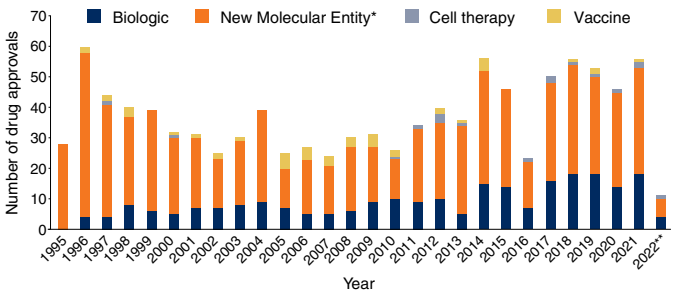
DATA PAGE

Drug pipeline 1Q22 — a raft of new modalities … and clinical blowups

This quarter, the US Food and Drug Administration (FDA) approved a slew of new therapeutic modalities. Immunocore's Kimmtrak soluble anti-gp100 TCR and Agio's Pyrukynd, an oral small-molecule allosteric activator of the red blood cell–specific form of pyruvate kinase, got the green light, as did two bispecific monoclonal antibodies (mAbs): Roche/Genentech's Vabysmo for wet age-related macular degeneration and Bristol Myers Squibb's Opdualag for melanoma. But the quarter also saw a large number of clinical holds: according to financial analysts Jefferies, there were as many as 13 in the first two months of 2022 alone. Among companies affected was Finch Therapeutics, with a complete response letter requesting information about SARS-CoV-2 screening of its live fecal microbiome product CP101. It wasn't all bad news for live biotherapeutics, however, with Ferring Pharmaceuticals publishing positive trial results of RBX2660 against *Clostridium difficile* and awaiting an upcoming Prescription Drug User Fee Act (PDUFA) decision. Next quarter will see many recombinant replacement enzymes, gene therapies and cell therapies being considered for registration, including pivotal decisions for Bluebird Bio's products Lenti-D for adrenoleukodystrophy and Zynteglo for β-thalassemia.

Historic US regulatory approvals by drug class



A slow quarter of drug approvals starting off the year. *New Molecular Entity (NME) class includes mainly small-molecule drugs, but also steroid, synthetic peptide and mixed compounds, excluding non-NME and new formation. **Partial year to March 31. Source: FDA (http://www.fdw.gov/) and BioMedTracker, a service of Sagient Research (http://www.biomedtracker.com).

Upcoming catalysts (3Q22)

Drug/company	Indication	Drug information
Pegunigalsidase alfa/Chiesi Farmaceutici	Fabry's disease	5/31/2022 EMA CHMP date for this PEGylated recombinant protein α-galactosidase A produced in a carrot (*Daucus carota*) cell culture expression system
Spesolimab/Boehringer Ingelheim	Psoriasis	6/1/2022 FDA PDUFA date for this humanized IgG1κ antibody that blocks activation of the interleukin-36 receptor
Lenti-D/Bluebird Bio	Adrenoleukodystrophy	6/7/2022 FDA PDUFA date for this autologous hematopoietic CD34+ stem cells transduced with a lentiviral vector encoding a human *ABCD1* cDNA gene therapy
Narsoplimab/Omeros	Transplant-associated thrombotic microangiopathy	7/1/2022 FDA PDUFA date for this human IgG4 mAb targeting mannan-binding lectin-associated serine protease-2
Teplizumab/Provention Bio	Diabetes mellitus, type I	7/1/2022 FDA PDUFA date 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
Olipudase alfa/Sanofi	Niemann–Pick disease	7/3/2022 FDA PDUFA date for this recombinant human acid sphingomyelinase
Myrcludex B/Gilead Sciences	Hepatitis D	7/19/2022 FDA PDUFA date for this synthetic 47-residue linear lipopeptide comprising a myristoylated N-terminal domain from the large hepatitis B virus surface antigen and a C-terminal carboxamide that binds to sodium bile acid co-transporter viral receptors on hepatocytes and blocks infection
AT-GAA/Amicus Therapeutics	Pompe disease	7/29/2022 and 9/1/2022 FDA PDUFA and EMA CHMP meeting dates for this biobetter combination of recombinant human acid α-glucosidase with optimized bis-phosphorylated mannose-6 phosphate glycans to enhance uptake together with miglustat, an *N*-butyl-deoxynojirimycin imino sugar that acts as a stabilizing agent
Zynteglo (betibeglogene autotemcel)/Bluebird Bio	Thalassemia	8/19/2022 FDA PDUFA date for these autologous CD34+ cells transduced ex vivo with a lentiviral vector pseudotyped with vesicular stomatitis virus glycoprotein G (BB305) carrying the gene encoding βA-T87Q-globin under the control of the β-globin enhancer and locus control region
Tabelecleucel/Atara Biotherapeutics	Post-transplant Epstein–Barr virus (EBV)+ lymphoproliferative disorder	8/1/2022 EMA CHMP date for these donor-derived, off-the-shelf, allogeneic EBV-specific cytotoxic T lymphocytes generated by exposure to EBV antigens
RBX2660/Ferring Pharmaceuticals	*Clostridium difficile*–associated diarrhea/infection	9/1/2022 FDA PDUFA date for this pathogen-screened stool-derived microbial suspension containing ≥10^7 live bacteria in a 0.9% saline/PEG 3350 vehicle derived from healthy donors, delivered via retention enema

