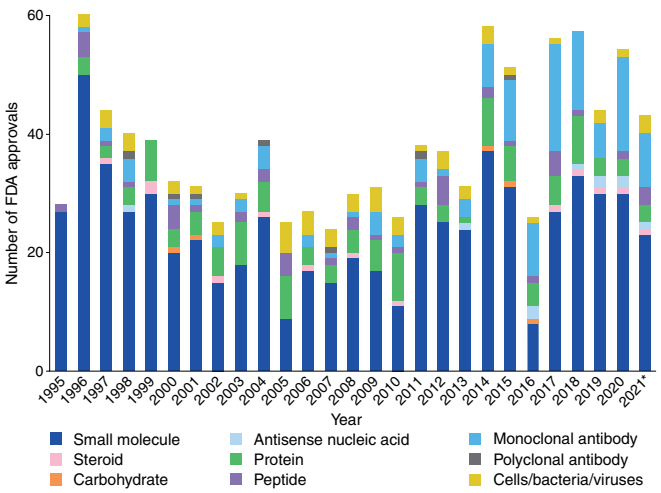
DATA PAGE

Drug pipeline 3Q21—mixed news for genetic therapies

Zydus Cadila Healthcare's COVID-19 vaccine—the world's first DNA vaccine approved for humans—got the nod in the form of an Emergency Use Authorization from India's Central Drugs Standard Control Organisation. Regeneron's monoclonal antibody (mAb) cocktail Ronapreve continued to shine in clinical trials, with the latest study reporting it protects people exposed to SARS-CoV-2. Meanwhile, the European Medicines Agency (EMA) got out ahead of the US Food and Drug Administration (FDA) with registrations of the first drug for achondroplasia (BioMarin's Voxzogo), the first bispecific mAb for psoriasis (UCB's Bimzelx), and the first gene therapy for cerebral adrenoleukodystrophy (Bluebird Bio's lentiviral product Skysona). All was not plain sailing for Bluebird, however, with the FDA putting a clinical hold on the program due to concerns over possible insertional mutagenesis leading to myelodysplastic syndrome. Preclinical liver tumorigenicity concerns added to previous hepatotoxicity, thrombotic microangiopathy and neurotoxicity issues associated with adeno-associated viral (AAV) vector gene therapies, as the FDA placed a clinical hold on BioMarin's AAV-5 gene therapy for phenylketonuria. A phase 1/2 trial of Arrowhead's cystic fibrosis siRNA drug Aro-ENAC was also halted due to a preclinical signal of lung inflammation.

FDA approvals by drug type

Approvals for the first three quarters almost equal the total for all of last year.



*Partial year to 30 June.

Notable regulatory setbacks (3Q21)

