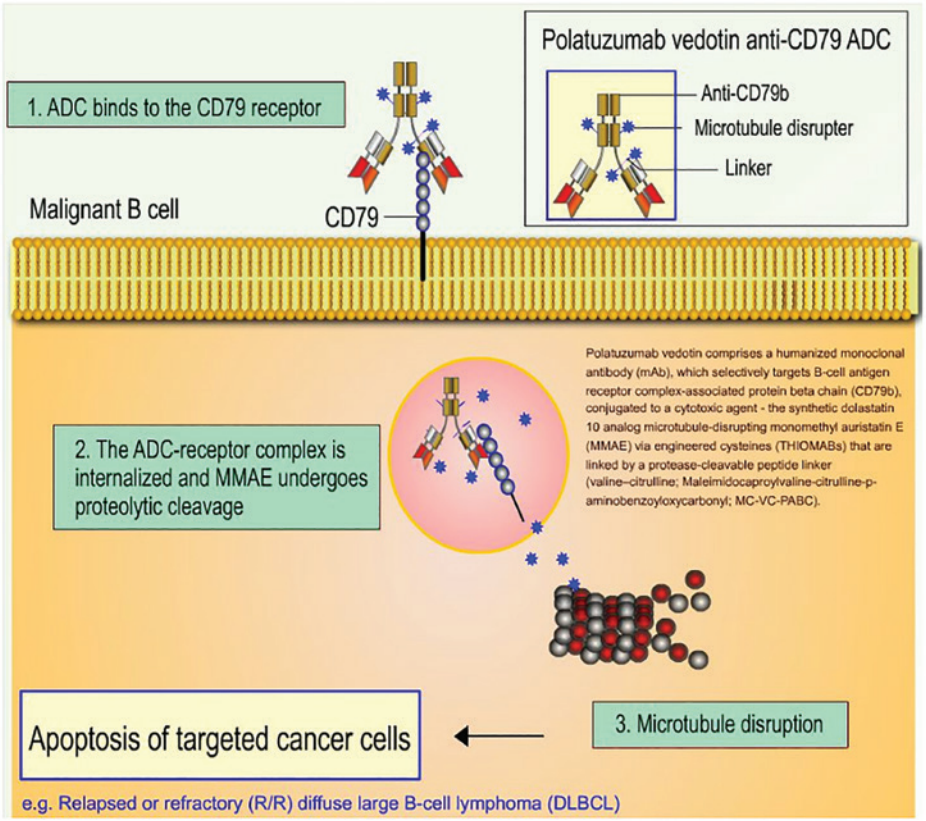

Figure 8. Polatuzumab vedotin is an antibody–drug conjugate (ADC) which consists of an anti-CD79b monoclonal antibody (MAb) conjugated to monomethyl auristatin E (MMAE) via a protease-cleavable peptide linker. It is indicated for use in combination with bendamustine plus rituximab, for the treatment of adults with relapsed or refractory diffuse large B-cell lymphoma who have received at least two prior therapies. The MAb is targeted to the CD79b protein, which is expressed specifically in the majority of B cells. The ADC binds to CD79b and destroys these B cells through the delivery of the antimicrotubule agent MMAE, while having a minimal effect on normal cells.

chemotherapy (OS 6.2 months vs. 4.7 months) in patients with relapsed/refractory FLT3-ITD AML (31). The drug, which has orphan drug status in Japan, was launched in October.

In November 2019, China's NMPA approved **flumatinib mesylate** (Hausen Xin Fu), developed by Jiangsu Hansoh and indicated for the treatment of chronic myeloid leukemia with Philadelphia chromosome-positive (Ph^+) mutation. The product received priority review. Flumatinib mesylate is a tyrosine-protein kinase ABL1 inhibitor that inhibits the activity of Bcr-Abl1 and the proliferation of tumor cells.

Exportin-1 (XPO1, CRM1) is a nuclear export receptor that is responsible for transporting proteins,

including tumor suppressor proteins, out of the nucleus. Nuclear export of tumor suppressor proteins is an important mechanism by which cancer cells avoid apoptosis and cell death. Overexpression of XPO1 leads to improper localization of cellular substrates and imparts poor prognosis. Last summer, the U.S. FDA granted accelerated approval to the first-in-class XPO1 receptor antagonist **selinexor** (Xpovio; Karyopharm) (Fig. 9), indicated for the treatment of adult patients with relapsed or refractory multiple myeloma who have received at least four prior therapies and whose disease is resistant to several other forms of treatment. Selinexor has orphan drug status in the U.S. for this indication.

The personalized antitumor medicine **entrectinib** (Rozlytrek; Chugai/Roche) was approved in Japan for the first time in June, and was approved and launched in the U.S. shortly thereafter. Entrectinib is a tyrosine kinase inhibitor that blocks the ROS1 (proto-oncogene c-Ros-1) and TRK (neurotrophin receptor) family. It is indicated in the U.S. for the treatment of adult and pediatric patients 12 years of age and older with solid tumors that have a neurotrophic tyrosine kinase receptor (NTRK) gene fusion without a known acquired resistance mutation, are metastatic or where surgical resection is likely to result in severe morbidity, and have progressed following treatment or have no satisfactory alternative therapy. NTRK fusion-positive cancer occurs when the *NTRK1/2/3* genes fuse with other genes, resulting in altered TRK proteins (TRKA/TRKB/TRKC) that can activate signaling pathways involved in proliferation of certain types of cancer. NTRK gene fusions are tumor-agnostic and have been identified in a broad range of solid tumor types, including breast, cholangiocarcinoma, colorectal, gynecological, neuroendocrine, non-small cell lung, salivary gland, pancreatic, sarcoma and thyroid cancers. Entrectinib is also indicated in the U.S. for treatment of adults with *ROS1* fusion-positive, metastatic non-small cell lung cancer. It has orphan drug status for both indications.

The Bruton tyrosine kinase inhibitor **zanubrutinib** (Brukinsa), developed by Chinese company BeiGene, was granted accelerated approval by the FDA and launched almost immediately last November. The drug is indicated for the treatment of adult patients with mantle cell lymphoma (MCL) who have received at least one prior therapy. The approval was based on efficacy results from two single-arm trials, with independent review committee-assessed ORR per 2014 Lugano Classification as the primary endpoint. Across both trials, zanubrutinib achieved an ORR of 84%. In the multicenter phase II trial of zanubrutinib in patients with relapsed or refractory MCL (NCT03206970), the ORR was 84%, including 59% CR (FDG-PET scan required) and 24% partial response. In this study, the median duration of response (DOR) was 19.5 months and median follow-up time on study was 18.4 months. In the global phase I/II trial (NCT02343120), the ORR was 84%, including 22% CR (FDG-PET scan not required) and 62% partial response. In this study, the median DOR was 18.5 months and median follow-up time on study was 18.8 months. Zanubrutinib is also undergoing regulatory review in China.

Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is an aggressive and rare disease of the bone marrow and blood that can affect multiple organs, including the lymph nodes and the skin. It often presents as leukemia or evolves into acute leukemia. The disease is more common in men than women and in patients aged 60 years and older. In late 2018, the U.S. FDA approved the first treatment for BPDCN: the CD123-directed cytotoxin **tagraxofusp** (Elzonris; Stemline Therapeutics). CD123 is a key marker in identifying BPDCN and was identified as a target for therapeutic intervention in this and a variety of other cancers. Tagraxofusp was launched in early 2019.

Immune checkpoint inhibitors are a growing class of immuno-oncology agents that are capable of restoring tumor immunity in a subset of carefully selected patients (32), including patients with lymphoid malignancies. Several new members of this class were added to the therapeutic armamentarium in 2019, all in China. Following a late 2018 approval, the anti-PD-1 MAb **sintilimab** (Tyvyt; Innovent Biologics/Lilly) was launched in February, indicated for the treatment of patients with relapsed or refractory classical Hodgkin's lymphoma (cHL). A few months later, Jiangsu Hengrui's anti-PD-1 MAb **camrelizumab** was approved and launched. Camrelizumab is indicated as third-line treatment for recurrent or refractory cHL in patients who have received second-line systemic chemotherapy; in

