TRENDS-in-MEDICINE

February 21, 2021

by Lynne Peterson

Quick Takes

…Highlights from this week's news relating to drugs and devices in development that are not covered in other *Trends-in-Medicine* reports…

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Top news of the week (*read details in other sections of* ***Quick Takes***)

✓ **BLUEBIRD BIO's LentiGlobin** (bb1111) – Two trials of this gene therapy for sickle cell disease were halted after a patient developed AML and another developed MDS.

✓ **CORTEXYME's atuzaginstat** (COR-388) – The FDA put it on clinical hold in Alzheimer's disease due to hepatic adverse events.

✓ **NOVARTIS' Entresto** (sacubitril + valsartan) was granted expanded approval to include treatment of heart failure with *preserved* ejection fraction (HFpEF).

✓ **Positive trial news:**

- **AMGEN's Corlanor and Servier's Procoralan/Corlentor** (ivabradine) – in POTS.
- **ASTELLAS' fezolinetant** – in menopausal hot flashes.
- **ASTRAZENECA and MERCK MSD's Lynparza** (olaparib) – in early breast cancer.
- **CHEMOCENTRYX's avacopan** (CCX-168) – in vasculitis.
- **IMMUNIC THERAPEUTICS' vidofludimus calcium** (IMU-838) – in primary sclerosing cholangitis.
- **JOHNSON & JOHNSON's Ad26.ZIKV.001** (JNJ-66684657) – a Zika vaccine.
- **KYOWA KIRIN's KHK-4083** – in atopic dermatitis.
- **LILLY's tirzepatide** – in Type 2 diabetes.
- **LYNXDX's MyProstateScore** – in prostate cancer detection.
- **NOVARTIS' Kymriah** (tisagenlecleucel, tisa-cel) – in durability in NHL.
- **ONCOPEPTIDES' melflufen** (melphalan flufenamide) – in multiple myeloma.
- **ROIVANT SCIENCES/DERMAVANT SCIENCES' tapinarof** – in atopic dermatitis and psoriasis.
- **SUMITOVANT BIOPHARMA/MYOVANT SCIENCES' Orgovyx** (relugolix) – in uterine fibroids.

SHORT TAKES

■ **ASTELLAS' fezolinetant**, an NK3R inhibitor, met all four primary endpoints in two Phase III trials – SKYLIGHT-1 and SKYLIGHT-2 – significantly reducing the frequency and severity of moderate-to-severe vasomotor symptoms (hot flashes) associated with menopause vs. placebo at Week 12. And the safety profile looked good.

- **ASTRAZENECA and MERCK MSD's Lynparza (olaparib)** – The independent data monitoring committee for the Phase III OlympiA trial said an interim analysis found this PARP inhibitor met the primary endpoint, showing superiority to placebo on disease-free survival in germline BRCA-mutated HER2-negative high-risk early breast cancer.

- **BECTON DICKINSON/C.R. BARD's Lutonix 014** – The FDA's Circulatory System Devices Advisory Committee rejected use of this drug-coated balloon (DCB) for treating below-the-knee peripheral artery disease (PAD), voting 15-2 (with one abstention) that it is not effective and 14-3 (with one abstention) that the benefits don't outweigh the risks. But the panel generally agreed the device is safe (vote 15 Yes, 2 No, 1 abstention).

- **BRAINCOOL's Cooral**, a medical cooling device for preventing oral mucositis after chemotherapy, was granted breakthrough device status by the FDA.

- **BRISTOL-MYERS SQUIBB and SANOFI's Plavix (clopidogrel)** – A judge in Hawaii ordered the companies to pay a total of $834 million to the state for failing to warn that the blood thinner has poor effects in people who can't metabolize it (e.g., East Asians and Pacific Islanders) or to promote a genetic test to identify poor/non-responders.

- **C2DX** bought **Stryker's T/Pump** product line which provides localized temperature therapy for pain relief and patient comfort.

- **CELLECTIS THERAPEUTICS** is collaborating with **Cytovia Therapeutics** on development of immunotherapies based on gene-edited allogeneic CAR T cells, combining Cellectis' TALEN technology with Cytovia's induced pluripotent stem cell platform.