Drug / company	Indication	Drug information
ARO-ENaC / Arrowhead Pharmaceuticals	Cystic fibrosis	7/2/2021 Company voluntarily halts phase 2 clinical trial of this inhaled nebulized solution of a small interfering (si)RNA targeting *SCNN1A* mRNA, encoding the epithelial sodium channel α-subunit (aENaC), encapsulated in peptide E (K16GACSERSMNFCG)-targeted DOTMA:DOPE liposomes, after a toxicology study in rats showed local lung inflammation
Teplizumab / Provention Bio	Diabetes mellitus, type I	7/2/2021 FDA issues a complete response letter for this humanized IgG1 mAb with an Fc engineered with leucine-to-alanine substitutions at residues 234 and 235 (in the CH2 region) to abolish Fc receptor binding directed against the CD3 ε-chain expressed on mature T lymphocytes
Lenti-D (elivaldogene autotemcel) / Bluebird Bio	Adrenoleukodystrophy	8/9/2021 FDA puts a clinical hold on this autologous hematopoietic CD34$^+$ stem cells transduced with a lentiviral vector encoding human *ABCD1* cDNA due to myelodysplastic syndrome potentially mediated by vector insertion
Verdiperstat / Biohaven Pharmaceuticals	Multiple system atrophy	9/27/2021 Company announces suspension of its phase 3 trial of this oral, small-molecule, brain-penetrant, irreversible inhibitor of myeloperoxidase due to lack of statistically significant improvement
BMN 307 / BioMarin	Phenylketonuria	9/6/2021 FDA puts a clinical hold on this an AAV-5-vectored gene therapy containing the gene for phenylalanine hydroxylase after mice developed liver tumors in a preclinical study
Ad26.Mos4.HIV vaccine / Johnson & Johnson	HIV	8/31/2021 Company announced that this tetravalent recombinant replication-deficient adenovirus 26 (Ad26) vectored vaccine comprising two Ad26 vectors containing a mosaic insert of the HIV envelope (Env) sequence and two Ad26 vectors containing mosaic inserts of Gag and Pol sequences, along with a booster dose of the trimeric clade C glycoprotein 140, achieved only 25.2% efficacy in a phase 2 trial
Ultomiris (ravulizumab-cwvz) / AstraZeneca	Amyotrophic lateral sclerosis	8/20/2021 Company discontinues phase 3 trial of this long-acting humanized IgG2/IgG4 anti-C5 mAb with an Fc engineered for increased human FcRn affinity (Xtend technology) due to lack of efficacy
Vicineum (oportuzumab monatox-qqrs) / Sesen Bio	Bladder cancer	8/16/2021 FDA issues a complete response letter for this fusion of anti-EpCAM humanized single-chain variable fragment (scFv) linked to a truncated form of *Pseudomonas* exotoxin A, requesting additional clinical and statistical data and analyses and citing chemistry, manufacturing and control issues
Aduhelm (aducanumab) / Biogen	Alzheimer's disease	8/11/2022 The US Department of Veterans Affairs announces it will not include in its formulary this fully human IgG1 mAb against a conformational epitope on β-amyloid plaques
COVID vaccine / Sanofi	COVID-19 prevention	9/29/2021 Company halts testing of this mRNA-based vaccine comprising the stabilized pre-fusion form of the SARS-CoV-2 spike glycoprotein delivered by a lipid nanoparticle comprising ionizable lipid, phosphatidylethanolamine, cholesterol and polyethylene glycol-lipid

Continued

DOTMA, 1,2-di-*O*-octadecenyl-3-trimethylammonium propane; DOPE, 1,2-dioleoyl-*sn*-glycero-3-phosphoethanolamine; IgG, immunoglobulin G; Fc, immunoglobulin constant fragment; FcRn, neonatal Fc receptor; C5, complement protein 5; EpCAM, epithelial cell adhesion molecule. Source: BioMedTracker, a service of Sagient Research (http://www.biomedtracker.com) and company press releases

Notable clinical trial results (3Q21)