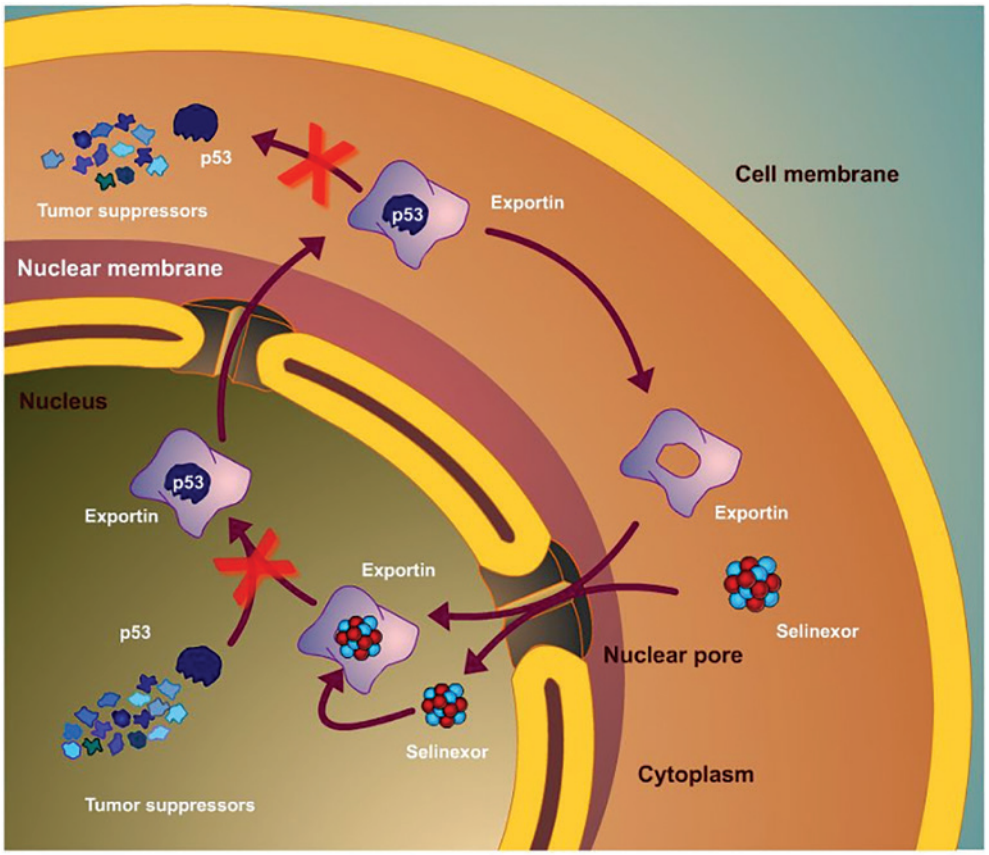

Figure 9. Exportin-1 (XPO1, CRM1) is a nuclear export receptor that is responsible for exporting proteins, including tumor suppressor proteins, out of the nucleus. Nuclear export of tumor suppressor proteins is an important mechanism by which cancer cells avoid apoptosis and cell death. Overexpression of XPO1 leads to improper localization of cellular substrates and imparts poor prognosis. The XPO1 antagonist selinexor is approved for the treatment of relapsed or refractory multiple myeloma.

December, BeiGene's humanized anti-PD-1 MAb **tislelizumab** was approved for the same indication. Finally, the anti-PD-1 MAb **toripalimab** (Tuoyi; Shanghai Junshi Biosciences) was launched for the treatment of locally advanced or metastatic melanoma in patients who have failed routine systemic treatment.

Nanobiotix's radioenhancing agent **NBTXR-3** (Hensify) was granted CE Mark approval by the EC in April for the treatment, in combination with concurrent radiation therapy, of locally advanced soft-tissue sarcoma. The product is an aqueous suspension of crystalline hafnium oxide nanoparticles designed for injection directly into a tumor prior to a patient's

first standard radiotherapy treatment. When exposed to ionizing radiation, Hensify amplifies the localized, intratumor killing effect of that radiation. The dose of X-ray delivered to the tumor is magnified, while the dose passing through healthy tissues remains unchanged. The primary tumor is killed via physical cell death, whereas any metastases are destroyed via activation of the immune system and immunogenic cell death.

Ophthalmic Drugs

Following FDA approval in March, Rocklatan (**netarsudil mesylate/latanoprost**), a new fixed-dose combination from Aerie Pharmaceuticals, was launched in the U.S. last May. It is indicated for the reduction of elevated intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension. Netarsudil is a Rho kinase (ROCK) inhibitor and latanoprost is a prostaglandin analogue; the two components work via complementary mechanisms of action to reduce IOP more effectively than either drug alone. Netarsudil works by restoring outflow through the trabecular meshwork, while latanoprost increases fluid outflow through a secondary mechanism known as the uveoscleral pathway.

Ocular angiogenesis, the abnormal formation of new blood vessels from the existing vasculature of the eye, is an important cause of ocular morbidity in patients with age-related macular degeneration (AMD). Angiogenesis inhibitors are especially appropriate for treating wet AMD, which is characterized by aberrant neovascularization. A new angiogenesis inhibitor, Novartis' **brolucizumab** (Beovu), was approved and launched in the U.S. last year for the treatment of wet AMD. Brolucizumab is a humanized monoclonal single-chain antibody Fv fragment (scFv) targeting VEGF-A. Approval was based on findings from the phase III HAWK and HARRIER trials (NCT02307682 and NCT02434328), which were 96-week, prospective, randomized, double-masked, multicenter studies designed to compare the efficacy and safety of intravitreal injections of brolucizumab 6 mg (HAWK and HARRIER) and 3 mg (HAWK only) versus the marketed angiogenesis inhibitor aflibercept in patients with wet AMD (33). In the trials, brolucizumab demonstrated noninferiority versus aflibercept in mean change in best corrected visual acuity at year 1 (week 48). In both trials, approximately 30% of patients gained at least 15 letters at year 1. In HAWK and HARRIER, brolucizumab showed greater reduction in central subfield thickness as early as week 16 and at year 1, and fewer patients had intraretinal and/or subretinal fluid. Eligible patients could be maintained on a 3-month dosing interval immediately after the loading phase. At year 1, over half of the patients were maintained on the 3-month dosing interval (56% in HAWK and 51% in HARRIER). The remaining patients in the study were treated on a 2-month dosing schedule. Brolucizumab exhibited an overall safety profile comparable to that of aflibercept.

Dextenza (**dexamethasone punctum plug**), a novel intraocular formulation of the anti-inflammatory glucocorticoid developed by Ocular Therapeutix, was launched last year in the U.S. for the treatment of ocular inflammation and pain following ophthalmic surgery. Dextenza is a preservative-free ophthalmic insert that is inserted in the lower lacrimal punctum and into the canaliculus. A single insert releases a 0.4-mg dose of dexamethasone for up to 30 days following insertion. As such, Dextenza has the potential to replace a complex eye drop regimen that, under the current standard of care, requires up to 70 topical ocular steroid drops.

Metabolic Drugs

Osteoporosis is a largely age-related disorder caused by an imbalance in the physiological process of bone remodeling. Its treatment has long been dominated by estrogens, bisphosphonates and the anti-RANKL antibody denosumab, all of which act by decreasing bone resorption, hence slowing bone loss. Less success has been achieved in the field of anabolic agents, i.e., those that promote the formation of new bone. Last year saw the approval and launch in Japan of a first-in-class agent with anabolic activity: the anti-sclerostin MAb **romosozumab** (Evenity; UCB/Amgen Astellas BioPharma) (Fig. 10). Sclerostin is a bone morphogenetic protein antagonist that inhibits the differentiation of osteoprogenitor cells and reduces osteoblast activity. Sclerostin is the product of the *SOST* gene that is produced in osteocytes buried in the bone and is a powerful inhibitor of bone formation. As osteoblasts become embedded

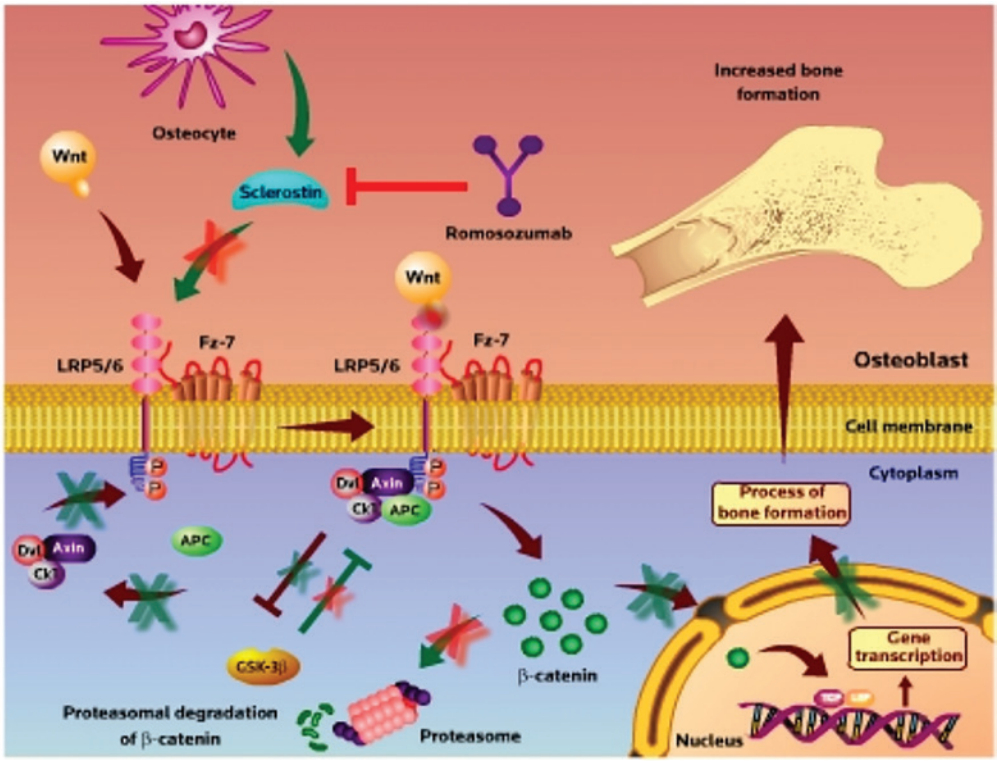

Figure 10. Sclerostin is a bone morphogenetic protein antagonist that inhibits the differentiation of osteoprogenitor cells and reduces osteoblast activity. Sclerostin is the product of the *SOST* gene that is produced in osteocytes buried in the bone and is a powerful inhibitor of bone formation. As osteoblasts become embedded in the mineralized matrix, they transform into osteocytes and begin expressing sclerostin, which controls bone formation and phosphate metabolism. The anti-sclerostin humanized monoclonal antibody romosozumab enhances osteoblast function, leading to simultaneous enhancement of bone formation and suppression of bone resorption.