- **CHARLES RIVER LABORATORIES** is buying **Cognate BioServices**, a cell and gene therapy contract development and manufacturing organization (CDMO).

- **CHEMOCENTRYX's avacopan (CCX-168)** – This C5a receptor inhibitor showed non-inferiority – but not superiority – to prednisone in achieving remission (one primary endpoint) in the 331-patient Phase III ADVOCATE trial in ANCA-associated vasculitis. On the co-primary endpoint of sustained remission at Week 52, avacopan was both non-inferior and superior to prednisone. The results were published in the ***New England Journal of Medicine***.

- **CORTEXYME's atuzaginstat (COR-388)** – The FDA imposed a clinical hold on the open-label extension phase of a Phase II/III trial of this small molecule novel virulence factor inhibitor (that targets *Porphyromonas gingivalis*) in Alzheimer's disease after an FDA review of the data identified hepatic adverse events.

- **DENALI THERAPEUTICS' HAE-4** – A mouse study, published in ***Science Translational Medicine***, suggests this ApoE4-targeting antibody has potential in Alzheimer's disease, reducing beta-amyloid accumulation in brain tissues and blood vessels without causing brain bleeds.

- **EVOLUS' Jeaveau (prabotulinumtoxinA-xvfs)** – AbbVie/Allergan and Medytox ended their legal challenge to this Botox (onabotulinumtoxinA) competitor, which has FDA approval to treat glabellar lines, in return for milestone and royalty payments.

- **Fabry disease** – A study, published in the ***Journal of Rare Diseases Research & Treatment***, found the cysts found in renal ultrasounds may be a sign of Fabry disease and could expedite diagnosis of the disease, allowing earlier treatment.

- **GLAXOSMITHKLINE** expanded its collaboration with **Vir Biotechnology** to include research and development on new therapies for influenza and respiratory viruses.

- **IMMUNIC THERAPEUTICS' vidofludimus calcium (IMU-838)** met the primary endpoint in an investigator-initiated, single-arm, open-label Phase II proof-of-concept trial of this oral DHODH inhibitor in primary sclerosing cholangitis, significantly decreasing serum alkaline phosphatase (ALP) at Week 24. However, the trial enrolled only 60% of the planned patients due to Covid-19, and only 11 patients completed the full course of treatment.

- **IMMUNOCORE's tebentafusp**, a bispecific – soluble gp100-targeting T cell receptor fused to an anti-CD3 – was granted breakthrough therapy designation by the FDA as a treatment for metastatic uveal (ocular) melanoma.

- **INCYTE's topical ruxolitinib** – The FDA granted priority review to this reformulation of Jakafi, a JAK inhibitor, for use in treating atopic dermatitis. The PDUFA date is June 21, 2021.

- **JOHNSON & JOHNSON's Ad26.ZIKV.001 (JNJ-66684657)** – A Phase I study, published in ***Annals of Internal Medicine***, found that this Zika vaccine produced immunity for up to a year in ≥80% of recipients.

- **KYOWA KIRIN's KHK-4083**, an anti-OX40, met the primary endpoint in a 274-patient Phase II trial in moderate-to-severe atopic dermatitis, showing superiority to placebo on EASI at Week 16.

- **LYNXDX's MyProstateScore** – A study, published in the ***Journal of Urology***, found that this urine-based test can

detect prostate cancer-specific genes and is an alternative to biopsies.

- **NOVADISCOVERY's JINKO** – **Sanofi** invested in this clinical trial simulation platform for predicting drug efficacy and helping with optimization of clinical trials.

- **ONCOPEPTIDES' melflufen (melphalan flufenamide)** – The results of the single-arm Phase II HORIZON trial, published in the ***Journal of Clinical Oncology***, showed this peptide-drug conjugate, in combination with dexamethasone, produced significant response in very refractory multiple myeloma.

- **PRECISION BIOSCIENCES' ARCUS** – Three-year follow-up data, published in the journal ***Molecular Therapy***, showed that gene editing with this genome-editing platform produced long-term, stable reduction of LDL in non-human primates.

