TRENDS-in-MEDICINE

November 17, 2019

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…

NOTE: Subscribe to ***Trends-in-Medicine*** for coverage of the **American Heart Association** (AHA) meeting in Philadelphia. *Remember, most items have a link.*

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

- ✓ AMARIN's Vascepa (icosapent ethyl) – An FDA advisory committee voted unanimously (16-0) to recommend expanded approval of this fish oil to reduce cardiovascular risk in high-risk patients.
- ✓ BOEHRINGER INGELHEIM and LILLY's Jardiance (empagliflozin) – An FDA advisory committee recommend ***against*** expanding approval of this SGLT2 inhibitor for use with insulin in Type 1 diabetes.
- ✓ INDIVIOR's Sublocade (buprenorphine extended-release injection) – The FDA plans to revoke the orphan drug status of this opioid use disorder drug.
- ✓ LIPOCINE's Tlando (LPCN-1021), an oral testosterone replacement drug, was rejected by the FDA for the third time.
- ✓ **Positive Phase III trials – *eight* of them:**
  - ASTRAZENECA's anifrolumab in moderate-to-severe systemic lupus erythematosus (SLE).
  - GLAXOSMITHKLINE's Nucala (mepolizumab) in hypereosinophilic syndrome (HES).
  - HUA MEDICINE's dorzagliatin in a Chinese trial in Type 2 diabetes.
  - KADMON's KD-025 in third-line chronic graft-versus-host disease.
  - LILLY's Taltz (ixekizumab) in non-radiographic axial spondyloarthritis (nr-axSpA).
  - NOVARTIS' Cosentyx (secukinumab) in nr-axSpA.
  - RHYTHM PHARMACEUTICALS' setmelanotide in two trials in obesity.
  - UCB's bimekizumab in moderate-to-severe psoriasis.
- ✓ **Negative Phase III trials (3):**
  - ASLAN PHARMACEUTICALS' varlitinib in second-line biliary tract cancer.
  - KIADIS PHARMA's ATIR-101 in patients undergoing stem cell transplant.
  - RESTORBIO's RTB-101 on preventing clinically symptomatic respiratory illness in elderly patients.

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SHORT TAKES

- ABBVIE's Imbruvica (ibrutinib) – A supplemental new drug application (sNDA) was submitted to the FDA for the use of this BTK inhibitor in combination with Roche's Rituxan (rituximab) as a first-line treatment for patients age ≤70 with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma.

- ABIOMED's Impella RP – A post approval study found that a protocol for appropriate use of this percutaneous ventricular assist device in right-sided heart failure improved 2-year survival to 72% in less sick patients (the patients studied for the FDA approval) vs. 14% in "salvage" support cases. This isn't to say that the device shouldn't be used for salvage patients, but that the same results can't be expected in those patients.

- AGENUS' zalifrelimab (AGEN-1884), an anti-CTLA4 antibody, was exclusively licensed to **UroGen Pharma** for intravesical delivery in combination with UGN-201 (mitomycin gel), UroGen's TLR-7/8 agonist for high-grade non-muscle invasive bladder cancer (HG NMIBC).

- AGILE THERAPEUTICS' Twirla (AG200-15, 120 µg levonorgestrel + 30 µg ethinyl estradiol) – The FDA extended by three months its review of this contraceptive patch because the company submitted additional data addressing issues raised at the positive advisory committee meeting that the FDA considered a major amendment. The new PDUFA date is February 16, 2020.

- ALLERGAN is collaborating with **Exicure** on development of hair loss drugs, using Exicure's SNA technology.

- AMARIN's Vascepa (icosapen ethyl) – The FDA's Endocrinologic and Metabolic Drugs Advisory Committee voted unanimously (16-0) to recommend expanded approval of this fish oil to reduce cardiovascular risk in high-risk patients.