in the mineralized matrix, they transform into osteocytes and begin expressing sclerostin, which controls bone formation and phosphate metabolism. Romosozumab and other agents that inhibit sclerostin enhance osteoblast function, leading to simultaneous enhancement of bone formation and suppression of bone resorption. Romosozumab is indicated in Japan for the treatment of osteoporosis in men and postmenopausal women at high risk of fracture. Later in 2019, romosozumab was approved and launched in the U.S., where it is indicated for the treatment of osteoporosis in postmenopausal women at high risk for fracture, or in patients who have failed or are intolerant to other available osteoporosis therapies.

Acute hepatic porphyria (AHP) is a family of ultra-rare genetic diseases characterized by potentially life-threatening attacks and, for some patients, chronic manifestations that negatively impact daily

functioning and quality of life. AHP is comprised of four types: acute intermittent porphyria, hereditary coproporphyria, variegate porphyria and ALA dehydratase-deficiency porphyria. Each type of AHP results from a genetic defect leading to deficiency in one of the enzymes in the heme biosynthesis pathway in the liver. Last year, the FDA approved Alnylam Pharmaceuticals' **givosiran** (Givlaari), a small interfering RNA (siRNA) targeting 5-amino levulinic acid synthase 1 (ALAS1), for the treatment of adults with AHP. The November approval, which followed a priority review, was based on results from the phase III ENVISION study in 94 patients with AHP (NCT03338816). In the pivotal, randomized, double-blind, placebo-controlled, multinational study, patients with AHP on givosiran experienced 70% fewer porphyria attacks than patients on placebo. Treatment with the agent also led to similar reductions in intravenous hemin use, as well as reductions in urinary aminolevulinic acid and urinary porphobilinogen. The most common adverse reactions associated with the treatment were nausea (27%) and injection-site reactions (25%).

In May 2019, Ionis Pharmaceuticals and its wholly owned subsidiary Akcea Therapeutics received conditional marketing authorization in the European Union for **volanesorsen** (Waylivra), indicated as an adjunct to diet in adult patients with genetically confirmed familial chylomicronemia syndrome (FCS) and at high risk for pancreatitis, in whom response to diet and triglyceride-lowering therapy has been inadequate. FCS is a rare autosomal recessive disorder caused by mutations in lipoprotein lipase, which leads to the accumulation of chylomicrons in plasma and hypertriglyceridemia (34). Among the complications produced by elevated triglycerides, the most serious is acute pancreatitis. Volanesorsen is an antisense oligonucleotide designed to reduce the production of apolipoprotein C-III (ApoC-III), a protein that regulates plasma triglycerides. As part of the conditional marketing authorization, Akcea and Ionis will conduct a noninterventional postauthorization safety study (PASS) based on a registry. In the phase III APPROACH study (NCT02211209), the largest study ever conducted in patients with FCS, treatment with the antisense drug led to clinically and statistically meaningful reduction in triglycerides compared with placebo over the study period. An analysis of patients with a history of recurrent pancreatitis events showed a significant reduction in pancreatitis attacks in volanesorsen-treated patients compared with those receiving placebo. The most common adverse events in the APPROACH trial were injection-site reactions and reductions in platelet levels. As a rare disease without effective treatment options, the development of volanesorsen was supported by several regulatory programs, including orphan drug designation in the E.U. and U.S. and Promising Innovative Medicine (PIM) designation in the U.K. The product was launched in Germany and France in August.

For a full list of all drugs launched in 2019, see Table III.

Looking Ahead to 2020

Just weeks into the new year, 2020 is already shaping up to be another busy year at the FDA and other regulatory agencies. On the basis of an analysis of *Cortellis Drug Discovery Intelligence* and *Cortellis Competitive Intelligence* data, these are a few of the drugs and biologics that we expect to see discussed in next year's edition of this article.

AR-101 (Palforzia; Aimmune Therapeutics), a peanut-derived oral immunotherapy, is on track to become the first approved desensitizing treatment for peanut allergy. Last September, the FDA's Allergenic Products Advisory Committee recommended approval of the product for use in children aged 4-17 years. The biologics license application (BLA) has a review action date of late January 2020.

Horizon Therapeutics' **teprotumumab**, a human monoclonal antibody directed against the human insulin-like growth factor 1 receptor (IGF-1R), will become the first treatment for patients with active thyroid eye disease, also known as Graves' orbitopathy. In December 2019, the FDA's Dermatologic and Ophthalmic Drugs Advisory Committee voted unanimously in support of approval. The FDA approved teprotumumab in mid-January, 2020, well ahead of the PDUFA action date of March 8.

Sunovion expects to get approval from the FDA this year to market **dasotraline**, a novel dopamine and norepinephrine reuptake inhibitor (DNRI), for the treatment of patients with moderate to severe binge

eating disorder (BED), a serious mental health condition with limited treatment options. BED is characterized by recurrent and persistent episodes of binge eating, defined as consuming large quantities of food in a short period of time, perception of loss of control during the episode, and intense feelings of shame, guilt and embarrassment afterwards.

Last November, Roche announced that the FDA had accepted the NDA and granted priority review for **risdiplam**, an investigational survival motor neuron-2 (SMN-2) splicing modifier for the treatment of SMA. Risdiplam is designed to increase and sustain SMN protein levels both throughout the CNS and peripheral tissues of the body. The FDA is expected to make a decision on approval by May 24, 2020. In the meantime, the company plans to run a global compassionate use program for eligible patients with type 1 SMA.

The EMA is reviewing a marketing authorization application (MAA) for Hansa Biopharma's **imlifidase**, indicated as desensitization therapy for patients undergoing kidney transplantation. Hansa Biopharma submitted responses to the Day 120 questions on December 22, 2019, and the review process is on track. An opinion from the CHMP is expected in the second quarter of 2020, according to the company, followed by a potential decision by the EC during the summer 2020.

For an overview of these and other 2020 predictions, see Table IV.

Disclosures

The authors are employees of Clarivate Analytics

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Table III. *New product intros 2019.*

Trade name (country)[1]	Company	Active ingredient	Indication
Piqray (US)	Novartis	Alpelisib, tablets, 50, 150 & 200 mg	In combination with fulvestrant for the treatment of postmenopausal women, and men, with hormone receptor-positive, HER2-negative ($HR^+/HER2^-$), *PIK3CA*-mutated, advanced or metastatic breast cancer
Katerzia (US)	Azurity	Amlodipine benzoate, oral suspension, 1 mg/mL	Used alone or in combination with other antihypertensive and antianginal agents for the treatment of: • Hypertension in adults and children 6 years and older, to lower blood pressure • Coronary artery disease (includes chronic stable angina; vasospastic angina; coronary artery disease in patients without heart failure or injection fraction < 40%)
Otezla (US)	Celgene	Apremilast, tablets, 10, 20 & 30 mg	Treatment of oral ulcers in patients with Behçet's disease*
Stemirac (JP)	Nipro	Autologous human bone marrow-derived mesenchymal stem cells expanded in autologous human serum	Treatment of spinal cord injury
Collategene (JP)	AnGes/Mitsubishi Tanabe	Beperminogene perplasmid, i.m. injections, 4 mg	For the improvement of ulcers in patients suffering from chronic arterial occlusion (arteriosclerosis obliterans and Buerger's disease) who have had an inadequate response to standard pharmacotherapy and who experience difficulty in undergoing revascularization
Vyleesi (US)	Palatin Technologies/ AMAG Pharmaceuticals	Bremelanotide, solution for s.c. injection in prefilled autoinjector pen, 1.75 mg/0.3 mL	Treatment of premenopausal women with acquired, generalized hypoactive sexual desire disorder
Zulresso (US)	Sage Therapeutics	Brexanolone, injections, 100 mg/20 mL (5 mg/mL) in single-dose vials	Treatment of postpartum depression
Beovu (US)	Novartis	Brolucizumab, solution for injection in prefilled syringe, 0.165 mL (6 mg/0.05 mL)	Treatment of wet age-related macular degeneration