- **QUOTIENT SCIENCES** bought **Arcinova**, a U.K. multi-service CDMO.

- **ROIVANT SCIENCES/DERMAVANT SCIENCES' tapinarof** – A preplanned interim analysis of the PSOARING 3 trial of this once-daily steroid-free cream showed good safety in atopic dermatitis and plaque psoriasis, with efficacy comparable to the first two Phase III PSOARING trials.

- **SENSEN BIO's vicineum** – The FDA accepted a biologics license application (BLA) and granted priority review to this recombinant fusion protein for treating high-risk, BCG-unresponsive non-muscle invasive bladder cancer (NMIBC). The PDUFA date is August 18, 2021. No advisory committee review is expected.

- **SUMITOVANT BIOPHARMA/MYOVANT SCIENCES' Orgovyx (relugolix)** – The results of the Phase III LIBERTY-1 and LIBERTY-2 trials, published in the ***New England Journal of Medicine***, showed this oral gonadotropin-releasing hormone (GnRH) receptor antagonist not only met the primary endpoint but also met six of the seven secondary endpoints in treating uterine fibroids.

Very early research news

- **Regenerative medicine** – A study by Australian researchers reported in the journal ***Nature*** on their discovery of a protein (nicotinamide phosphoribosyltransferase, NAMPT) that stimulates the growth of muscle stem cells and healing in zebrafish and mice, opening the possibility of using regenerative medicine to treat muscle injuries.

NEWS IN BRIEF

AMGEN

- **Corlanor and Servier's Procoralan/Corlentor (ivabradine).** A study, published in the ***Journal of the American College of Cardiology***, found that this selective I_f inhibitor significantly improved patients with hyperadrenergic postural orthostatic tachycardia syndrome (POTS), including heart rate, quality of life, and plasma norepinephrine levels.

- **Sotorasib**, a $KRAS^{G12C}$ inhibitor, was granted priority review by the FDA as an adjuvant treatment for patients with KRAS G12C-mutated locally advanced/metastatic non-small cell lung cancer (NSCLC) after ≥1 prior systemic therapy. The PDUFA date is August 16, 2021.

BEIGENE

- Is collaborating with **Boston Immune Technologies and Therapeutics** (BITT) on development and commercialization in Asia (excluding Japan), Australia, and New Zealand of tumor necrosis factor receptor 2 (TNFR2) antagonists. The lead candidate is BITT's BITR-2101, and it will be studied in combination with BeiGene's tislelizumab, a PD-1 inhibitor.

- **Brukinsa (zanabrutinib).** The FDA accepted for review a supplemental new drug application (sNDA) of this BTK inhibitor to treat Waldenström's macroglobulinemia. The PDUFA date is October 18, 2021.

BIOGEN and EISAI's aducanumab

- The Institute for Clinical and Economic Review (ICER) announced today it has extended its timeline for assessing the comparative clinical effectiveness and value of aducanumab for the treatment of Alzheimer's disease. The new dates are:
  - May 5, 2021 – draft evidence report
  - May 5 - June 2 – public comments accepted
  - June 30 – revised evidence report due
  - July 15 – public meeting and evidence presentation
  - August 5 – final report and policy recommendations

- Acting FDA Commissioner Janet Woodcock, MD, rejected Public Citizen's request for a firewall between regulators and drug companies to prevent what Public Citizen called "inappropriate close collaboration" that it believed had occurred over aducanumab. Dr. Woodcock said the proposed firewall would "reduce the efficiency" and "cause delays in drug development," adding that a firewall is not necessary to ensure the integrity of FDA's decision-making.

BLUEBIRD BIO

- **LentiGlobin (bb1111).** Two trials of this gene therapy for sickle cell disease were halted while two cancer cases are investigated: one patient who developed acute myeloid leukemia (AML) and another who developed myelodysplastic syndrome (MDS).
- **Zynteglo (betibeglogene autotemcel, bb305).** Sales of this EU/U.K.-approved gene therapy for beta thalassemia were suspended until the LentiGlobin cancer cases are investigated.