- ASLAN PHARMACEUTICALS' varlitinib missed both co-primary endpoints in the pivotal, global, 127-patient Phase III Treetop trial in second-line biliary tract cancer, failing to beat control on either progression-free survival (2.83 months vs. 2.79 months) or overall response rate (9.4% vs. 4.8%).

- ASTRAZENECA's anifrolumab, an interferon α/β receptor inhibitor, met the primary endpoint in the 365-patient Phase III TULIP-2 trial in moderate-to-severe systemic lupus erythematosus (SLE), significantly (and clinically meaningfully) decreasing disease activity at Week 52 (47.8% of patients achieving a significant decrease in BICLA) vs. 31.5% of placebo patients.

- BAYER is collaborating with **Dewpoint Therapeutics** on new treatments for heart disease and women's health, combining Dewpoint's biomolecular condensates technology with Bayer's small molecule library.

- BIOGEN and ALKERMES' Vumerity (diroximel fumarate), a newly approved oral therapy for relapsing multiple sclerosis that is similar to Tecfidera (dimethyl fumarate) but may have fewer gastrointestinal side effects, was priced at $88,000/year. That price drew a protest from the National Multiple Sclerosis Society, which noted this is "only $500 lower than the least expensive oral disease-modifying treatment" and "does not show the commitment to affordable access that we had hoped."

- BIOMARIN PHARMACEUTICAL's vosoritide – In a Phase II trial, children with achondroplasia who took the 15 µg/kg/day dose of this analog of C-type Natriuretic Peptide (CNP) for 54 months gained an average of 9.0 cm in additional height, a significant improvement vs. a natural history cohort.

- BOEHRINGER INGELHEIM and LILLY's Jardiance (empagliflozin) – The FDA's Endocrinologic and Metabolic Drugs Advisory Committee voted 14-2 against granting this SGLT2 inhibitor expanded approval for use with insulin in Type 1 diabetes, saying the benefits do not outweigh the risks in that patient population.

- BOSTON SCIENTIFIC's Watchman – The FDA said it will publicly share information on the four patients who died after getting this left atrial appendage (LAA) closure device after it receives the information from the company.

- BRISTOL-MYERS SQUIBB's Opdivo (nivolumab) + Yervoy (ipilimumab) – The FDA accepted for priority review a supplemental biologics license application (sBLA) for expanded use of this immunotherapy combination in advanced hepatocellular carcinoma (HCC) previously treated with Bayer's Nexavar (sorafenib), and the FDA granted the combination breakthrough therapy designation. The PDUFA date is March 10, 2020.

- DARÉ BIOSCIENCE is buying **Microchips Biotech**, which has innovative drug delivery technology.

- DURECT's DUR-928 – In a Phase IIa trial, presented at the American Association for the Study of Liver Diseases (AASLD) meeting in Boston, ***all*** of the alcoholic hepatitis patients treated with this endogenous sulfated oxysterol survived at Day 28, with no drug-related serious adverse events. DUR-928 patients also had a significant reduction in bilirubin at Days 7 and 28, and in MELD at Day 28.

- ESPERION THERAPEUTICS' bempedoic acid – The results of the 779-patient 52-week, Phase III CLEAR Wisdom trial of this once-daily oral cholesterol-lowering therapy (an add-on to a statin) were published in the ***Journal of the American Medical Association*** (JAMA), showing significant reduction in LDL at Week 12, with a durable effect out to Week 52.

- EXPESICOR's EXP-1801 – The company got a one-year $408,000 grant from the National Institutes of Health to further develop this PET agent, which can enable pain visualization and measurement.

- FORTY SEVEN is collaborating with **bluebird bio** on an all-antibody conditioning regimen for use in combination with autologous lentiviral vector hematopoietic stem cell gene therapy, combining Forty Seven's FSI-174 (an anti-cKIT antibody) and magrolimab (an anti-CD47) with bluebird's *ex vivo* lentiviral vector hematopoietic stem cell (LVV HSC) gene therapy platform.

