DATA PAGE

Drug pipeline 1Q21—the old and the new

The US Food and Drug Administration (FDA) continues to approve products at a rapid clip, with 17 new molecular entity (NME) and biologic approvals in the quarter. Over 40 years after the first monoclonal antibody (mAb) was approved—muromonab (Ortho Kung/OKT3), an anti-CD3 murine mAb for use in graft-versus-host disease—FDA will consider a humanized version of the drug for type 1 diabetes. Elsewhere, CRISPR Therapeutics published promising one-year results on its CRISPR-Cas9 therapy against the *BCL11A* erythroid-specific enhancer in transfusion-dependent β -thalassemia and sickle cell disease. Bristol Myers Squibb (BMS) and bluebird bio's Abecma (idecabtagene vicleucel) became the first chimeric antigen receptor (CAR)-T cell therapy to be approved for multiple myeloma and the first directed against an antigen other than CD19. Regeneron's Evkeeza (evinacumab-dgnb) is the first mAb approved for familial hypercholesterolemia that targets the angiopoietin-like 3 protein. A double dose of bad news came in Huntington's disease, with clinical setbacks for two antisense oligonucleotide (ASO) therapies: Ionis/Roche's tominersen and Wave's WVE-120102. Lilly reported positive trial results for its Alzheimer's disease therapy mAb donanemab; by next quarter's end, Biogen might finally get an answer from regulators on its controversial anti-Alzheimer's disease mAb, aducanumab.

Historic US regulatory approvals by drug class

A healthy crop of new approvals in quarter 1, skewed toward small molecules.

*New molecular entity (NME) class includes mainly small-molecule drugs, but also steroid, synthetic peptide and mixed compounds, excluding non-NME and new formulation. **Partial year to March 31. Source: BioMedTracker, a service of Sagient Research (<http://www.biomedtracker.com>).

Notable drug approvals (1Q21)

Drug/company	Indication	Drug information
Lupkynis (voclosporin)/Aurinia	Lupus nephritis	1/22/2021 FDA approved this small-molecule calcineurin phosphatase inhibitor, the first oral drug for lupus nephritis
Breyanzi (lisocabtagene maraleucel)/BMS	Diffuse large B cell lymphoma	2/5/2021 FDA approved autologous CAR-T cells, expanded in culture, expressing CD19 and a truncated epidermal growth factor receptor (EGFR)
Ukoniq* (umbralisib)/TG Therapeutics	Marginal zone lymphoma; indolent non-Hodgkin's lymphoma	2/5/2021 FDA granted accelerated approval to this small molecule targeting phosphatidylinositol 3-OH kinase (PI3K)- δ and casein kinase 1 (CK1)- ϵ .
Evkeeza (evinacumab-dgnb)/Regeneron	Dyslipidemia/hypercholesterolemia	2/11/2021 FDA approved this fully human IgG4 mAb against angiopoietin-like 3 that has a stabilizing mutation in the hinge.
Amondys 45* (casimersen)/Sarepta Therapeutics	Duchenne muscular dystrophy	2/25/2021 FDA gave accelerated approval to this 22-residue exon-45-skipping phosphorodiamidate ASO.
Nulibry (fosdenopterin)/BridgBio Pharma	Molybdenum cofactor deficiency	2/28/2021 FDA approved cyclic pyranopterin monophosphate, an intermediate in the synthesis of molybdenum cofactor
Abecma (idecabtagene vicleucel)/BMS	Multiple myeloma	3/29/2021 FDA approved this CAR-T cell therapy with anti-B-cell maturation antigen (BCMA) single-chain variable fragment (scFv) fused to the CD137 (4-1BB) co-stimulatory and CD3 ζ signaling domains