LILLY

- **Tirzepatide.** This once-weekly GIP/GLP-1 agonist significantly reduced both HbA_{1c} and weight in two Phase III trials in Type 2 diabetes (SURPASS-3 and SURPASS-5), meeting both the primary and all key secondary endpoints in each trial. In SURPASS-3, tirzepatide reduced HbA_{1c} by 2.37% and body weight by 13.9% (12.9 kg). In SURPASS-5, HbA_{1c} dropped 2.59% and weight by 11.6% (10.9 kg).
- Bought the exclusive worldwide rights to **Rigel Pharmaceuticals**' RIPK1 inhibitors, including R-552, in all indications, including autoimmune and inflammatory disorders and neurodegeneration.

Multiple myeloma (MM)

The Institute for Clinical and Economic Review (ICER) released its *draft* report on three anti-BCMA therapies to treat relapsed/refractory multiple myeloma:

- ✓ **Bristol-Myers Squibb and bluebird bio's idecabtagene vicleucel** (ide-cel)
- ✓ **GlaxoSmithKline's Blenrep** (belantamab mafodotin-blmf)
- ✓ **Johnson & Johnson/Janssen and Legend Biotech's ciltacabtagene autoleucel** (cilta-cel).

Among the ICER findings were:

- The overall response rate in triple-class refractory MM (TCRMM) is 63% with ide-cel, 75% with cilta-cel, and 32% with belantamab.
- **The bottom line:** ICER concluded that ide-cel and cilta-cel improve outcomes in TCRMM, with higher rates of response and longer survival than with current therapies. Belantamab appears equivalent, or slightly superior, to current treatments for quad- and penta-refractory MM patients, but there is a "small possibility" of net harm from this treatment.

The report is open for public comments until March 11, 2021, and there will be a public meeting on the report on April 16, 2021.

NOVARTIS

- Got a grant from the Gates Foundation to support the discovery and development of a single-administration, *in vivo* gene therapy to cure sickle cell disease.
- **Kymriah (tisagenlecleucel, tisa-cel).** Five-year data from a small study of this CAR T therapy in non-Hodgkin's lymphoma showed impressive durability, with 46% having a complete remission and 31% having progression-free survival.

REGULATORY NEWS

Regulatory tidbits

- **340B discounts –** A federal judge dismissed a case brought by hospitals that use contract pharmacies that accused the Department of Health and Human Services (HHS) of failing to force drug companies to pay them 340B discounts. The judge said the case is premature because HHS did not release any final action about the discounts.

FDA approvals/clearances

- ACUITIVE TECHNOLOGIES' Citregen, a knotless suture anchor, was granted 510(k) clearance for use in attachment of tissue to the bone during orthopedic surgeries.
- ADDITIVE ORTHOPAEDICS' Patient Specific Talus Spacer, a 3D-printed implant, was granted humanitarian use device approval for replacing the talus (an ankle joint bone) in patients with avascular necrosis of the ankle joint.
- AXONICS MODULATION TECHNOLOGIES' INS, a third-generation implantable neurostimulator, was granted premarket approval for use in treating urinary and bowel dysfunction.
- ELECTROCORE's gammaCore, a non-invasive vagus nerve stimulator, was granted expanded 510(k) clearance for use in treating migraines in adolescents age 12-17.
- FX SOLUTIONS' Easytech, a stemless shoulder replacement, was granted 510(k) clearance.
- JOHNSON & JOHNSON/JANSSEN's Simponi Aria (golimumab for infusion), a TNF inhibitor, was granted a label expansion to include language that it can improve fatigue (on FACIT-F) in adults with active psoriatic arthritis or moderately-to-severely active rheumatoid arthritis. This is the first TNF inhibitor to get this claim.

- **MEDTRONIC's InterStim II and InterStim Micro**, sacral neuromodulation systems, were granted expanded MRI labeling, allowing for shorter wait times between scans and a wider range of MRI scan parameters.
- **NOVARTIS' Entresto (sacubitril + valsartan)** was granted expanded approval that opens the door for use in treating some patients with heart failure with *preserved* ejection fraction (HFpEF) as well as the original approval in heart failure with *reduced* ejection fraction (HFrEF).