(Continued)

Table III. *New product intros 2019. (Cont.)*

Trade name (country)[1]	Company	Active ingredient	Indication
Breztri Aerosphere (JP)	AstraZeneca	Budesonide/glycopyrronium bromide/ formoterol fumarate***, metered-dose inhaler delivering 160 µg/9 µg/5 µg per inhalation	To relieve symptoms of chronic obstructive pulmonary disease
(CN)	Jiangsu Hengrui	Camrelizumab, injections, 200 mg	Third-line treatment for recurrent or refractory classical Hodgkin's lymphoma
Invokana (US)	Mitsubishi Tanabe/ Janssen	Canagliflozin, tablets, 100 & 300 mg	To reduce the risk of end-stage kidney disease, doubling of serum creatinine, cardiovascular death and hospitalization for heart failure in adults with type 2 diabetes and diabetic nephropathy with albuminuria*
Nubeqa (US)	Bayer/Orion	Darolutamide, tablets, 300 mg	Treatment of patients with nonmetastatic castration-resistant prostate cancer
Dextenza (US)	Ocular Therapeutix	Dexamethasone, intraocular (intracanalicular) insert, 0.4 mg***	Treatment of ocular inflammation and pain following ophthalmic surgery
Dovato (US)	ViiV Healthcare	Dolutegravir/lamivudine**, tablets, 50 mg/ 300 mg	Treatment of HIV-1 infection in adults with no antiretroviral treatment history and with no known resistance to either dolutegravir or lamivudine
Slynd (US)	Exeltis USA	Drospirenone, tablets, 4 mg	For use by females of reproductive potential to prevent pregnancy
Dupixent (US)	Regeneron/Sanofi	Dupilumab, injections, 300 mg/2 mL solution in prefilled syringe	For use with other medicines to treat chronic rhinosinusitis with nasal polyposis in adults whose disease is not controlled*
Soliris (US)	Alexion	Eculizumab, injections, 300 mg/30 mL in single-dose vials	Treatment of neuromyelitis optica spectrum disorder in adult patients who are anti-aquaporin-4 (AQP4) antibody-positive*
Trikafta (US)	Vertex	Elexacaftor/tezacaftor/ivacaftor**, tablets, fixed-dose combination containing elexacaftor 100 mg/tezacaftor 50 mg/ ivacaftor 75 mg; co-packaged with tablets, ivacaftor 150 mg	Treatment of cystic fibrosis in patients aged 12 years and older who have at least one copy of the F508del mutation in the *CFTR* gene

(Continued)

Table III. *New product intros 2019. (Cont.)*

Trade name (country)[1]	Company	Active ingredient	Indication
Gamifant (US)	NovImmune/Sobi	Emapalumab, infusion, 10 mg/2 mL & 50 mg/10 mL	Treatment of adult and pediatric (newborn and older) patients with primary hemophagocytic lymphohistiocytosis
Rozlytrek (US)	Chugai/Roche	Entrectinib, capsules, 100 & 200 mg	• Treatment of adult and pediatric patients 12 years of age and older with solid tumors that have an NTRK gene fusion without a known acquired resistance mutation, are metastatic or where surgical resection is likely to result in severe morbidity, and have progressed following treatment or have no satisfactory alternative therapy • Treatment of adults with *ROS1* fusion-positive, metastatic non-small cell lung cancer
Balversa (US)	Janssen	Erdafitinib, tablets, 3, 4 & 5 mg	Treatment of adult patients with locally advanced or metastatic urothelial carcinoma that has susceptible *FGFR3* or *FGFR2* genetic alterations and progressed during or following at least one line of prior platinum-containing chemotherapy
Minnebro (JP)	Exelixis/Daiichi Sankyo	Esaxerenone, tablets, 1.25, 2.5 & 5 mg	Treatment of hypertension
Spravato (US)	Janssen	Esketamine hydrochloride, nasal spray***, 28 mg	In conjunction with an oral antidepressant, for treatment of adults with treatment-resistant depression*
Bijuva (US)	TherapeuticsMD	17β-Estradiol/progesterone**, capsules, 1 mg/100 mg	Treatment of moderate to severe vasomotor symptoms due to menopause in women with a uterus
Orkedia (JP)	Kyowa Kirin	Evocalcet, tablets, 1 & 2 mg	Treatment of hypercalcemia in patients with parathyroid carcinoma or primary hyperparathyroidism who are unable to undergo parathyroidectomy or relapse after parathyroidectomy*

(Continued)

Table III. *New product intros 2019. (Cont.)*

Trade name (country)[1]	Company	Active ingredient	Indication
Inrebic (US)	Celgene	Fedratinib, capsules, 100 mg	Treatment of adult patients with intermediate-2 or high-risk primary or secondary (post-polycythemia vera or post-essential thrombocythemia) myelofibrosis
Baqsimi (US)	Lilly	Glucagon, single-dose intranasal device*** containing dry powder, 3 mg	Treatment of severe hypoglycemia in patients with diabetes ages 4 years and older
Gvoke (US)	Xeris Pharmaceuticals	Glucagon, single-dose prefilled HypoPen autoinjector***, 0.5 mg/0.1 mL & 1.0 mg/0.2 mL; single-dose prefilled syringe, 0.5 mg/0.1 mL & 1.0 mg/0.2 mL	Treatment of severe hypoglycemia in pediatric and adult patients with diabetes ages 2 years and older
Vyondys 53 (US)	Sarepta Therapeutics	Golodirsen, injections, 100 mg/2 mL (50 mg/mL) in single-dose vials	Treatment of Duchenne muscular dystrophy in patients with a confirmed mutation amenable to exon 53 skipping
Oligomannate (CN)	Shanghai Green Valley Pharmaceuticals	GV-971, capsules	Treatment of mild to moderate Alzheimer's disease
Duobrii (US)	Bausch Health	Halobetasol propionate/tazarotene**, lotion, 0.01%/0.045%	Topical treatment of plaque psoriasis in adults
Asceniv (US)	ADMA Biologics	Immune globulin intravenous, human-slra, liquid for intravenous injection, 10%	Treatment of primary humoral immunodeficiency in adults and adolescents (12 to 17 years of age)
Xembify (US)	Grifols	Immune globulin subcutaneous, human-klhw, solution for subcutaneous injection, 20%	Treatment of primary humoral immunodeficiency in patients 2 years of age and older
Taltz (US)	Lilly	Ixekizumab, solution in single-dose prefilled autoinjector, 80 mg/mL; solution in single-dose prefilled syringe, 80 mg/mL	Treatment of adults with active ankylosing spondylitis*
Xenleta (US)	Nabriva Therapeutics	Lefamulin, tablets, 600 mg; vials for injection, 150 mg/15 mL	Treatment of adults with community-acquired bacterial pneumonia caused by susceptible microorganisms
Inbrija (US)	Acorda Therapeutics	Levodopa, inhalation powder in capsules*** containing 42 mg levodopa for use with the Inbrija inhaler	Intermittent treatment of "off" episodes in patients with Parkinson's disease treated with carbidopa/levodopa

(Continued)

Table III. *New product intros 2019. (Cont.)*

Trade name (country)[1]	Company	Active ingredient	Indication
Reblozyl (US)	Acceleron/Celgene	Luspatercept, lyophilized powder in single-use vials, 25 & 75 mg, for reconstitution and subcutaneous injection	Treatment of anemia in adult patients with β-thalassemia who require regular red blood cell transfusions
Tarlige (JP)	Daiichi Sankyo	Mirogabalin besylate, tablets, 2.5, 5, 10 & 15 mg	Treatment of peripheral neuropathic pain
Jynneos (US)	Bavarian Nordic	MVA-BN orthopox vaccine, suspension for subcutaneous injection in single-use vials, 0.5 mL	Prevention of monkeypox disease in adults 18 years of age and older determined to be at high risk*
Efleira (RU)	Biocad	Netakimab, subcutaneous injections, 60 mg/mL	Treatment of moderate to severe plaque psoriasis
Rocklatan (US)	Aerie Pharmaceuticals	Netarsudil mesylate/latanoprost***, ophthalmic solution, 0.2 mg/mL (0.02%) netarsudil/0.05 mg/mL (0.005%) latanoprost	Reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension
Ofev (US)	Boehringer Ingelheim	Nintedanib, capsules, 100 & 150 mg	To slow the rate of decline in pulmonary function in patients with systemic sclerosis-associated interstitial lung disease*
Nuzyra (US)	Paratek	Omadacycline, lyophilized powder, 100 mg in single-dose vials for reconstitution and further dilution before i.v. infusion; tablets, 150 mg	Treatment of adult patients with the following infections caused by susceptible microorganisms: community-acquired bacterial pneumonia; acute skin and skin structure infections
Zolgensma (US)	AveXis (Novartis)	Onasemnogene abeparvovec, suspension for intravenous infusion in single-use vials, 5.5 mL or 8.3 mL, containing a nominal concentration of 2.0×10^{13} vector genomes (vg) per mL	Treatment of pediatric patients < 2 years of age with spinal muscular atrophy with biallelic mutations in the *SMN1* gene
Smyraf (JP)	Astellas	Peficitinib hydrobromide, tablets, 50 & 100 mg	Treatment of rheumatoid arthritis, including prevention of structural joint damage, in patients who have an inadequate response to conventional therapies
Turalio (US)	Plexxikon/Daiichi Sankyo	Pexidartinib hydrochloride, capsules, 200 mg	Treatment of adult patients with symptomatic tenosynovial giant cell tumor associated with severe morbidity or functional limitations and not amenable to improvement with surgery