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

Notable clinical trials for COVID-19 products

Drug/company	Indication	Drug information
Immctez/Creative Medical Holdings	COVID-19 acute respiratory distress syndrome (ARDS)	1/7/2021 In a double-blind, placebo-controlled phase 2a trial for COVID-19 with ARDS, patients treated with two infusions of umbilical-cord-derived mesenchymal stem cells had a significant decrease in cytokines and improved survival (91% versus 42%) <i>Stem Cells Transl. Med.</i> https://doi.org/10.1002/sctm.20-0472 , 2021)
Etesevimab plus bamlanivimab/Eli Lilly	COVID-19	1/21/2021 In a phase 2 randomized trial of bamlanivimab, a fully human IgG1k mAb targeting an epitope on the receptor-binding domain (RBD) of SARS-CoV-2 spike (S) protein, no effect was seen on viral load in unhospitalized patients with mild-to-moderate COVID-19; the addition of etesevimeb (another fully human IgG1k mAb that targets a different S protein RBD epitope), however, did result in significant reduction (<i>J. Am. Med. Assoc.</i> 325 , 632–644, 2021)
Peginterferon lambda/Eiger BioPharmaceuticals	COVID-19	2/5/2021 In a double-blind, placebo-controlled trial, this PEGylated interferon- λ accelerated the decline in SARS-CoV-2 viral load from 3 days onward (<i>Lancet Resp. Med.</i> https://doi.org/10.1016/S2213-2600(20)30566-X , 2021)
Actemra (tocilizumab)/Roche	COVID-19	2/25/2021 In a phase 3 trials with hospitalized patients, this humanized IgG1k mAb targeting interleukin-6 receptor (IL-6R) did not improve clinical status at 28 days (<i>N. Engl. J. Med.</i> https://doi.org/10.1056/NEJMoa2028700 , 2020)
Tocilizumab and sarilumab/Roche	COVID-19	2/25/2021 In an adaptive trial of this humanized IgG1k mAb targeting IL-6R (tocilizumab) and human IgG1 mAb targeting IL-6R α (sarilumab), the group receiving both drugs showed improved survival at 90 days (<i>N. Engl. J. Med.</i> https://doi.org/10.1056/NEJMoa2100433 , 2020)
PegIHep (PEGylated interferon alpha-2b)/Zydus Cadila	COVID-19	3/10/2021 In a phase 2 randomized, open-label trial of PEGylated interferon- α 2b, 95% of SARS-CoV-2-positive patients with moderate symptoms had achieved clinical improvement on day 15 compared with 68% subjects in standard of care (<i>Int. J. Infect. Dis.</i> 105 , 516–521, 2021)

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

Upcoming catalysts (3Q21)

Drug/company	Indication	Drug information
Aducanumab/Biogen	Alzheimer's disease	6/7/2021, 7/1/2021 FDA and European Medicines Agency Committee for Medicinal Products for Human Use decisions for this this fully human IgG1 mAb against a conformational epitope on β -amyloid plaques
Leukotac (inolimomab)/Elsalys Biotech	Graft-versus-host disease	06/30/2021 FDA PDUFA date for this murine IgG1k mAb that targets the interleukin-2 receptor- α
Teplizumab/Provention Bio	Diabetes mellitus, type 1	07/02/2021 FDA PDUFA date for this humanized IgG1 mAb against the CD3 ϵ chain expressed on mature T lymphocytes
Anifrolumab/AstraZeneca	Systemic lupus erythematosus	07/05/2021 FDA PDUFA date for this fully human IgG1k mAb against subunit 1 of the type I interferon receptor
Narsoplimab/Omeros	Transplant-associated thrombotic microangiopathy	7/16/2021 FDA PDUFA date for this human IgG4 mAb targeting mannan-binding lectin-associated serine protease-2
Amivantamab/Johnson & Johnson	Non-small-cell lung cancer	8/3/2021 FDA PDUFA date for this Fc-enhanced bispecific mAb targeting EGFR and cMET
AMG 510/Amgen	Non-small-cell lung cancer	8/16/2021 FDA PDUFA date for this first-in-class small-molecule inhibitor of mutated KRAS (G12C)
Vicineum (oportuzumab monatox)/Sesen Bio	Bladder cancer	08/18/2021 FDA PDUFA date for this antibody-drug conjugate epithelial cell adhesion molecule-specific scFv fused to <i>Pseudomonas</i> exotoxin A, a protein synthesis inhibitor
Belumosudil/Kadmon Holdings	Graft-versus-host disease	8/30/2021 FDA PDUFA date for this small-molecule inhibitor of Rho-associated coiled-coil kinase 2 (ROCK2)
Belzutifan/Merck	Renal cell cancer	09/15/2021 FDA PDUFA date for this small-molecule antagonist of hypoxia-induced factor 2- α