FDA recalls/warnings

- **ACELRX PHARMACEUTICALS' Dsuvia (sufentanil sublingual tablet)** – The FDA issued a warning letter to the company for false and misleading promotion of this opioid analgesic.
- **BOSTON SCIENTIFIC's Emblem S-ICD**, a subcutaneous implantable cardioverter defibrillator, was recalled (Class I) due to the risk of a short-circuit due to moisture getting inside.
- **Covid-19** – The FDA sent a warning letter for selling unapproved products with fraudulent Covid-19 claims to: **Evolved Ayurvedic Discoveries** and to **Dr. Paul's Lab**.
- **MEDTRONIC's Valiant Navion**, a thoracic stent graft system for use in treating large blood vessels at risk of aneurysm rupture, was recalled after reports of three stent fractures and the death of a patient in an international trial.
- **Pulse oximeters** – The FDA issued a safety communication to inform patients and healthcare providers about the limitations of these devices – and the risk of inaccuracy in some cases.
- **SHILPA MEDICARE** – The FDA imposed a ban on the import of most products from this company's plant in India – allowing exceptions only for injectable azacitidine for myelodysplastic syndrome (MDS) and cyclophosphamide capsules and erlotinib tablets for cancer patients.

European Regulatory News

- **DYNAVAX TECHNOLOGIES' Heplisav B**, a hepatitis B vaccine, was approved by the European Commission.
- **HORIBA MEDICAL's Microsemi CRP**, a hematology analyzer, was granted a CE Mark.
- **OPSENS' OptoWire III**, a next-generation fiber optic pressure guidewire to treat and diagnose coronary artery disease, was granted a CE Mark.
- **SIEMENS HEALTHINEERS**' purchase of **Varian Medical Systems** received conditional approval from the European Commission.

Regulatory news from other countries

- ***Canada.*** **SOUNDBITE MEDICAL SOLUTIONS' SoundBite Crossing System Peripheral** (0.014-inch active-wire version) was approved by Health Canada to treat peripheral artery disease (PAD).
- ***China.*** **PROVENTION BIO's PRV-3279** – The Greater China rights to this bispecific antibody (DART) were outlicensed to Huadong Medicine/Hangzhou Zhongmei Huadong Pharmaceutical.
- ***Japan.*** **PFIZER and BIONTECH's BNT-162b2** – This Covid-19 vaccine was approved for use in Japan.