(Continued)

Table III. *New product intros 2019. (Cont.)*

Trade name (country)[1]	Company	Active ingredient	Indication
Polivy (US)	Genentech	Polatuzumab vedotin, lyophilized powder in single-use vials, 140 mg	Treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma, in combination with bendamustine plus rituximab
Fulaimei (CN)	Hansoh Pharma	Polyethylene glycol loxenatide, prefilled pen or syringe for subcutaneous injection, long-acting, 0.1 and 0.2 mg/0.5 mL	Treatment of type 2 diabetes in adults
(US)	TB Alliance/Mylan	Pretomanid, tablets, 200 mg	As part of a combination regimen with bedaquiline and linezolid for the treatment of adults with pulmonary, extensively drug-resistant (XDR), treatment-intolerant or nonresponsive multidrug-resistant (MDR) tuberculosis
Vanflyta (JP)	Daiichi Sankyo	Quizartinib, tablets, 17.7 & 26.5 mg	Treatment of adult patients with relapsed/refractory FLT3-ITD acute myeloid leukemia, as detected by a test approved by Japan's Ministry of Health, Labour and Welfare (MHLW)
Ultomiris (US)	Alexion	Ravulizumab, single-dose vials for i.v. injection, 300 mg/30 mL (10 mg/mL)	• Treatment of adult patients with paroxysmal nocturnal hemoglobinuria • Treatment of adults and pediatric patients 1 month of age and older with atypical hemolytic uremic syndrome, to inhibit complement-mediated thrombotic microangiopathy
Relumina (JP)	Takeda/Aska	Relugolix, tablets, 40 mg	Relief of symptoms of uterine fibroids
Remo (IN)	Glenmark/Avolynt	Remogliflozin etabonate, tablets, 100 mg	Treatment of type 2 diabetes in adults
Aemcolo (US)	Cosmo Pharmaceuticals/ RedHill Biopharma	Rifamycin, delayed-colonic release tablets***, 194 mg	Treatment of travelers' diarrhea caused by noninvasive strains of *Escherichia coli* in adults
Skyrizi (US, GB)	AbbVie/Boehringer Ingelheim	Risankizumab, single-dose prefilled syringe for s.c. injection, 75 mg/0.83 mL	Treatment of moderate to severe plaque psoriasis in adult patients

(Continued)

Table III. *New product intros 2019. (Cont.)*

Trade name (country)[1]	Company	Active ingredient	Indication
Evenity (JP)	UCB/Amgen Astellas BioPharma	Romosozumab, prefilled syringe for s.c. injection, 105 mg/1.17 mL	Treatment of osteoporosis in men and postmenopausal women at high risk of fracture
Besremi (AT, DE)	PharmaEssentia/AOP Orphan	Ropeginterferon alfa-2b, prefilled pen, 250 µg/0.5 mL & 500 µg/0.5 mL	As monotherapy in adults for the treatment of polycythemia vera without symptomatic splenomegaly
Airuizhuo (CN)	FibroGen/AstraZeneca	Roxadustat, capsules, 50 mg	Treatment of anemia caused by chronic kidney disease in patients who are dialysis-dependent
Mosquirix (MW)	GlaxoSmithKline	RTS,S/AS01E, powder and suspension for suspension for injection; after reconstitution, 1 dose (0.5 mL) contains 25 mg of RTS,S1,2 adjuvanted with AS01E	Prevention of malaria in children up to 2 years of age
Jakafi (US)	Incyte	Ruxolitinib phosphate, tablets, 5, 10, 15, 20 & 25 mg	Treatment of steroid-refractory acute graft-vs-host disease in adults and pediatric patients 12 years and older*
Seysara (US)	Paratek/Almirall	Sarecycline hydrochloride, tablets, equiv. to 60, 100 & 150 mg sarecycline base	Treatment of inflammatory lesions of non-nodular moderate to severe acne vulgaris in patients 9 years of age and older
Annovera (US)	Population Council/ TherapeuticsMD	Segesterone acetate (SA)/ethinyl estradiol (EE)**, silicone elastomer vaginal system containing 103 mg SA and 17.4 mg EE, which releases on average 0.15 mg/day SA and 0.013 mg/day EE	For use by females of reproductive potential to prevent pregnancy
Xpovio (US)	Karyopharm	Selinexor, tablets, 20 mg	In combination with dexamethasone, for the treatment of adult patients with relapsed or refractory multiple myeloma who have received at least four prior therapies and whose disease is resistant to several other forms of treatment
Rybelsus (US)	Novo Nordisk	Semaglutide, tablets, 7 & 14 mg***	As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes
Tyvyt (CN)	Innovent Biologics/ Lilly	Sintilimab, intravenous injections, 100 mg/ 10 mL	Treatment of patients with relapsed or refractory classical Hodgkin's lymphoma

(Continued)

Table III. *New product intros 2019. (Cont.)*

Trade name (country)[1]	Company	Active ingredient	Indication
Mayzent (US)	Novartis	Siponimod fumarate, tablets, 0.25 & 2 mg	Treatment of adults with relapsing forms of multiple sclerosis, to include clinically isolated syndrome, relapsing–remitting disease and active secondary progressive disease
Lokelma (DK, FI, NO, SE)	AstraZeneca	Sodium zirconium cyclosilicate, oral suspension, 5 & 10 g	Treatment of adults with hyperkalemia
Sunosi (US)	Jazz Pharmaceuticals	Solriamfetol hydrochloride, tablets, 75 & 150 mg	To improve wakefulness in adult patients with excessive daytime sleepiness associated with narcolepsy or obstructive sleep apnea
Elzonris (US)	Stemline Therapeutics	Tagraxofusp, solution in single-dose vials, 1 mL containing 1000 µg tagraxofusp	Treatment of blastic plasmacytoid dendritic cell neoplasm in adults and in pediatric patients 2 years and older
(CN)	Tianji Pharma	Tapinarof, cream	Treatment of moderate stable psoriasis vulgaris in adults
K-CAB (KR)	RaQualia/ CJ HealthCare	Tegoprazan, tablets, 50 mg	Treatment of gastroesophageal reflux disease, including erosive esophagitis and nonerosive reflux disease
Tuoyi (CN)	Shanghai Junshi Biosciences	Toripalimab, vials, 240 mg	Treatment of locally advanced or metastatic melanoma in patients who have failed routine systemic treatment
Itulazax (DE)	ALK-Abelló	Tree pollen sublingual immunotherapy (SLIT), sublingual tablets, 12 SQ-Bet standardized allergen extract of pollen from white birch (*Betula verrucosa*)	Treatment of adult patients with moderate to severe allergic rhinitis and/or conjunctivitis, induced by pollen from the birch homologous family of trees
Trecondi (DE)	Medac	Treosulfan, powder for solution for i.v. infusion in vials, 50 mg/mL	In combination with fludarabine as part of conditioning treatment prior to allogeneic hematopoietic stem cell transplantation in adult patients with malignant and nonmalignant diseases and in pediatric patients older than 1 month with malignant diseases*

(Continued)

Table III. *New product intros 2019. (Cont.)*

Trade name (country)[1]	Company	Active ingredient	Indication
Aklief (US)	Galderma	Trifarotene, cream, 0.005%	Topical treatment of acne vulgaris in patients 9 years of age and older
Esperoct (DE, CH)	Novo Nordisk	Turoctocog alfa pegol, powder and solvent for solution for injection, 500, 1000, 1500, 2000 & 3000 IU	Treatment and prophylaxis of bleeding in patients 12 years and above with hemophilia A (congenital factor VIII deficiency)
Rinvoq (US)	AbbVie	Upadacitinib tartrate, tablets, extended-release, 15 mg	Treatment of adults with moderately to severely active rheumatoid arthritis who have had an inadequate response or intolerance to methotrexate
Waylivra (DE, FR)	Akcea Therapeutics (Ionis Pharmaceuticals)	Volanesorsen, solution for injection, 285 mg	As an adjunct to diet in adult patients with genetically confirmed familial chylomicronemia syndrome and at high risk for pancreatitis, in whom response to diet and triglyceride-lowering therapy has been inadequate
Oxbryta (US)	Global Blood Therapeutics	Voxelotor, tablets, 500 mg	Treatment of sickle cell disease in adults and children 12 years of age and older
Brukinsa (US)	BeiGene	Zanubrutinib, capsules, 80 mg	Treatment of adult patients with mantle cell lymphoma who have received at least one prior therapy

[1]Country codes are the abbreviations used by the World Intellectual Property Organization.
*New indication.
**New combination.
***New formulation.