- GENFIT's NIS4 – A study, presented at AASLD, showed that this non-invasive, algorithm-driven blood test for non-alcoholic steatohepatitis (NASH) outperformed other non-invasive diagnostics in identifying NASH in Type 2 diabetics, showing statistical superiority to FIB4, NFS, ELF, and Fibrometer.

- GLAXOSMITHKLINE's Nucala (mepolizumab) – In a 108-patient Phase III trial in hypereosinophilic syndrome (HES), this anti-IL-5 (added to standard of care) met the primary endpoint, reducing HES flares by a significant 56% vs. 28% with standard of care alone. Key secondary endpoints were also met.

- HDL THERAPEUTICS' PDS-2 System – The results of the pivotal, open-label HALO-FH trial showed that this acute care therapeutic device, which is used to give patients weekly serial infusions of autologous selectively delipidated pre-beta HDL-enriched plasma to coronary atheroma led to a statistically significant 18% reduction in total atheroma area. The effect was even more pronounced in low-density atheroma.

- HUA MEDICINE's dorzagliatin, a dual-acting glucokinase modulator, met the primary endpoint in a Phase III monotherapy trial in China in Type 2 diabetes, significantly reducing HbA_{1c} vs. placebo at Week 24 (-1.07% HbA_{1c} vs. 0.5% with placebo.

- ILLUMINA proposed offering licenses to **Pacific Biosciences**' intellectual property to **Oxford Nanopore Technologies** or any third party to address concerns from U.K. regulators about its acquisition of PacBio.

- INVITAE is buying **Clear Genetics**, a DNA-counseling chat-bot developer.

- INDIVIOR's Sublocade (buprenorphine extended-release injection) – The FDA said it plans to revoke the orphan drug status of this opioid use disorder drug, explaining that orphan drug status should never have been granted in the first place.

- KADMON's KD-025 met the primary endpoint in an interim analysis of the pivotal ROCKstar trial in third-line chronic graft-versus-host disease, with an overall response rate of 64% with the 200 mg QD dose and 67% with the 200 mg BID.

- KIADIS PHARMA's ATIR-101 – The company terminated a Phase III trial of this T cell immunotherapy vs. cyclophosphamide midstream after a higher than expected dropout rate in the drug arm led to a review that determined the trial was unlikely to succeed. Kiadis plans to concentrate instead on its NK cell immunotherapy programs instead.

- KOPP DEVELOPMENT bought **Mednovus**, which develops MRI accessories, including the FerrAlert Target scanner.

- LENKBAR's Marrow Marxman – The company licensed this device for harvesting inherent stem cells from bone marrow, developed by Robert Marx, DDS, chief of oral and maxillofacial surgery at the University of Miami Miller School of Medicine. Marrow Marxman, an unbreakable, flexible device that remains in the bone marrow to move along the inner cortical surface in bone, where most of the stem cells (e.g., CD34+ and CD105+) can be harvested, will be featured at the World Stem Cell Summit in Miami in January 2020.

- LEXENT BIO's Confera Dx – Lexent is partnering with **Illumina** on development of an *in vitro* diagnostic (IVD) kit for this investigational next-generation sequencing-based cancer diagnostics.

- LILLY's Taltz (ixekizumab) – This anti-IL-15 met the primary endpoint in the 52-week, 303-patient Phase III COAST-X trial in non-radiographic axial spondyloarthritis (nr-axSpA) patients with objective signs of inflammation who were biologic disease-modifying anti-rheumatic drug (bDMARD)-naïve, significantly improving signs and symptoms on the ASAS40 and inflammation by MRI vs. placebo. The study, presented at the American College of Rheumatology (ACR) meeting in Atlanta, also met all key secondary endpoints.

- LIPOCINE's Tlando (LPCN-1021), an oral testosterone replacement drug, was rejected by the FDA as a treatment for male hypogonadism for the ***third*** time. The FDA issued a

complete response letter, citing the drug's failure to meet three secondary endpoints (maximal testosterone concentrations) in the pivotal trial.

