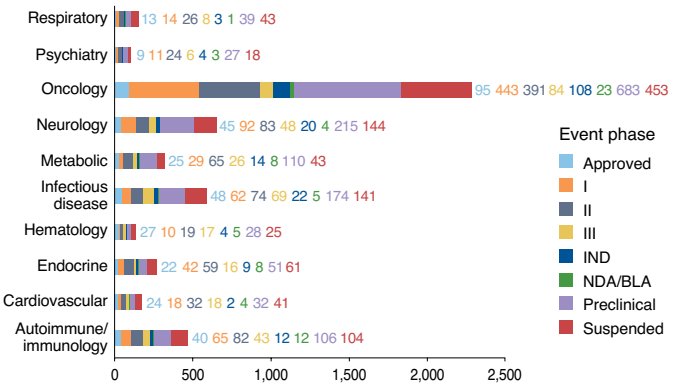
DATA PAGE

Drug pipeline 4Q21

The year that brought impressive initial results from one molecular therapy, in the first systemic CRISPR trial — Intellia Therapeutics' transthyretin amyloidosis Cas9 mRNA therapy — closed with the approval of another: Novartis's Leqvio, the first small interfering RNA (siRNA) therapy approved for a mass market. Controversy over the pricing of bluebird bio's Lenti-D — a lentiviral human *ABCD1* cDNA gene therapy for adrenoleukodystrophy — prompted the company to withdrew its application (recalling gene therapy's first commercial bust, uniQure's Glybera). Two efficacy trials, from Galmed Pharmaceuticals and Inventiva Pharma, reported positive data in non-alcoholic steatohepatitis. Humanigen presented positive results for its anti-COVID-19 monoclonal antibody (mAb) lenzilumab, but the emergence of the Omicron (B.1.1.529) SARS-CoV-2 variant has exposed the vagaries of antiviral development, severely compromising the neutralizing activity of many Emergency Use Authorized COVID-19 mAbs. In January, the FDA pulled the authorizations for Lilly's and Regeneron's mAb cocktails. Only Vir Biotechnology's Xevudy (sotrovimab) and the combination of amubarvimab and romlusevimab from TSB Therapeutics (Beijing) retain potency in vitro. Up next for approval are bluebird bio's Zynteglo lentiviral gene therapy and Immunocore's novel monoclonal T cell receptor therapy tebentafusp.

Top ten disease groups by pipeline size



The oncology pipeline remains strong. Source: BioMedTracker a service of Sagient Research (http://www.biomedtracker.com).

Notable drug approvals (4Q21)

Drug/company	Indication	Drug information
Rethymic (RVT802)/ Enzyvant Therapeutics	Congenital athymia	10/8/2021 FDA approves this partially T-cell-depleted cultured allogeneic decapsulated postnatal thymic tissue
Tavneos (avacopan)/ ChemoCentryx	ACNA-associated vasculitis	10/8/2021 FDA approves this small- molecule inhibitor of complement factor 5a receptor
Scemblix (asciminib)/ Novartis	Chronic myelogenous leukemia	10/29/2021 FDA grants accelerated approval to this small-molecule allosteric BCR-ABL inhibitor that selectively targets the ABL myristoyl pocket
Susvimo (ranibizumab)/ Roche	Wet age-related macular degeneration	10/22/2021 FDA approves this antigen-binding segment of an anti-IgG1 mAb against VEGF
Besremi (ropeginterferon alfa-2b)/PharmaEssentia	Polycythemia vera	11/12/2021 FDA approves this single pegylated proline interferon-α2b
Voxzogo (vosoritide)/ BioMarin	Achondroplasia	11/19/2021 FDA approves this stabilized analog of C-type natriuretic peptide containing 17 extra amino acids (PGQEHPNARKYKGANKK) appended to the native hormone's N terminus
Livtencity (maribavir)/ Takeda	Cytomegalovirus infection	11/23/2021 FDA approves this benzimidazole small-molecule inhibitor of UL97 kinase that interferes with viral DNA synthesis and capsid maturation
Tezspire (tezepelumab-ekko)/Amgen	Asthma	12/17/2021 FDA approves this fully human IgG2a mAb against thymic stromal lymphopoietin
Vyvgart (efgartigimod alfa)/Argenx	Myasthenia gravis	12/17/2021 FDA approves this human IgG1 antibody Fc fragment engineered with high affinity for the neonatal Fc receptor
Leqvio (inclisiran)/ Novartis	Dyslipidemia/ hypercholesterol-emia	12/22/2021 FDA approves this triantennary GalNAc-conjugated phosphorothioate, 2′-*O*-methyl, 2′-fluoro and 2′-deoxynucleic acid-modified siRNA targeting proprotein convertase subtilisin kexin type 9 (*PCSK9*) mRNA

FDA, US Food and Drug Administration; ANCA, anti-neutrophil cytoplasmic antibodies; mAb, monoclonal antibody; GalNAc, *N*-acetylgalactosamine; PEG, polyethylene glycol; VEGF, vascular endothelial growth factor. Source: BioMedTracker, a service of Sagient Research (http://www.biomedtracker.com).