Continued

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

Notable clinical trial results (1Q22)

Drug/company	Indication	Drug information
Aduhelm (aducanumab)/ Biogen	Alzheimer's disease	3/16/2022 In two randomized, double-blind, placebo-controlled phase 3 trials of this anti-β-amyloid IgG1 mAb, only one (EMERGE) met its primary endpoint (but still failed to meet secondary endpoints) after post hoc analysis showed evidence of treatment effects in six domains of clinical dementia rating in the high-dose cohort (*J. Prevent. Alzheimers Dis.* https://doi.org/10.14283/jpad.2022.30, 2022)
Enhertu (fam-trastuzumab deruxtecan-nxki)/Daiichi Sankyo	Non-small-cell lung cancer (NSCLC)	01/20/2022 In a phase 2 trial of previously treated HER2-mutated NSCLC, this antibody–drug conjugate, comprising an anti-HER2 humanized IgG1 mAb attached to a novel topoisomerase I inhibitor exatecan-derivative payload via a tetrapeptide-based linker, provided objective response in 55% of treated patients (*N. Eng. J. Med.* **386**, 241–251, 2022)
Roctavian (valoctocogene roxaparvovec)/BioMarin	Hemophilia A	3/17/2022 In a phase 3, single arm, open study, this replication-defective AAV-5 vector encoding hFVIII-SQ (a codon-optimized B-domain-deleted human FVIII with A2 and A3 domains linked by a 14-amino acid B domain sequence containing a furin cleavage site, all under the control of the hybrid liver-specific promoter), 90% of participants had either no or fewer treated bleeds after one infusion (*N. Engl. J. Med.* **386**, 1013–1025, 2022)
RBX2660/Ferring Pharmaceuticals	*Clostridium difficile*-associated diarrhea/infection	3/12/2022 In a phase 2 open label trial, this enema-delivered, pathogen-screened, stool-derived microbial suspension containing $\geq 10^7$ live bacteria derived from healthy donors in a 0.9% saline/PEG 3350 vehicle produced a 79% treatment success rate in reducing recurrent *C. difficile* infection versus 31% for the historical control arm (*BMC Infect. Dis.* **22**, 245, 2022)
Beremagene geperpavec (B-Vec)/Krystal Biotech	Epidermolysis bullosa	3/28/2022 In a phase 1/2 trial of this topically delivered, episomal, replication-incompetent herpes simplex virus-1 vector encoding human collagen VII, repeat applications were associated with durable wound closure, full-length cutaneous type VII collagen expression, and anchoring fibril assembly (*Nat. Med.* **28**, 780–788, 2022)
Seladelpar/CymaBay Therapeutics	Primary biliary cholangitis and hepatic fibrosis	3/30/2022 In a dose-ranging open-label trial, this breakthrough-designated small-molecule PPAR agonist showed dose-dependent improvement in liver enzymes, with a composite response of 33% at week 52 for alkaline phosphatase at the highest dose (10 mg) (*J. Hepatol.* https://doi.org/10.1016/j.jhep.2022.02.033, 2022)

IgG, immunoglobulin G; PPAR, peroxisome proliferator-activated receptor. Source: BioMedTracker, a service of Sagient Research (http://www.biomedtracker.com).