PDUFA, Prescription Drug User Fee Act. Source: BioMedTracker, a service of Sagient Research (<http://www.biomedtracker.com>)

Notable regulatory setbacks (1Q21)

Drug/company	Indication	Drug information
Ultomiris (ravulizumab)/Alexion	COVID-19	1/13/2021 Data monitoring committee recommended pausing enrollment of this anti-C5 humanized IgG2/IgG4 chimeric mAb (comprising human κ light chain constant region, a IgG2 heavy-chain CH1 domain and hinge region, a hybrid IgG2/IgG4 CH2 domain and an IgG4 CH3 domain) due to lack of efficacy over standard of care
Ropeginterferon alfa-2b/Pharmasentia	Polycythemia vera	3/14/2021 FDA issued a complete response letter for this PEGylated proline-interferon- α 2b, requesting more information on the prefilled syringes, owing to delay in inspection of site in Taiwan
WVE-120102/Wave Life Sciences	Huntington's disease	3/29/2021 The company stopped clinical development of this stereopure phosphorothioate ASO due to lack of statistically significant reduction in mutant huntingtin
Tominersen/Roche	Huntington's disease	3/22/2021 Company discontinued phase 3 trial of this chimeric 2'-O-(2-methoxyethyl)-modified gapmer ASO conjugated to an mAb targeting transferrin receptor on basis of review of risk/benefit ratio by IDMC
Tesetaxel/Odonate Therapeutics	Metastatic breast, colorectal, solid tumors	3/23/2021 Company discontinued trials of this oral synthetic taxane after FDA indicated the data are unlikely to support approval
RG6356/Sarepta Therapeutics	Duchenne muscular dystrophy	1/7/2021 Phase 2 study of this adeno-associated virus (AAV) serotype rh74 containing the human microdystrophin gene under an muscle-specific <i>MHCK7</i> promoter failed to show statistical improvement in function compared with placebo, although it did meet primary biological endpoint (protein level)
OV101 (gaboxadol)/Ovid Therapeutics	Angelman's syndrome	12/2/2020 Company discontinued trial on this extrasynaptic δ -selective γ -amino butyric acid A (GABA _A) receptor agonist as it missed the primary endpoint in pivotal phase 3 trial

IDMC, independent data monitoring committee. Source: BioMedTracker, a service of Sagient Research (<http://www.biomedtracker.com>)

Notable clinical trial results (1Q21)

