Drug pipeline: 2Q18

Laura DeFrancesco

Through the first half of 2018, US Food and Drug Administration (FDA) approvals lagged relative to last year, but the agency's calendar looks busy ahead, with decisions for several acute myelogenous leukemia drugs in particular. Amgen's monoclonal antibody (mAb) Aimovig (erenumab) was approved for migraine; and there was a rash of approvals for both rare disorders (X-linked hyperphosphatemia; immune

thrombocytopenic purpura; familial amyloidotic cardiomyopathy and phenylketonuria) and infectious diseases (urinary/reproductive tract infections and river blindness). Europe pulled conditional approval of Sarepta's exon-skipping drug, Exondys 51, for Duchenne muscular dystrophy; the FDA continues to monitor closely experimental gene-edited cell therapies being taken into the clinic.

Historic US regulatory approvals by lead indication

Off to a slow start in 2018

*2018 shows partial year, from January 1 to June 30. Source: BioMedTracker, a service of Sagient Research (<http://www.biomedtracker.com>)

Notable regulatory setbacks (2Q18)

Drug/company	Indication	Drug information
Exondys 51 (eteplirsen)/Sarepta	Duchenne muscular dystrophy (DMD)	5/31/2018 Negative CHMP opinion of phosphorodiamidate morpholino oligomer (PMO) designed to induce the skipping of exon 51 in the dystrophin gene
CTX001/CRISPR Therapeutics	Sickle cell anemia	5/30/2018 FDA imposed clinical trial hold on <i>ex vivo</i> CRISPR-Cas9-edited primary human hematopoietic stem and progenitor CD34 ⁺ cells of the erythroid-specific enhancer region of <i>BCL11A</i>
CD19/Intrexon	Hematologic cancer	6/18/2018 Questions related to chemistry, manufacturing and controls (CMC) caused FDA to impose clinical trial hold on CAR-T cell program using non-viral Sleeping Beauty transposon to deliver CAR under control of Gal4-ecdysone receptor/small-molecule veledimix gene switch
Verubecestat/Merck	Alzheimer's disease	5/3/2018 Company suspended phase 2/3 clinical trials of small-molecule β -site amyloid precursor protein cleaving enzyme 1 inhibitor because of lack of improvement in cognitive function and some adverse effects
Zemdiri (plazomicin)/Achaogen	Septicemia or bacteremia	6/25/2018 FDA issued a complete response letter due to lack of effectiveness in bloodstream infections

CHMP, The Committee for Medicinal Products for Human Use; IND, investigational new drug. Source: BioMedTracker, a service of Sagient Research (<http://www.biomedtracker.com>)

Notable clinical trial results (2Q18)

Drug/company	Indication	Drug information
LentiGlobin/bluebird bio	Anemia	4/18/2018 In phase 1/2 clinical trial of autologous CD34 ⁺ cells transduced with lentivirus with fully functional human beta-globin gene (beta(A-T87Q)) the need for long-term red-cell transfusions in 22 patients with severe β -thalassemia was reduced or eliminated. (<i>N. Engl. J. Med.</i> 378 , 1479, 2018)
Setmelanotide/Rhythm	Obesity	5/7/2018 Three severely obese leptin receptor-deficient individuals given melanocortin 4 receptor agonist with rilinsulin had durable weight loss. (<i>Nat. Med.</i> 24 , 551, 2018)
Inclisiran/The Medicines Co.	Dyslipidemia/hypercholesterolemia	5/7/2018 In phase 2 placebo, double-blind, randomized clinical trial of an N-acetyl galactosamine (GalNAc) conjugated small-interfering RNA targeting the mRNA encoding proprotein convertase subtilisin/kexin type 9 systemically delivered via diinoleylmethyl-4-dimethylaminobutylate lipid particles, several metabolites (apolipoprotein B, non-high density lipoprotein C, and very low-density lipoprotein C) were reduced over 210 days. (<i>Circulation</i> doi:10.1161/CIRCULATIONAHA.118.034710, 2018)
Epidiolex/GW Pharmaceuticals	Lennox-Gastaut Syndrome (LGS; epilepsy)	5/16/2018 Plant-derived cannabidiol at a dose of 10 mg or 20 mg per kg per day added to a conventional antiepileptic regimen resulted in greater reductions in the frequency of drop seizures than placebo. (<i>N. Engl. J. Med.</i> 378 , 1888, 2018)
Dupixent (dupilumab)/Regeneron	Asthma	5/21/2018 In two phase 3 studies, this IgG4 mAb against IL-4 improved exacerbations and expiratory volume with largest benefit in patients with more severe asthma. (<i>N. Engl. J. Med.</i> 378 , 2486, 2018)

Source: BioMedTracker, a service of Sagient Research (<http://www.biomedtracker.com>)

Laura DeFrancesco is Senior Editor at Nature Biotechnology.