Table IV. *Approvals and candidates for approval in 2020.*

Product name	Organization(s)	Country/ region	Indication	Status/notes
Abicipar pegol	Allergan/Molecular Partners	U.S., E.U.	Treatment of patients with neovascular (wet) age-related macular degeneration	Mid-2020 PDUFA date in U.S.; E.U. approval expected in second half 2020
Ad26.ZEBOV (rHAd26), in combination with MVA-BN Filo	Janssen	E.U.	As a heterologous prime–boost vaccine regimen for the prevention of Ebola virus disease caused by Zaire ebolavirus	MAAs for each vaccine submitted in Nov 2019 (accelerated assessment)
Alalevonadifloxacin mesylate	Wockhardt	India	For ABSSSIs, including diabetic foot infections and concurrent bacteremia	Approved in India in Jan 2020
AR-101 (Palforzia)	Aimmune Therapeutics	U.S., E.U.	Peanut allergy desensitization in children and adolescents aged 4 to 17 years	Decision expected in U.S. in Jan 2020; in E.U. in second half of 2020
Avapritinib	Blueprint Medicines	U.S.	Unresectable or metastatic GIST harboring a *PDGFRA* exon 18 mutation, including *PDGFRA* D842V mutations	Approved in Jan 2020 in US; MAA under review in E.U.
Belantamab mafodotin	GlaxoSmithKline	U.S.	Treatment of patients with relapsed or refractory multiple myeloma whose prior therapy included an immunomodulatory agent, a proteasome inhibitor and an anti-CD38 antibody	BLA submitted in Dec 2019
Bempedoic acid and bempedoic acid/ ezetimibe	Esperion Therapeutics	U.S., E.U.	Treatment of patients with elevated LDL cholesterol (LDL-C) who need additional LDL-C lowering despite the use of currently accessible therapies	Approvals expected in first half of 2020
Berotralstat hydrochloride	BioCryst	U.S.	Prevention of hereditary angioedema attacks	NDA submitted in Dec 2019
BP-101 (Libicore)	Ivix	Russian Federation	Female hypoactive sexual desire disorder	Application submitted in Sept 2019

(Continued)

Table IV. *Approvals and candidates for approval in 2020. (Cont.)*

Product name	Organization(s)	Country/ region	Indication	Status/notes
Cabotegravir & cabotegravir/ rilpivirine	ViiV Healthcare	U.S., E.U.	Lead-in treatment for HIV-1-infected adults whose viral load is suppressed, in combination with rilpivirine and prior to the commencement of injectable therapy	Applications filed in Apr 2019 (U.S.) and July 2019 (E.U.)
Chiglitazar	Chipscreen Biosciences	China	Type 2 diabetes	Application accepted in Sept 2019
Daprodustat	GlaxoSmithKline	Japan	Treatment of anemia associated with CKD	Application filed in Japan in Aug 2019
Dasotraline hydrochloride	Sunovion	U.S.	Treatment of patients with moderate to severe binge eating disorder	PDUFA date of May 14, 2020
Delgocitinib	Japan Tobacco (JT) Torii	Japan	Atopic dermatitis	Approved in Jan 2020
Dotinurad	Fuji Yakuhin/Mochida	Japan	Treatment of hyperuricemia with or without gout	Approved in Jan 2020
Eflapegrastim	Spectrum Pharmaceuticals	U.S.	Treatment of chemotherapy-induced neutropenia	PDUFA date of Oct 24, 2020
Eptinezumab	Alder Biopharmaceuticals	U.S.	Prevention of chronic and episodic migraine; Infusion; Intravenous	PDUFA date of Feb 21, 2020
Fenfluramine hydrochloride	Zogenix	U.S., E.U.	Treatment of seizures associated with Dravet syndrome	Approvals expected in Q1 2020
Filgotinib	Galapagos/Gilead	U.S., E.U., Japan	Rheumatoid arthritis	Applications filed in Aug 2019 (E.U.), Oct 2019 (Japan) and Dec 2019 (U.S.)
Flortaucipir F 18	Lilly	U.S.	For imaging tau in patients with Alzheimer's disease	
Fostemsavir	ViiV Healthcare	U.S., E.U.	For use in combination with other antiretroviral agents in heavily treatment-experienced adults infected with multidrug-resistant HIV-1 infection who are unable to form a suppressive regimen due to resistance, intolerance or safety considerations	NDA filed in U.S. in Dec 2019; MAA filed in E.U. in Jan 2020

(Continued)

Table IV. *Approvals and candidates for approval in 2020. (Cont.)*

Product name	Organization(s)	Country/ region	Indication	Status/notes
HSK-3486	Haisco Pharmaceutical Group	China	Induction of general anesthesia and sedation of patients undergoing endoscopic diagnosis	Application granted priority review in Aug 2019
Imlifidase	Hansa Biopharma	E.U.	For the desensitization of patients prior to kidney transplant	Decision expected during summer of 2020
Inebilizumab	Viela Bio	U.S.	Treatment of NMO and NMOSD	PDUFA date of June 11, 2020
Isatuximab	Sanofi	U.S., E.U., Japan	Multiple myeloma	PDUFA date of Apr 30, 2020 in U.S.; applications also under review in E.U. and Japan
Levonadifloxacin arginine salt	Wockhardt	India	For ABSSSIs, including diabetic foot infections and concurrent bacteremia	Approved in India in Jan 2020
Lisocabtagene maraleucel	Celgene	U.S.	Treatment of adult patients with relapsed or refractory LBCL after at least two prior therapies	BLA submitted in Dec 2019
Lonafarnib	Eiger BioPharmaceuticals/Progeria Research Foundation	U.S.	Treatment of progeria and progeroid laminopathies	Rolling submission started in Dec 2019, expected to complete in Q1 2020
LY-900014 (Ultra-rapid lispro)	Lilly	U.S., E.U., Japan	Type 1 and 2 diabetes	Applications submitted in Q1 2019
Margetuximab	MacroGenics	U.S.	Treatment of patients with metastatic HER2-positive breast cancer in combination with chemotherapy	BLA submitted in Dec 2019
Nadofaragene firadenovec	FKD Therapies	U.S.	Treatment of patients with high-grade Bacillus Calmette–Guérin (BCG)-unresponsive nonmuscle-invasive bladder cancer	BLA accepted for priority review in Nov 2019
Orelabrutinib	InnoCare Pharma	China	Treatment of patients with relapsed or refractory chronic lymphocytic leukemia/small lymphocytic lymphoma	Filing accepted in China in Nov 19, granted priority review in Jan 2020
Osilodrostat	Recordati	E.U.	Treatment of endogenous Cushing syndrome in adults	Approved in Jan 2020

(Continued)

Table IV. *Approvals and candidates for approval in 2020. (Cont.)*

Product name	Organization(s)	Country/ region	Indication	Status/notes
OTL-200	Orchard Therapeutics	E.U.	Metachromatic leukodystrophy	MAA filed in Nov 2019, accelerated assessment
Ozanimod	Celgene	U.S., E.U.	Treatment of relapsing forms of multiple sclerosis	PDUFA date of Mar 25, 2020 in U.S.; decision expected in E.U. in first half 2020
Pemigatinib	Incyte	U.S., E.U.	Previously treated, locally advanced or metastatic cholangiocarcinoma with FGFR2 fusions or rearrangements	PDUFA date of May 30, 2020 in U.S.; MAA under review in E.U.
PPE (Viaskin Peanut)	DBV Technologies	U.S.	Treatment of peanut allergy in children 4 to 11 years of age	PDUFA date of Aug 5, 2020
REGN-3470-3471-3479 (atoltivimab/ odesivimab/ maftivimab)	Regeneron	U.S.	Ebola virus infection	Rolling submission started in Sept 2019
Remimazolam	PAION, Mundipharma (Japan), Yichang Humanwell Pharmaceutical (China), Hana Pharm (South Korea), Cosmo Pharmaceuticals (US)	Japan, U.S., China, South Korea, E.U.	General anesthesia (Japan, South Korea); procedural sedation (U.S., China, E.U.)	Approved in Japan for general anesthesia in Jan 2020; PDUFA date in U.S. is Apr 5, 2020; Applications filed in China, South Korea and E.U. in Nov 2018, Dec 2019 and Nov 2019, respectively
Rimegepant	BioHaven Pharmaceutical	U.S.	Treatment of acute migraine	PDUFA date in Q1 2020
Ripretinib	Deciphera	U.S.	In patients with advanced GIST who have received treatment with prior anticancer therapies, including imatinib, sunitinib and regorafenib	NDA filed in Dec 2019
Risdiplam	Roche	U.S.	Spinal muscular atrophy	PDUFA date of May 24, 2020
Sacituzumab govitecan	Immunomedics	U.S.	Treatment of patients with metastatic triple-negative breast cancer who have received at least two prior therapies for metastatic disease	PDUFA date of June 2, 2020
Satralizumab	Chugai Pharmaceutical/ Roche	Japan, E.U., U.S.	Treatment of NMO and NMOSD	Applications submitted in Aug 2019 (E.U.), Oct 2019 (U.S.), Nov 2019 (Japan)