Drug/company	Indication	Drug information
Lumevoq/GenSight	Leber's hereditary optic neuropathy	1/13/2021 In a phase 1/2a open-label, dose-escalation trial of this AAV-2 gene therapy encoding wild-type NADH dehydrogenase 4 gene (ND4), patients achieved improvement in visual acuity over the 5-year study period (<i>BioDrugs</i> 35 , 201-214, 2021)
Engensis/Helixmith	Diabetic peripheral neuropathy	1/19/2021 In a phase 3 double-blind, placebo-controlled trial, two isoforms of angiogenesis-promoting hepatocyte growth factor, HGF ₇₂₈ and HGF ₇₂₃ , delivered into leg muscle via a DNA plasmid vector (pCK) comprising cytomegalovirus 5' untranslated region upstream and full-length immediate-early promoter, reduced pain at up to 12 months (<i>Clin. Transl. Sci.</i> https://doi.org/10.1111/cts.12977 , 2021)
Ublituximab/TG Therapeutics	Chronic lymphocytic leukemia, small-cell lymphocytic lymphoma	2/21/2021 In a phase 3 trial, a combination of ibritinib plus this chimeric anti-CD20 IgG1mAb with a low-fructose Fc region for enhanced antibody-dependent cell-mediated cytotoxicity via CD16A (Fc γ RIIIa) binding resulted in a statistically significant overall response rate as compared with ibritinib monotherapy (<i>Lancet Haematol.</i> 8 , e254-e266, 2021)
Donanemab (LY3002813)/Eli Lilly	Alzheimer's disease	3/15/2021 In a randomized, placebo-controlled, double-blind phase 2 trial of this humanized IgG1 mAb targeting amyloid- β_{p3-42} , the N-terminally truncated pyroglutamate-3 isoform, patients with early disease showed significantly less decline at 76 weeks than those on placebo (<i>N. Engl. J. Med.</i> https://doi.org/10.1056/NEJMoa2100708 , 2021)
CTX001/CRISPR Therapeutics	Transfusion-dependent β -thalassemia (TDT) and sickle cell disease (SCD)	1/21/2021 In a phase 1/2 trial, more than a year after one person with TDT and one with SCD received autologous CD34 ⁺ hematopoietic stem and progenitor cells electroporated ex vivo with CRISPR-Cas9 and gRNA targeting the <i>BCL11A</i> erythroid-specific enhancer, high levels of allelic editing were detected in bone marrow and blood, with pancellular fetal hemoglobin distribution, transfusion independence, and (for SCD) elimination of vaso-occlusive episodes (<i>N. Engl. J. Med.</i> 384 , 252-260, 2021)
Abecma (idecabtagene vicleucel)/BMS	Multiple myeloma	2/24/2021 In a phase 2 pivotal trial, of patients receiving this CAR-T cell therapy with anti-BCMA scFv fused to 4-1BB co-stimulatory and CD3 ζ signaling domains, 73% overall responded and 33% had a complete response or better (<i>N. Engl. J. Med.</i> 384 , 705-716, 2021)
Teplizumab/Provention Bio	Diabetes mellitus, type 1	3/3/2021 In a phase 2 trial of at-risk people, one injection of this humanized IgG1 mAb against the CD3 ϵ chain (developed by grafting six complementarity-determining regions from OKT3 into a human framework containing leucine-to-alanine substitutions at residues 234 and 235 in the CH2 region to abolish Fc receptor binding) delayed onset; onset averaged 5 years compared with 2 years for untreated individuals (<i>Sci. Transl. Med.</i> 13 , eabc8980, 2021)
Sotatercept/Acceleron	Pulmonary arterial hypertension and pulmonary hypertension	4/1/2021 In a phase 2 randomized double-blind, placebo-controlled trial of this glycosylated, dimeric fusion protein comprising the extracellular domain of the human activin receptor type IIA and the Fc region of human IgG1, patients receiving the drug had statistically significant reduction in vascular resistance (<i>N. Engl. J. Med.</i> 384 , 1204-1215, 2021)
Vigil (gemogenovatucl-T)/Gradalis	Ovarian cancer	3/11/2021 In a phase 2b placebo-controlled trial, this autologous tumor cell product transduced ex vivo with a DNA plasmid encoding short-hairpin RNA against furin (which blocks immunosuppressive transforming growth factor- β 1 and β 2) and recombinant human granulocyte macrophage colony stimulating factor (which activates T cells) extended overall survival and recurrence-free survival as compared with placebo (<i>Gynecol. Oncol.</i> https://doi.org/10.1016/j.jgyno.2021.03.009 , 2021)
Lirentelimab/Allakos	Gastroenteritis	10/22/2020 In a phase 2 randomized, placebo-controlled trial, this anti-Siglec-8 IgG1 mAb reduced gastrointestinal eosinophils (<i>N. Engl. J. Med.</i> 383 , 1624-1634, 2020).

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

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