Notable regulatory approvals (2Q18)

Drug/company	Indication	Drug information
Praxbind (idarucizumab)/Boehringer Ingelheim	Reversal anticoagulant for uncontrolled bleeding in patients treated with dabigatran	4/12/2018 FDA approved this fully humanized IgG1 monoclonal antibody (mAb) fragment against dabigatran etexilate
Crysvita (burosumab)/UltraGenyx	X-linked hypophosphatemia	4/17/2018 FDA approved this fully human IgG1 anti-fibroblast growth factor 23
Tavalisse (fostamatinib)/Rigel	Immune thrombocytopenic purpura	4/17/2018 FDA approved this small-molecule spleen tyrosine kinase inhibitor
Aimovig (erenumab)/Amgen	Migraine and other headaches	5/17/2018 FDA approved this fully human IgG 2 mAb against calcitonin-gene-related peptide receptor
Palynziq (pegvaliase)/BioMarin	Phenylketonuria	5/24/2018 FDA approved this recombinant PEGylated version of <i>Anabaena variabilis</i> phenylalanine ammonia lyase
Epidiolex (cannabidiol)/GW Pharmaceuticals	Dravet syndrome (epilepsy), Lennox-Gastaut syndrome	6/25/2018 FDA approved this oral liquid formulation of plant-derived cannabidiol, non-psychoactive molecule
Andexxa (andexanet alfa)/Portola	Reversal anticoagulant for uncontrolled bleeding in patients treated with rivaroxaban and apixaban	5/3/2018 FDA granted accelerated approval to this modified recombinant derivative of factor Xa, which has a higher affinity to the FXa inhibitor than natural FXa
Braftovi (encorafenib)/Array Biopharma	Melanoma	6/27/2018 FDA approved this small-molecule RAF inhibitor in patients with BRAFV600E mutation
Moxidectin/Medicines Development for Global Health	River blindness	6/13/2018 FDA approves this macrocyclic lactone anthelmintic that binds to glutamate-gated chloride ion channels
Zemdiri (plazomicin)/Achaogen	Urinary tract and reproductive tract infections	6/25/2018 FDA approves this neoglycoside with broad-spectrum bactericidal activity against multi-drug-resistant Gram-negative bacteria

Breakthrough therapy designation

OTL-101/Orchard Therapeutics	Primary Immunodeficiencies	4/20/2018 Autologous CD34 ⁺ hematopoietic stem cells modified <i>ex vivo</i> with a lentiviral vector encoding adenosine deaminase deficiency under control of elongation factor alpha short promoter
OMS721/Omeros	Hemolytic uremic syndrome	4/26/2018 IgG3 mAb directed against mannan-binding lectin-associated serine protease-2 (MASP-2)
Instiladrin/FKD Therapies	Bladder cancer	5/3/2018 Recombinant adenoviral vector expressing hybrid-interferon alpha 2b gene with Syn3, a polyamide surfactant excipient that enhances viral transduction to the bladder epithelium
Vyndaqel (tafamidis meglumine)/Pfizer	Transthyretin amyloid (ATTR) cardiomyopathy	5/23/2018 Small-molecule stabilizer of transthyretin (TTR), preventing dissociation into monomers, and inhibiting TTR amyloid fibril formation
Lenti-D/bluebird bio	Adrenomyeloneuropathy (adrenoleukodystrophy)	5/23/2018 Autologous CD34 ⁺ hematopoietic stem cells transduced with lentiviral vector encoding the human ABCD1 cDNA
Wakix (pitolisant)/Harmony Biosciences	Narcolepsy	5/21/2018 Small-molecule selective histamine H3-receptor antagonist/inverse agonist

Source: BioMedTracker, a service of Sagient Research (<http://www.biomedtracker.com>)

Notable upcoming catalysts (4Q18)

Drug/company	Indication	Drug information
Omadacline/Paratek Pharmaceuticals	Skin infections and community-acquired pneumonia	10/2/2018 PDUFA for this aminomethylcycline tetracycline derivative
Tegsedi/Ionis	Transthyretin (TTR)-related hereditary amyloidosis, CLL	10/5/2018 FDA PDUFA for 2'-O-methoxyethyl antisense oligonucleotide that blocks production of mutant and wild-type human transthyretin
Duvelisib/Verastem	Indolent non-Hodgkin's lymphoma, CLL	10/5/2018 FDA PDUFA for this small-molecule inhibitor of phosphoinositide-3-kinase (PI3K) delta and PI3K gamma
Cemiplimab/Regeneron	Squamous cell carcinoma	10/26/2018 FDA PDUFA for this fully human monoclonal antibody (mAb) against PD-1
Moxetumomab Pasudotox/AstraZeneca	Hairy cell leukemia	9/1/2018 FDA PDUFA for this murine IgG1 disulfide-stabilized anti-CD22 Fv mAb fused to a 38-kD fragment of <i>Pseudomonas</i> exotoxin A
Emapalumab/NovImmune	Inflammatory disorders	11/20/2018 FDA PDUFA for this fully human IgG1 mAb that inhibits interferon-gamma
Larotrectinib/Loxo Oncology	Solid tumors	11/26/2018 FDA PDUFA for this selective small-molecule inhibitor of the Trk family of receptor tyrosine kinases
Gilteritinib/Astellas	Acute myelogenous leukemia	11/29/2018 FDA PDUFA against small-molecule multi-tyrosine kinase inhibitor active against FLT3 and AXL
ATIR101/Kiadis Pharma	Acute myelogenous leukemia	10/1/2018 CHMP opinion of haploidentical CD34 ⁺ cells followed by donor allogeneic lymphocytes photo-depleted of potential graft-versus-host-disease-inducing donor immune cells
Seysara (sarecycline)/Allergan	Acne	10/1/2018 FDA PDUFA for tetracycline-derived, narrow-spectrum antibiotic
N8-GP/Novo Nordisk	Hemophilia A	11/2/2018 CHMP opinion for B-domain O-glycan PEGylated factor VIII derivative, which following thrombin cleavage, creates a FVIII fragment similar to native fragment but with greater stability

CLL, chronic lymphocytic leukemia; PDUFA, Prescription Drug User Fee Act; CHMP, The Committee for Medicinal Products for Human Use. Source: BioMedTracker, a service of Sagient Research (<http://www.biomedtracker.com>)