Upcoming catalysts (2Q22)

Drug / company	Indication	Drug information
Ronapreve (casirivimab imdevimab)/ Regeneron	COVID-19	4/13/2022 FDA PDUFA date for this cocktail of two neutralizing human IgG1 mAbs targeting SARS-CoV-2 spike glycoprotein epitopes
Vutrisiran/Alnylam	Hereditary transthyretin amyloidosis with polyneuropathy (familial amyloid polyneuropathy)	4/14/2022 FDA PDUFA date for this 2′-fluoro, 2′-methoxy-modified phosphorothioate GalNAc siRNA targeting transthyretin
Toripalimab/Coherus Biosciences	Nasopharyngeal cancer	4/29/2022 FDA PDUFA date for this humanized IgG4 mAb against human PD-1 receptor
Mavacamten/Bristol Myers Squibb	Hypertrophic cardiomyopathy	4/28/2022 FDA PDUFA date for this allosteric inhibitor of myosin that decreases the adenosine triphosphatase activity of the cardiac myosin heavy chain,
Parsaclisib/Incyte	Marginal zone lymphoma mantle cell lymphoma	4/29/2022 FDA PDUFA date for this selective PI3Kδ inhibitor
Surufatinib/Hutchmed	Neuroendocrine tumors	4/29/2022 FDA PDUFA date for this small- molecule multi-tyrosine-kinase receptor inhibitor targeting VEGFR1, VEGFR2, VEGFR3, FGFR1 and CSF-1R
Zynteglo/bluebird bio	Thalassemia	5/20/2022 FDA PDUFA date for autologous CD34⁺ cells transduced ex vivo with the gene encoding βA-T87Q-globin, under the control of the β-globin enhancer and locus control region, via a BB305 lentiviral vector pseudotyped with vesicular stomatitis virus glycoprotein G
Tirzepatide/Eli Lilly	Diabetes mellitus, type 2	5/30/2022 FDA PDUFA date for this dual glucose-dependent insulinotropic polypeptide and glucagon-like peptide 1 receptor agonist
Tebentafusp/Immunocore	Uveal melanoma	2/23/2022 and 4/30/2022 FDA PDUFA and EMA CHMP decision on this soluble bispecific fusion of a high-affinity monoclonal TCR specific for gp100 (melanocytic protein) in the context of HLA-A*0201 and an anti-CD3 scFv fragment.

CHMP, Committee for Medicinal Products for Human Use; EMA, European Medicines Agency; GalNAc, *N*-acetylgalactosamine; HLA, human leukocyte antigen; PDUFA, Prescription Drug User Fee Act; PI3K, phosphatidylinositol 3-kinase; scFv, single-chain variable fragment; siRNA, small interfering RNA; VEGFR, vascular endothelial growth factor receptor; FGFR1, fibroblast growth factor receptor 1; CSF-1R, colony-stimulating factor 1 receptor. Source: BioMedTracker, a service of Sagient Research (http://www.biomedtracker.com).

Notable regulatory setbacks (4Q21)

Drug / company	Indication	Drug information
Aduhelm (aducanumab)/ Biogen	Alzheimer's disease	12/17/2021 EMA rejects this fully human IgG1 mAb against a conformational epitope on β-amyloid plaques after a negative CHMP vote in November due to questionable clinical improvement
Plinabulin/BeyondSpring	Neutropenia/leukopenia	12/1/2021 FDA issues a complete response letter for this marine *Aspergillus*-derived small-molecule halimide with selective immunomodulating microtubule-binding activity owing to insufficient data from a single registrational trial
Tanezumab/Pfizer	Osteoarthritis and osteoarthritis pain	10/27/2021 FDA issues a complete response letter on this humanized IgG2 mAb that blocks nerve growth factor because of rapid progression of osteoarthritis
Narsoplimab/Omeros	Transplant-associated thrombotic microangiopathy	10/1/2021 FDA issues a complete response letter on this human IgG4 mAb targeting mannan-binding lectin-associated serine protease-2
Lenti-D/bluebird bio	Adrenoleukodystrophy	10/21/2021 bluebird withdraws marketing authorization from the European Union for its autologous hematopoietic CD34⁺ stem cells transduced with a lentiviral vector encoding human *ABCD1* cDNA gene therapy, citing an "untenable" pricing situation
Devimistat/Rafael Pharmaceuticals	Multiple cancers	10/28/2021 Company announces the data monitoring committee has recommended the phase 3 trial of its infused small-molecule 6,8-bisbenzylsulfanyloctanoic acid, a lipoic acid analog Krebs cycle inhibitor, be stopped owing to lack of efficacy
Elamipretide (systemic delivery)/Stealth BioTherapeutics	Dilated cardiomyopathy	10/20/2021 FDA issued a refuse to file letter for this infused short racemic four-amino-acid peptide (D-arginyl-2,6-dimethyl-L-tyrosyl-L-lysyl-L-phenylalaninamide) that concentrates in the inner mitochondrial membrane and reduces the production of reactive oxygen species, owing to insufficient trial data
NNZ-2591/Neuren Pharmaceuticals	Angelman syndrome	10/1/2021 FDA puts a clinical hold on the phase 2 trial of this peptide diketopiperazine, a synthetic analog of cyclic glycine-proline, as a result of insufficient safety assessment
Fordadistrogene movaparvovec /Pfizer	Duchenne muscular dystrophy	12/20/2025 Company halts the phase 1b clinical trial of this AAV9 gene therapy because of a patient death
Bamlanivimab with etesevimab/Eli Lilly	COVID-19 treatment	1/24/2022: FDA issues statement limiting the use to patients known to have a susceptible variant
REGEN-COV (casirivimab and imdevimab)/ Regeneron	COVID-19 treatment	1/24/2022: FDA issues statement limiting the use to patients known to have a susceptible variant