(Continued)

Table IV. *Approvals and candidates for approval in 2020. (Cont.)*

Product name	Organization(s)	Country/ region	Indication	Status/notes
Selumetinib sulfate	AstraZeneca	U.S.	Treatment of pediatric patients aged 3 years and older with neurofibromatosis type 1 and symptomatic, inoperable plexiform neurofibromas	PDUFA date in Q2 2020
Somapacitan	Novo Nordisk	U.S., E.U.	Treatment of adults with growth hormone deficiency	Applications filed in Sept 2019
Surufatinib	Hutchison China MediTech (Chi-Med)	China	Treatment of advanced nonpancreatic neuroendocrine tumors	Application granted priority review in Dec 2019
Tafasitamab	MorphoSys	U.S.	Treatment of relapsed or refractory diffuse LBCL in combination with lenalidomide	Application submitted in Dec 2019
Tazemetostat	Epizyme	U.S.	Treatment of patients with metastatic or locally advanced epithelioid sarcoma not eligible for curative surgery; Treatment of patients with relapsed or refractory follicular lymphoma, both with or without EZH2 activating mutations, who have received at least two prior lines of systemic therapy	Approved for epithelioid sarcoma in Jan 2020; NDA for follicular lymphoma submitted in Dec 2019
Teprotumumab	Horizon Therapeutics	U.S.	Treatment of Graves orbitopathy (active thyroid eye disease)	Approved in Jan 2020
TetraMen-T	Sanofi	U.S., E.U.	Prevention of meningococcal meningitis in persons 2 years of age and older	PDUFA date of Apr 25, 2020 in U.S.; MAA submitted in E.U. in Oct 2019
Tirabrutinib hydrochloride	Ono	Japan	Treatment of Waldenström macroglobulinemia and lymphoplasmacytic lymphoma; treatment of recurrent or refractory primary central nervous system lymphoma	Separate applications submitted in Aug and Nov 2019

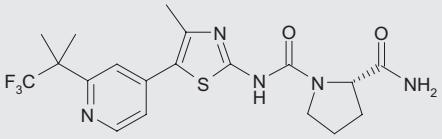
(Continued)

Table IV. *Approvals and candidates for approval in 2020. (Cont.)*

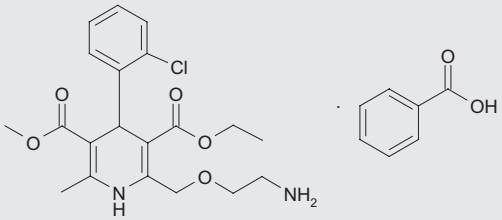
Product name	Organization(s)	Country/ region	Indication	Status/notes
Triheptanoin	Ultragenyx	U.S.	Treatment of long-chain fatty acid oxidation disorders, including carnitine palmitoyltransferase, very long-chain acyl-CoA dehydrogenase and long-chain 3-hydroxy-acyl-CoA dehydrogenase deficiencies	PDUFA date of July 31, 2020
Tucatinib	Array BioPharma/ Seattle Genetics	U.S.	In combination with trastuzumab and capecitabine, for the treatment of patients with locally advanced unresectable or metastatic HER2-positive breast cancer, including patients with brain metastases, who have received at least three prior HER2-directed agents separately or in combination, in the neoadjuvant, adjuvant or metastatic setting	NDA submitted in Dec 2019
Vadadustat	Mitsubishi Tanabe Pharma	Japan	Treatment of patients with renal anemia secondary to CKD	Application filed in Japan in July 2019
Valoctocogene roxaparvovec	BioMarin	U.S., E.U.	Treatment of adults with hemophilia A	Applications filed in late 2019
Veverimer	Tricida	U.S.	Treatment of metabolic acidosis in patients with CKD	PDUFA date of Aug 22, 2020
Viloxazine hydrochloride	Supernus	U.S.	Attention deficit hyperactivity disorder	NDA filed in Nov 2019
Viltolarsen	Nippon Shinyaku	U.S., Japan	Duchenne muscular dystrophy	Rolling submission completed in Oct 2019 in U.S.; application accepted in Japan in Nov 2019
Yimitasvir	HEC Pharm	China	Hepatitis C virus infection	Application granted priority review in Nov 2019

ABSSSIs, acute bacterial skin and skin structure infections; BLA, biologics license application; CKD, chronic kidney disease; GIST, gastrointestinal stromal tumor; LBCL, large B-cell lymphoma; MAA, marketing authorization application; NDA, new drug application; NMO, neuromyelitis optica; NMOSD, neuromyelitis optica spectrum disorder; PDUFA, Prescription Drug User Fee Act.
Source: *Cortellis Drug Discovery Intelligence* and *Cortellis Competitive Intelligence*. Information current as of January 24, 2020.

Chemical structures of NCEs launched in 2019



Alpelisib



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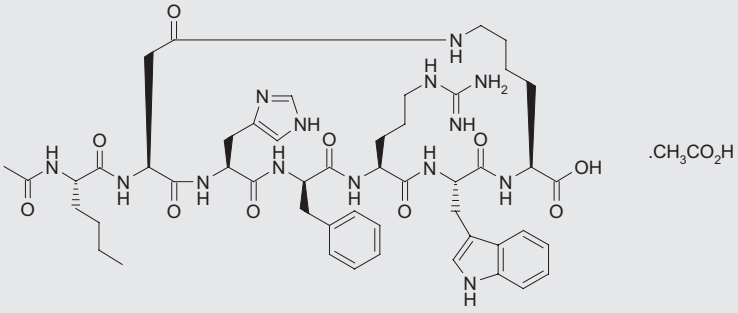
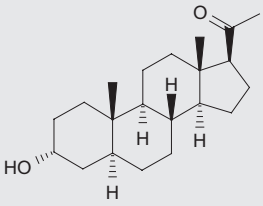


Bremelanotide



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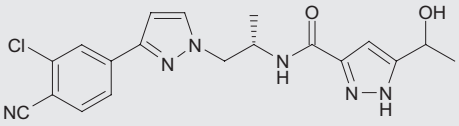

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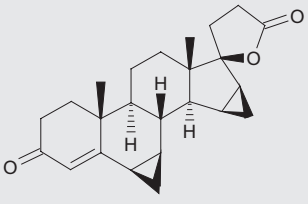
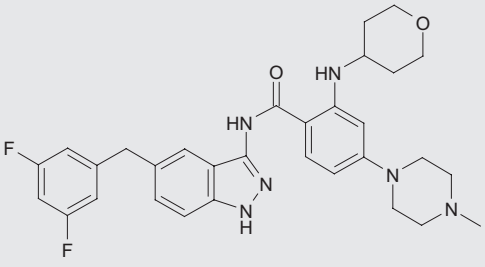
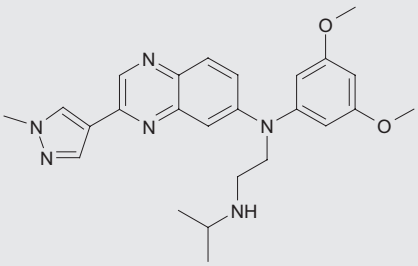


Drospirenone

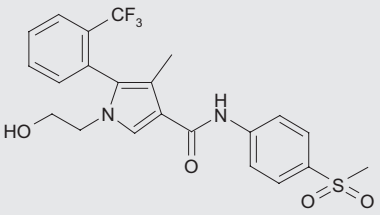


Entrectinib

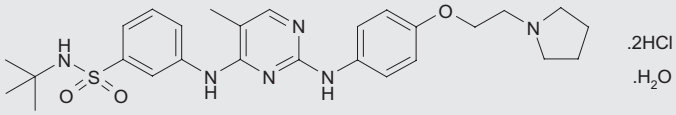
Chemical structures of NCEs launched in 2019