- MEDTRONIC's Micra AV – In the 75-patient MARVEL-2 trial, presented at the AHA meeting and published in the ***Journal of the American College of Cardiology: Clinical Electrophysiology***, this leadless pacemaker (with new algorithms) met the primary endpoint, significantly improving synchrony and cardiac function in patients with atrioventricular block.

- MENLO THERAPEUTICS is merging with **Foamix Pharmaceuticals**.

- MERCK MSD bought **Calporta**, which has treatments for neurodegenerative and lysosomal storage disorders in preclinical development, from **COI Pharmaceuticals**.

- MESA LABS bought **Gyro Protein Technologies** which specializes in immunoassays and peptide synthesis.

- MYRIAD GENETICS' Vectra – Data presented at ACR showed that this test can predict the risk of radiographic progression in rheumatoid arthritis (RA) patients within one year. In addition, combining the test with other clinical measures can predict the risk of a cardiovascular event in RA patients. A 973-patient study by University of Alabama Birmingham researchers found that the adjusted Vectra score was a better predictor of radiographic progression at one year than CRP, DAS28-CRP, CDAI, or swollen joint count. As the Vectra score rose, so did the risk of permanent joint damage. Myriad is working on enhancing Vectra to provide patients with an "individual risk" score for radiographic progression in one year.

- REGENXBIO's RGX-314 – The company sued the FDA, contending the Agency violated its own regulations when it failed to provide an explanation for the clinical hold placed on this investigational gene therapy.

- REMEGEN's telitacicept (RC-18) – In the 249-patient Phase IIb APRIL trial in systemic lupus erythematosus (SLE), presented at ACR, this oral recombinant fusion protein met the primary endpoint with significantly more telitacicept patients achieving a >4-point reduction in the SLE Responder Index (SRI4) vs. placebo (75.8% with 240 mg vs. 33.9%). The most common treatment-related adverse events were upper respiratory tract infection and injection site reactions.

- RESTORBIO's RTB-101, a TORC1 inhibitor, failed in the Phase III PROTECTOR-1 trial, doing numerically ***worse*** than placebo on preventing clinically symptomatic respiratory illness among elderly (age ≥65) patients. The company is not giving up. It plans to try the drug in combination with sirolimus (Pfizer's Rapamune) in Parkinson's disease.

- RHYTHM PHARMACEUTICALS' setmelanotide – Preliminary results of two Phase III trials of this selective MC_4 receptor agonist, presented at Obesity Week in Las Vegas, showed it met the primary endpoint in both trials, significantly improving weight loss and lessening hunger in adults, adolescents, and children with obesity caused by pro-opiomelanocortin and leptin receptor deficiencies. In one study, 8 of 10 patients lost ≥10% body weight; in the other study 5 of 11 patients had a similar outcome.

- SANFORD HEALTH and **UnityPoint Health** decided not to merge after all.

- SAREPTA THERAPEUTICS bought the exclusive license to four CNS gene therapies from **Stride Bio** – for Dravet syndrome, Angelman syndrome, Niemann-Pick disorder, and Rett syndrome – with Stride handling preclinical development. Sarepta also got an option to add another four targets in the future.

- SGLT2 inhibitors – A population-based cohort study, presented at ACR, found that Type 2 diabetics who took an SGLT2 inhibitor had a lower prevalence of gout over 177 days of follow-up vs. Type 2 diabetics on a GLP-1 agonist (4.9 events vs. 8.1 events per 1,000 person-years).

- SOLID BIOSCIENCES' SGT-001 – The Phase I/II IGNITE-DMD trial of this gene therapy for Duchenne muscular dystrophy was put on clinical hold by the FDA for the second time after a 7-year-old boy on a high dose developed serious complications (decrease in red blood cell count, acute kidney injury, and a drop in platelets), side effects similar to the patient who was responsible for the first clinical hold (but who was on a lower dose).