Drug / company	Indication	Drug information
Tebentafusp / Immunocore	Uveal melanoma	9/22/2021 In a phase 3 open-label trial, patients receiving this soluble bispecific fusion of a high-affinity monoclonal T-cell receptor (mTCR) specific for gp100 (melanocytic protein) in the context of HLA-A*0201 and an anti-CD3 scFv fragment had 73% overall survival at one year compared with 59% in control group (*N. Engl. J. Med* **385**, 1196–1206, 2021)
Uproleselan / Glycomimetics	Acute myelogenous leukemia	9/20/2021 In a phase 2/3 study of this synthetic glycomimetic small-molecule E-selectin antagonist, which sensitizes leukemic cells to the chemotherapeutic cytarabine by mobilizing them from their protective bone marrow niche, patients showed increased remission rates and improved survival (*Blood* https://doi.org/10.1182/blood.2021010721, 2021)
Ensartinib / Xcovery	Non-small cell lung cancer	9/2/2021 In a phase 3 open label randomized trial of this aminopyridazine-based small-molecule ALK inhibitor, the drug doubled progression-free survival compared with that seen with the small-molecule kinase inhibitor crizotinib (*JAMA Oncol.* https://doi.org/10.1001/jamaoncol.2021.3523, 2021)
Lumevoq / GenSight	Leber's hereditary optic neuropathy	8/31/2021 In a long-term follow up study of this AAV-2 gene therapy encoding the wild-type NADH dehydrogenase 4 gene (*ND4*), treated patients showed progressive and sustained improvement of best-corrected visual acuity up to 52 months (*J. Neuroophthalmol.* **41**, 309–315, 2021)
Balstilimab / Agenus	Cervical cancer	8/25/2021 In a phase 2 study of this fully human IgG4 mAb targeting programmed death 1 receptor (PD-1), treated patients had a 20% response rate with median duration not reached at 14.6 months (*Gynecologic Oncol.* https://doi.org/10.1016/j.ygyno.2021.08.018, 2021)
Apabetalone / Resverlogix	Cardiovascular disease	8/24/2021 In a randomized trial with patients at risk for a cardiovascular event, patients with low baseline scores receiving this small-molecule bromodomain and extraterminal domain (BET) inhibitor that reduces vascular inflammation and calcification scored better on cognitive tests (J. Alzheimers Dis. https://doi.org/10.3233/JAD-210570, 2021)
Miplyffa (arimoclomol) / CytRx	Niemann-Pick disease	8/21/2021 In a randomized, placebo-controlled trial, patients receiving this small-molecule co-inducer of heat shock protein HSF1 had a 65% relative reduction in annual progression (*J. Inherit. Metab. Dis.* https://doi.org/10.1002/jimd.12428, 2021)
RVT-802 / Enzyvant Therapeutics	DiGeorge syndrome	8/4/2021 In ten single-arm, open-label studies in which 105 patients were treated with allogeneic cultured decapsulated thymic tissue, 77% survived one year (*J. Allergy Clin. Immunol.* https://doi.org/10.1016/j.jaci.2021.06.028, 2021)
Rinvoq (upadacitinib) / AbbVie	Atopic dermatitis	8/4/2020 In a phase 3 randomized comparator controlled study, this small-molecule inhibitor of Janus kinase 1 (JAK1) showed superiority to dupilumab (*JAMA Dermatol.* https://doi.org/10.1001/jamadermatol.2021.3023, 2021)
Masitinib / AB Science	Amyotrophic lateral sclerosis	7/19/2021 In a randomized, placebo-controlled trial, this oral, small-molecule inhibitor of wild-type and mutated forms of c-Kit (stem cell factor receptor), Lyn and platelet-derived growth factor receptor kinases prolonged survival by over two years provided treatment was begun before severe impairment (*Ther. Adv. Neurol. Dis.* https://doi.org/10.1177/17562864211030365, 2021)
Kineret (anakinra) / Swedish Orphan Biovitrum	COVID-19 treatment	9/3/2021 In phase 3 randomized, placebo-controlled trial of patients at risk for severe disease, this recombinant, non-glycosylated form of human interleukin-1 receptor antagonist reduced the odds of worse outcome to 0.36 at day 28 (*Nat. Med.* https://doi.org/10.1038/s41591-021-01499-z, 2021)
Ronapreve (casirivimab imdevimab) / Regeneron	COVID-19 prevention	8/4/2021 In a phase 3 trial of people exposed in the home to COVID-19, this cocktail of two neutralizing human IgG1 mAbs targeting SARS-CoV-2 spike glycoprotein epitopes reduced the incidence of systemic infection by 77% (N. Engl. J. Med. https://doi.org/10.1056/NEJMoa2109682, 2021)

ALK, anaplastic lymphoma kinase. Source: BioMedTracker, a service of Sagient Research (http://www.biomedtracker.com)

Notable drug approvals (3Q21)