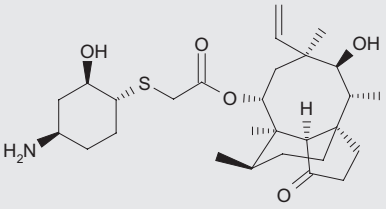
Erdafitinib



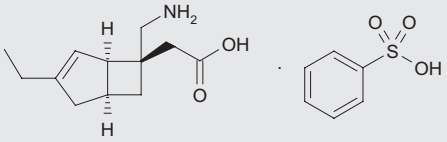
Esaxerenone



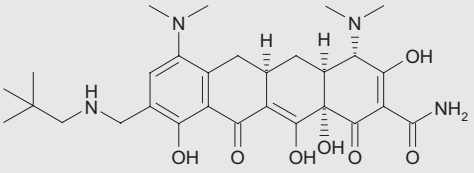
Fedratinib hydrochloride



Lefamulin



Mirogabalin besylate



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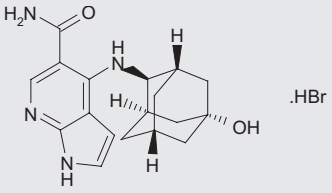
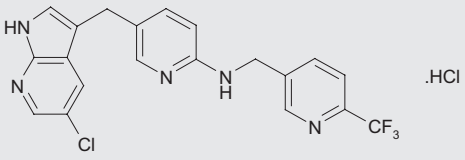
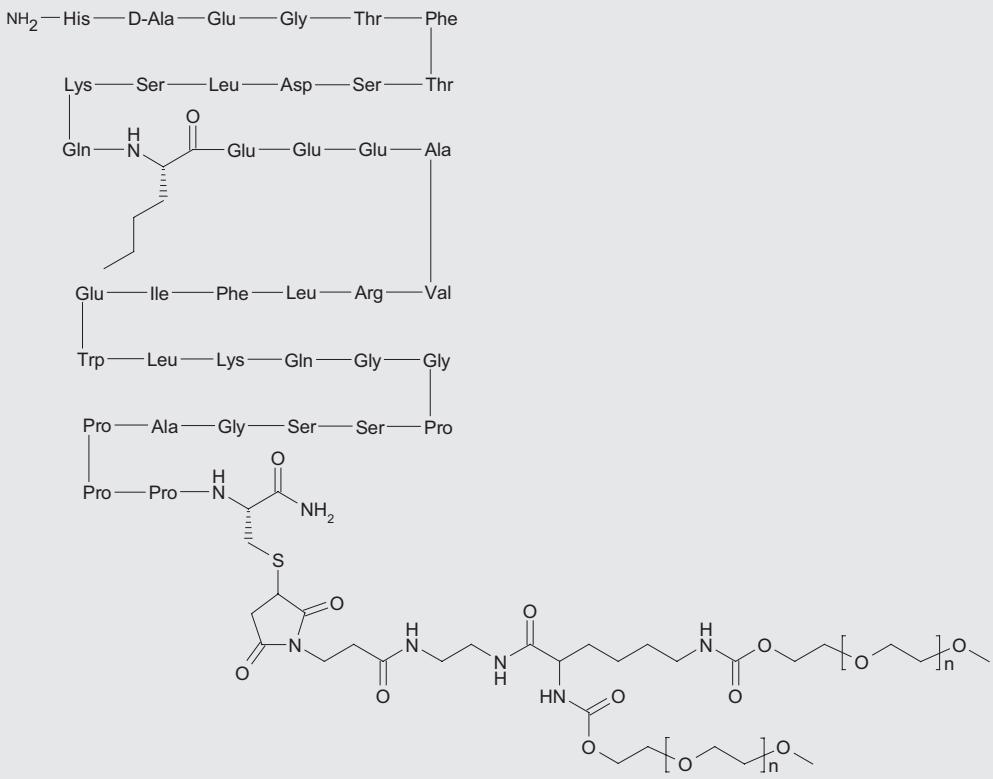


Peficitinib hydrobromide

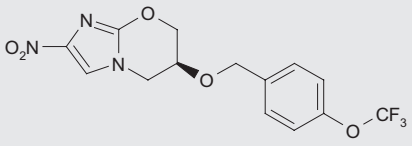


Pexidartinib hydrochloride

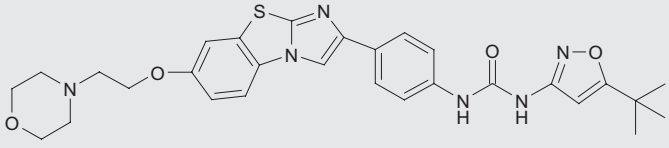
Chemical structures of NCEs launched in 2019



Polyethylene glycol loxenatide

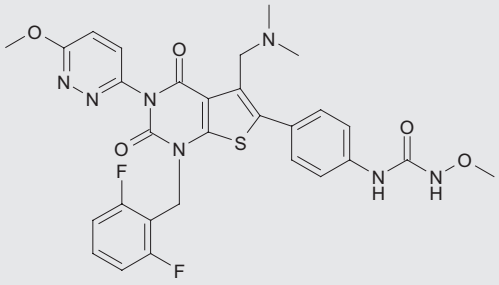


Pretomanid

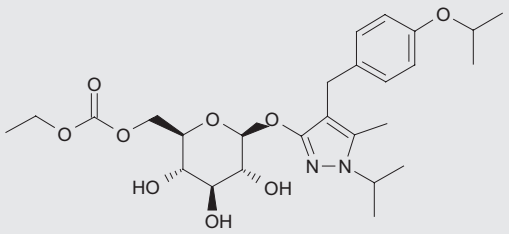


Quizartinib

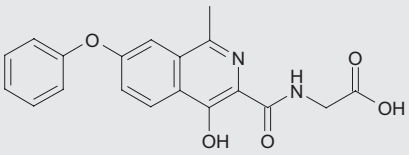
Chemical structures of NCEs launched in 2019



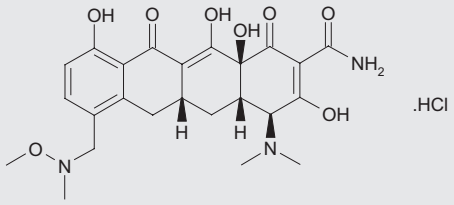
Relugolix



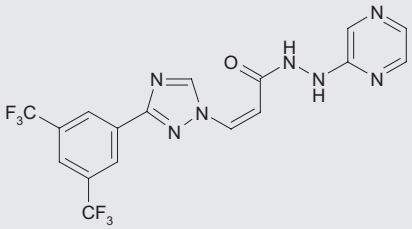
Remogliflozin etabonate



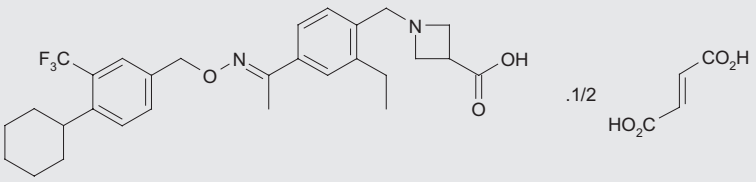
Roxadustat



Sarecycline hydrochloride

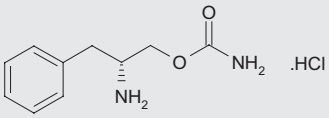


Selinexor

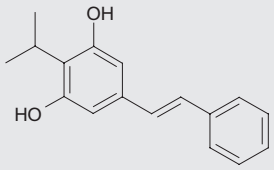


Siponimod fumarate

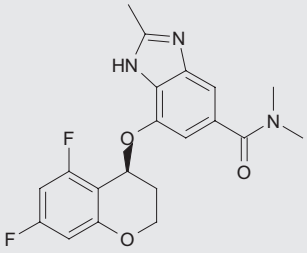
Chemical structures of NCEs launched in 2019



Solriamfetol hydrochloride



Tapinarof



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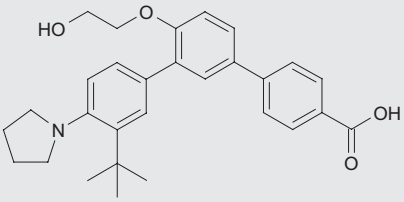
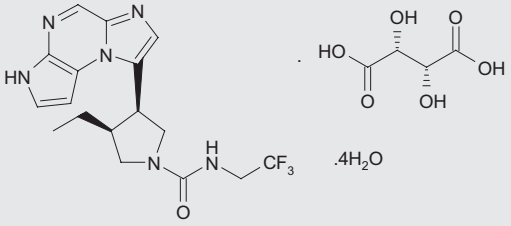
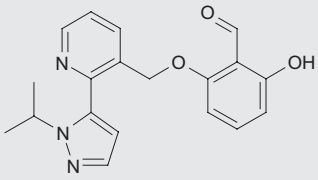


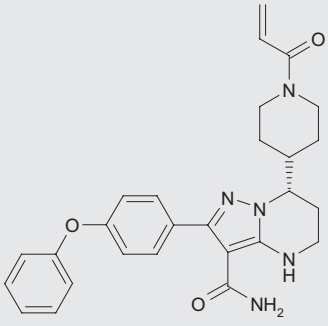
Trifarotene



Upadacitinib tartrate



Voxelotor



Zanubrutinib