- TAKEDA expanded its collaboration with **Finch Therapeutics** on microbiome-based therapeutics to include Crohn's disease.

- TEVA's vincristine – The company reversed itself, saying it will resume making this pediatric cancer drug – which has been in alarmingly short supply.

- THERMO FISHER SCIENTIFIC reportedly wants to buy **Qiagen**.

- UCB's bimekizumab, an IL-17A/F inhibitor, met both primary endpoints in the Phase III BE READY trial in moderate-to-severe psoriasis, with significantly more patients achieving PASI-90 and clear/almost clear skin at Week 16 vs. placebo.

- VISTAGEN THERAPEUTICS' AV-101 – In top-line results from the Phase II ELEVATE trial in major depressive disorder, this NMDA antagonist missed the primary endpoint, failing to improve the MADRS-10 score vs. placebo.

- X4 PHARMACEUTICALS' mavorixafor, a CXCR4 inhibitor, was granted breakthrough therapy designation by the FDA as a treatment for WHIM syndrome.

- Zika – A study by York University researchers, published in the Centers for Disease Control and Prevention (CDC)'s journal ***Emerging Infectious Diseases***, found that a Zika vaccine that offered 60%-90% protection for women of reproductive age in the 18 countries affected by the 2015-2017 Zika outbreak in the Americas would be cost-effective during a Zika outbreak if it were priced <$16 per vaccination. The researchers also estimated that the vaccinations would prevent ~75% of microcephaly cases.

NEWS IN BRIEF

CELGENE

- Is collaborating with **Skyhawk Therapeutics** on autoimmune disorders, oncology, and immuno-oncology, using Skyhawk's SkySTAR technology platform.

- Otezla (apremilast). The results of a 207-patient Phase III trial, published in the ***New England Journal of Medicine***, showed that this oral PDE4 inhibitor was effective in treating oral ulcers in Behçet's syndrome patients, with 53% of apremilast vs. 22% of placebo patients free from oral ulcers at Week 12. There was also improvement in overall disease activity, patient-reported outcomes, and pain.

Gene therapy – the ICER approach

The Institute for Clinical and Economic Review (ICER) is changing how it assesses the value of one-time and short-term curative treatments like gene therapies or CAR T therapies, and will assess them differently from standard drugs taken chronically because of uncertainties over both the costs and benefits over time.

- ICER plans to provide both optimistic and conservative scenarios when analyzing these therapies.
- ICER will include a discussion of how long the treatment would need to last to meet the $150,000 per quality-life adjusted life year (QALY) threshold.
- Patient views about the risks/benefits of alternatives will be taken into account.
- ICER will discuss how undergoing a one-time treatment could affect a patient's ability to get future curative therapies.

MARKER THERAPEUTICS' MultiTAA

- A Phase II trial of this T cell therapy for post-allogeneic hematopoietic stem cell transplant in acute myeloid leukemia (AML) patients was put on clinical hold by the FDA, which wants additional information on quality and technical specifications for two reagents supplied by third-party vendors that are used in the manufacturing process.
- The company scrapped a Phase II trial in ovarian cancer altogether for futility.

MYOKARDIA's mavacamten

The company reported

- Positive top-line data in ***non-obstructive*** hypertrophic cardiomyopathy from the Phase II MAVERICK-HCM trial, with "meaningful reductions" in cardiac stress biomarkers and "clear signals of clinical benefit" in a subgroup of patients with elevated cardiac filling pressures and in a pre-specified group of higher-risk patients.
- Positive results from 12 patients with 48-week data in the open-label PIONEER-OLE study, being presented at AHA, in **obstructive** hypertrophic cardiomyopathy, showing continued safety and durability of effect.