Notable drug approvals (1Q22)

Drug/company	Indication	Drug information
Quviviq (daridorexant)/ Idorsia Pharmaceuticals	Insomnia	1/7/2022 FDA approves this small-molecule dual orexin receptor antagonist with improved balance between nighttime sleepiness and daytime functioning
Kimmtrak (tebentafusp-tebn)/ Immunocore	Uveal melanoma	1/25/2022 FDA approves this bispecific fusion protein comprising a high-affinity TCR specific to gp100 antigen fused to an anti-CD3 scFv
Vabysmo (faricimab-svoa)/ Roche/Genentech	Wet age-related macular degeneration	1/31/2022 FDA approves this humanized bispecific IgG1 mAb that binds VEGF-A on one arm and angiopoietin-2 on the other
Carvytik (ciltacabtagene autoleucel)/Johnson & Johnson	Multiple myeloma	2/28 2022 FDA approves this CAR-T cell created ex vivo using a lentiviral vector to deliver two BCMA-targeting scFvs, a 4-1BB co-stimulatory domain and a CD3ζ signaling cytoplasmic domain
Opdualag (nivolumab relatlimab-rmbw)/ Bristol Myers Squibb	Melanoma	3/18/2022 FDA approves this fixed-dose combination of two checkpoint inhibitor IgG4κ mAbs: relatlimab, which targets LAG-3, and nivolumab, an approved mAb that targets PD-1
Vonjo[a] (pacritinib)/ CTI BioPharma	Myelofibrosis	2/28/2022 FDA grants accelerated approval for this small-molecule multiple kinase inhibitor (JAK–STAT, FLT-3 and IRAK1)
Pyrukynd (mitapivat)/Agios	Pyruvate kinase deficiency	2/17/2022 FDA approves this first-in-class small-molecule allosteric activator of wild-type and mutated pyruvate kinase

[a]Accelerated approval. CAR, chimeric antigen receptor; BCMA, B cell maturation antigen; FLT-3, fms-like tyrosine kinase 3; IgG, immunoglobulin G; IRAK1, interleukin-1 receptor-associated kinase 1; JAK, Janus-associated kinase; STAT, signal transducer and activator of transcription; LAG-3, lymphocyte activation gene 3; PD-1, programmed death receptor 1; scFv, single-chain variable fragment; TCR, T cell receptor; VEGF-A, vascular endothelial growth factor A. Source: BioMedTracker, a service of Sagient Research (http://www.biomedtracker.com).

Notable regulatory setbacks (1Q22)

Drug/ company	Indication	Drug information
Tiragolumab/ Roche	Small-cell lung cancer	3/29/20221 Company suspended clinical trial on first-in-class anti-TIGIT with Tecentriq (atezolizumab, an anti-PDL1) as it failed to slow progression in a phase 3 randomized, placebo-controlled trial
Sintilimab/ Eli Lilly	Non-small-cell lung cancer	3/24/2022 FDA issued a complete response letter for this fully human IgG4κ mAb against PD-1 as it did not meet an unmet need. In addition, the clinical trial failed to meet requirements for a trial conducted in a foreign country (China).
Arimoclomol/ Orphazyme	Niemann–Pick disease	2/23/2022 EMA's CHMP committee voted against marketing approval for this small-molecule co-inducer of heat shock protein HSF1, even though the ad hoc committee had a positive outcome. The company then withdrew the marketing application.
HMI-102/ Homology Medicines	Phenylketonuria	2/18/2022 FDA put a clinical hold due to elevated liver function tests on this hepatotropic human hematopoietic stem cell-derived AAVHSC15 vector encoding codon-optimized human phenylalanine hydroxylase under control of a liver-specific synthetic promoter comprising a hepatic control region (HCR1), the SERPINA1 (AAT) promoter, and a 5′ UTR with an SV40 late polyadenylation signal
CP101/Finch Therapeutics	*Clostridium difficile*–associated diarrhea/ infection	2/24/2022 FDA put a clinical hold on the phase 3 trial of this encapsulated, orally administered, lyophilized full-spectrum live fecal microbiota product harvested from healthy human donors, requesting more information on COVID-19 testing of donors

IDMC, independent data monitoring committee; TIGIT, T-cell immunoglobulin and ITIM domain; PAH, phenylalanine hydroxylase; PD-1, programmed death 1; PDL1, PD-1 ligand 1; AAVHSC15: adeno-associated viral vector serotype HSC. Source: BioMedTracker, a service of Sagient Research (http://www.biomedtracker.com).

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