AAV, adeno-associated virus; CAR, chimeric antigen receptor. Source: BioMedTracker, a service of Sagient Research (http://www.biomedtracker.com) and company press releases.

Notable clinical trial results (4Q21)

Drug / company	Indication	Drug information
Xevudy (sotrovimab)/Vir Biotechnology	COVID-19	10/27/2021 In this double-blind, placebo-controlled phase 3 trial of a human IgG1κ mAb engineered with an Fc domain with increased FcRn binding affinity that targets SARS-CoV-2 spike protein receptor binding domain, only 1% of treated patients with high-risk COVID progressed, versus 7% of untreated patients (*N. Eng. J. Med.* **385**, 1941–1950, 2021, https://doi.org/10.1056/NEJMoa2107934)
Aramchol/ Galmed Pharmaceuticals	Non-alcoholic steatohepatitis	10/7/2021 In a phase 2b randomized, placebo-controlled trial of arachidylamidocholanoic acid, a fatty acid bile acid conjugate that downregulates stearoyl CoA saturase 1, resolution without worsening fibrosis was achieved in 17% of treated versus 5% of untreated patients (*Nat. Med.* **27**, 1825–1835, 2021, https://doi.org/10.1038/s41591-021-01495-3)
Lanifibranor/ Inventiva Pharma	Non-alcoholic steatohepatitis	10/20/2021 In a phase 2b randomized trial of this pan-PPAR agonist, the percentage of patients who had a decrease in Steatosis, Activity, Fibrosis score without worsening of fibrosis was 55% at the highest dose, versus 33% in placebo controls (*N. Eng. J. Med.* **385**, 1547–1558, 2021, https://doi.org/10.1056/NEJMoa2036205)
Zyesami (aviptadil acetate)/NrX Pharmaceuticals	COVID-19	10/2/2021 In a phase 2b/3 trial of this inhaled synthetic 28-amino-acid vasoactive intestinal polypeptide analog that binds specifically to alveolar type II cells, 81% of patients at high risk of death receiving treatment survived, versus 21% receiving standard of care (*J. Infect. Dis. Treat.* **7**, 52, 2021, https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3665228)
Lenzilumab/ Humanigen	COVID-19	12/1/2021 In a randomized, placebo-controlled phase 3 trial of a humanized IgG1κ mAb against granulocyte–macrophage colony stimulating factor, hospitalized patients had 54% improvement in survival without ventilator (*Lancet* 2021, https://doi.org/10.1016/S2213-2600(21)00494-X)
Cipaglucosidase alfa and miglustat/ Amicus Therapeutics	Pompe disease	11/18/2021 In a phase 3 trial of this combination of recombinant human acid α-glucosidase with optimized bisphosphorylated mannose-6-phosphate glycans to enhance uptake and miglustat, a stabilizer of cipaglucosidase alfa, distance walked improved versus standard of care (20.8 m versus 7.2 m) (*Lancet* **20**, 1027–1037, 2021, https://doi.org/10.1016/S1474-4422(21)00331-8)
Zynteglo (betibeglogene autotemcel)/ bluebird bio	Thalassemia	12/11/2021 In a phase 3 open label clinical trial of 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, 20 of 22 patients achieved transfusion independence at a median of 29 months (*N. Engl. J. Med.* 2021, https://doi.org/10.1056/NEJMoa2113206)

FcRn, neonatal Fc receptor; PPAR, peroxisome proliferator–activated receptor; ALK, anaplastic lymphoma kinase; PPAR, peroxisome proliferator-activated receptor. Source: BioMedTracker, a service of Sagient Research (http://www.biomedtracker.com).

Laura DeFrancesco
Senior Editor, Nature Biotechnology.

Published online: 15 February 2022
https://doi.org/10.1038/s41587-022-01216-2