Drug/company	Indication	Drug information
Opzelura (ruxolitinib) / Incyte	Atopic dermatitis	9/21/2921 FDA approves this small-molecule JAK/STAT inhibitor formulated as a cream
Tivdak (tisotumab vedotin-tftv) / Seagen	Cervical cancer	9/20/2021 FDA grants accelerated approval to this human tissue factor IgG1κ mAb targeting tissue factor conjugated to MMAE via a protease-cleavable linker
Exkivity (mobocertinib) / Takeda	Non-small-cell lung cancer	9/15/2021 FDA grants accelerated approval to this small-molecule selective tyrosine kinase inhibitor targeting EGFR and human EGFR2 exon insertion 2
Voxzogo (vosoritide) / BioMarin	Achondroplasia	8/27/2021 EMA approves this stabilized 39-residue analog of C-type natriuretic peptide containing 17 extra amino acids (PGQEHPNARKYKGANKK) appended to the native hormone's N terminus
Bimzelx (bimekizumab) / UCB	Psoriasis	8/24/2021 EMA approved this humanized bispecific IgG1 mAb that neutralizes both IL-17A and IL-17F
Korsuva (difelikefalin) / Cara Therapeutics	Pruritus	8/23/2021 FDA approves this small-molecule κ-opioid receptor agonist
Evrenzo (roxadustat) / AstraZeneca	Anemia due to chronic renal failure	8/19/2021 EMA approves this second-generation hypoxia-inducible factor prolyl hydroxylase inhibitor
Nexviazyme (avalglucosidase alfa-ngpt) / Sanofi	Pompe disease	8/6/2021 FDA approves this α-glucosidase enzyme replacement therapy targeting mannose-6-phophate receptor to facilitate cellular uptake
Saphnelo (anifrolumab-fnia) / AstraZeneca	Systemic lupus erythematosus	7/30/2021 FDA approves this fully human IgG1 mAb targeting interferon-α receptor 1
Skysona (Lenti-D, (elivaldogene autotemcel) / Bluebird Bio	Cerebral adrenoleukodystrophy	7/21/2021 EMA approves these autologous hematopoietic CD34$^+$ stem cells transduced with a lentiviral vector encoding human *ABCD1* cDNA under the control of a modified enhancer/promoter of myeloproliferative sarcoma virus
Bylvay (odevixibat) / Albireo Pharma	Progressive familial intrahepatic cholestasis	7/20/2021, 7/19/2021 FDA and EMA approve this small-molecule inhibitor of ileal bile acid transporter
Rezurock (belumosudil) / Kadmon Holdings	Graft versus host disease treatment	7/16/2021 FDA approves under its real-time approval review process this small-molecule selective oral inhibitor of Rho-associated coiled-coil kinase 2 (ROCK2) involved in inflammatory responses
Zy-CoV-D / Zydus Cadila	COVID-19 prevention	8/20/2021 India's Drugs Controller General grants an EUA to this DNA vaccine encoding the spike glycoprotein of SARS-CoV-2 and IgE signal peptide delivered intradermally via the PharmaJet Tropis ID fluid-stream injection device

ABCD gene, ATP-binding cassette D; EGFR, epidermal growth factor receptor; EUA, Emergency Use Authorization; IgE, immunoglobulin E; IL, interleukin; MMAE, monomethyl auristatin E. Source: BioMedTracker, a service of Sagient Research (http://www.biomedtracker.com)

Upcoming catalysts (1Q22)

Drug / company	Indication	Drug information
Tezepelumab / Amgen	Asthma	1/10/2022 FDA PDUFA date for this human IgG2κ mAb against thymic stromal lymphopoietin
Maribavir / Takeda	Cytomegalovirus infection	1/21/2021 FDA PDUFA date for this selective ATP competitor of viral DNA polymerase
Oteseconazole / Mycovia Pharmaceuticals	Non-systemic fungal infections	1/27/2022 FDA PDUFA date for this small-molecule inhibitor of lanosterol demethylase (CYP51), an enzyme involved in the synthesis of fungal cell wall sterols
Mavacamten / Bristol Myers Squibb	Hypertrophic cardiomyopathy	1/28/2022 FDA PDUFA date for this first-in-class small-molecule allosteric modulator of cardiac myosin
Faricimab / Roche	Diabetic macular edema/ wet age-related macular degeneration	1/31/2022 FDA PDUFA date for this IgG1 bispecific mAb against vascular endothelial growth factor A and angiopoietin-2
Mitapivat / Agios	Pyruvate kinase deficiency	2/17/2022 FDA PDUFA date for this first-in-class small-molecule allosteric activator of wild-type and mutated pyruvate kinase
Bardoxolone methyl / Reata Pharmaceuticals	Alport syndrome	2/25/2022 FDA PDUFA date for this small-molecule (synthetic triterpenoid) activator of nuclear factor erythroid 2-related factor 2 (Nrf2), which suppresses NF-κB- and STAT3-mediated inflammation
Roctavian (valoctocogene roxaparvovec) / BioMarin	Hemophilia A	12/31/2021 EMA's CHMP opinion due date for this AAV-8 vector encoding a factor VIII gene therapy

PDUFA, Prescription Drug User Fee Act; CHMP, Committee for Medicinal Products for Human Use (Europe); IgG, immunoglobulin G. Source: BioMedTracker, a service of Sagient Research (http://www.biomedtracker.com)

Laura DeFrancesco
Senior Editor, Nature Biotechnology.

Published online: 9 November 2021
https://doi.org/10.1038/s41587-021-01119-8