2021 FDA Advisory Committees and Other Regulatory Dates of Interest *RED are new since last week*		
Date	**Topic**	**Committee/Event**
Missed PDUFA dates with no new date		
November 25	**Revance Therapeutics' daxibotulinumtoxinA** for glabellar lines	PDUFA date *Delayed by FDA No new date announced*
December tba	**Pfizer and Lilly's tanezumab** to treat moderate-to-severe osteoarthritis pain	PDUFA date missed *No decision announced yet*
January 27	**Protalix BioTherapeutics and Chiesi's pegunigalsidase alfa** (PRX-102) for Fabry disease	PDUFA date *No decision announced yet*
January 28	**Amgen's Nplate** (romiplostim) – expanded approval to treat hematopoietic syndrome of acute radiation syndrome	PDUFA date *No decision announced yet*
February 2	**Mallinckrodt's StrataGraft**, a regenerative skin tissue therapy	PDUFA date *Decision delayed due to Covid-19*
2021 Events		
February 24	Latest in a series on **Covid-19 test** development and validation	FDA virtual town hall
February 26	**Johnson & Johnson's Ad26.COV2.S** (JNJ-78436735), a one-dose, room temperature-stable Covid-19 vaccine	FDA's Vaccines and Related Biological Products Advisory Committee virtual meeting
February 28	**Regeneron Pharmaceuticals and Sanofi's Libtayo** (cemiplimab) for locally-advanced/metastatic NSCLC	PDUFA date
February 28	**Athenex's oral paclitaxel** (with encequidar) for metastatic breast cancer	PDUFA date
March 3-4	Quality of **active pharmaceutical ingredient** manufacturing	FDA webinar
March 5	FDA **Rare Disease** Day	FDA virtual public meeting
March 8	Patient-focused drug development for **vitiligo**	FDA virtual public meeting
March 20	**FibroGen and AstraZeneca's roxadustat** for anemia of chronic kidney disease	PDUFA date *Extended by FDA from December 20, 2020*
March 23	Benefits and risks of **dermal fillers**	FDA's General and Plastic Surgery Devices Advisory Committee virtual meeting
March 24-25	**Pfizer and Lilly's tanezumab** to treat moderate-to-severe osteoarthritis pain	FDA's Arthritis Advisory Committee, meeting jointly with the Drug Safety and Risk Management Advisory Committee ***This virtual meeting is unusual in that it will last 1.5 days***
March 27	**Bristol-Myers Squibb and bluebird bio's idecabtagene vicleucel** (ide-cel, bb-2121), a CAR T therapy for relapsed/refractory multiple myeloma	PDUFA date
March 29-30	The risk of **nitrosamine contamination** in drugs	FDA virtual workshop
March 30-31	**Oncology** drug development	FDA virtual workshop
April 14-16	**Biostatistics forum** to discuss statistical issues related to drugs and biologics	FDA virtual joint meeting with the Drug Information Agency (DIA)
April 15	**CellTrans' donislecel** for Type 1 diabetes	FDA's Cellular, Tissue, and Gene Therapies Advisory Committee virtual meeting
April 28-29	**Generic Drugs Forum**	FDA virtual conference
May tba	**Roche's Esbriet** (pirfenidone) – expanded approval to treat unclassifiable interstitial lung disease	PDUFA date
May 14	**Apellis Pharmaceuticals' pegcetacoplan** for treating PNH	PDUFA date
May 18	**Sanofi's avalglucosidase alfa** for Pompe disease	PDUFA date
May 20	**Bristol-Myers Squibb's Opdivo** (nivolumab) – expanded approval as adjuvant therapy for resected esophageal or gastroesophagel junction cancer	PDUFA date
May 21	**ADC Therapeutics' loncastuximab tesirine** for relapsed/refractory DLBCL	PDUFA date
May 25	**Bristol-Myers Squibb's Opdivo** (nivolumab) – expanded approval for use in combination with chemotherapy as a first-line treatment for gastric cancer	PDUFA date
May 30	**Kadmon's belumosudil** for chronic graft-versus-host disease after hematopoietic stem cell transplant	PDUFA date
May 30	**Bristol-Myers Squibb's Zeposia** (ozanimod) for ulcerative colitis	PDUFA date
June 7	**Biogen and Eisai's aducanumab** for Alzheimer's disease	PDUFA date Extended 3 months by FDA from March 7
June 21	**Incyte's topical ruxolitinib** to treat atopic dermatitis	PDUFA date
June 30	**Lupin Pharmaceuticals' Solosec** (secnidazole) – expanded approval to treat trichomoniasis	PDUFA date
July tba	**Bayer's finerenone** (BAY-94-8862) for Type 2 diabetes patients with CKD	PDUFA date
July 2	**Provention Bio's teplizumab** (PRV-031) for preventing/delaying clinical Type 1 diabetes	PDUFA date
July 18	**Merck MSD's V114**, a 15-valent pneumococcal conjugate vaccine	PDUFA date

2021 FDA Advisory Committees and Other Regulatory Dates of Interest *RED are new since last week*		
Date	**Topic**	**Committee/Event**
July 20	**Albireo Pharma's odevixibat** (A-4250) to treat pruritus in patients with progressive familial intrahepatic cholestasis (PFIC)	PDUFA date
July 25	**Iterum Therapeutics' sulopenem etzadroxil/probenecid** for uncomplicated urinary tract infections	PDUFA date
August 16	**Amgen's sotorasib** for KRAS G12C-mutated NSCLC	PDUFA date
August 18	**Sensen Bio's vicineum** for non-muscle invasive bladder cancer	PDUFA date
October tba	**Pfizer and OPKO Health's somatrogon** for growth hormone deficiency	PDUFA date
October 18	**BeiGene's Brukinsa** (zanabrutinib) – expanded approval to treat Waldenström's macroglobulinemia	PDUFA date