NOVARTIS

- Bimagrumab. In preliminary findings from a 75-patient Phase II trial, presented at Obesity Week, this anti-ActR-IIB was safe and effective in reducing weight at 48 weeks in obese patients with Type 2 diabetes, with a 21% reduction in body fat mass and a 6.5% decrease in body weight vs. 0.5% and 0.8% decreases for placebo.

- Cosentyx (secukinumab) met the primary endpoint in the 555-patient Phase III PREVENT trial in non-radiographic axial spondyloarthritis (nr-axSpA), with 42.2% of patients achieving ASAS40 at Week 16. Key secondary endpoints were also met.

- SANDOZ is buying the Japanese generic drugs business of **Aspen Global**.

ROCHE

- Gazyva (obinutuzumab). The results of the 125-patient Phase II NOBILITY trial in proliferative lupus nephritis, presented at both the American Society of Nephrology's Kidney

Week in Washington DC and the ACR meeting, showed that this anti-CD20, in combination with standard of care, more than doubled the percent of patients achieving complete renal response vs. standard of care alone (40% vs. 18%) at Week 76. Gazyva also met the key secondary efficacy endpoints.

- Kadcyla (ado-trastuzumab emtansine, T-DM1). A study, presented at the Advanced Breast Cancer Fifth International Consensus Conference (ABC5) in Lisbon, Portugal, and published in ***Clinical Breast Cancer***, found that patients with HER2+ advanced breast cancer who progressed on Perjeta (pertuzumab), responded to this agent. Overall survival after 1 year of Kadcyla was 82%. An expert said, "These results suggest that for 30%-40% of patients, T-DM1 can make an important difference. The result that 82% of patients were alive after one year is impressive and proves once again the importance of continuing to treat these patients with anti-HER2 therapies."
- Is buying Promedior, which will give it PRM-151, an investigational treatment for idiopathic pulmonary fibrosis with breakthrough therapy designation from the FDA.
- Risdiplam (RG-7916), an SMN2 modulator, met the primary endpoint in the pivotal 180-patient Part 2 of the SUNFISH trial in Type 2/3 spinal muscular atrophy (SMA), significantly improving the MFM-32 scale at Year 1 vs. placebo.

Vaping update

- By the CDC's latest count, there have now been 2,172 confirmed and probable EVALI (e-cigarette and vaping-associated lung injury) cases, with 42 confirmed deaths.
- Data in the CDC's ***Morbidity and Mortality Weekly Report***, cigarette smoking by U.S. adults reached an all-time low of 13.7% in 2018, with e-cigarettes 3.2%.

REGULATORY NEWS

Regulatory tidbits

- Antibiotics. An updated CDC report noted that antibiotic-resistant bacteria and fungi cause >2.8 million infections and >35,000 deaths in the U.S. each year – on average someone in the U.S. gets an antibiotic-resistant infection every 11 seconds, and someone dies every 15 minutes. This is nearly double the number of deaths from antibiotic-resistant infections in 2013.
- Device exports. The FDA issued final guidance explaining the reasons under which it might deny an export certificate to foreign government requests for medical devices and how to seek a review when that happens.
- Drug prices
  - HHS Secretary Alex Azar said President Trump wants changes to his administration's proposal for an International Pricing Index so that U.S. drug prices would be even lower than those other countries. Under the current proposal, the U.S. would pay less than it currently pays but more than the average from other developed countries, but the President wants the U.S. to get "the best deal" among developed countries.
  - Democratic presidential hopefuls Sen. Cory Booker (D-NJ) and Sen. Bernie Sanders (I-VT) proposed establishment of a Bureau of Prescription Drug Affordability and Access that would have the authority to control list prices and dismantle patent protections for drug companies that don't cooperate on pricing.
- Insulin. The World Health Organization (WHO) created a pilot prequalification program designed to increase access to insulin for Type 2 diabetics around the world. Products to be considered for the program must have regulatory approval.
- Sterilization. The FDA's General Hospital and Personal Use Devices Advisory Committee held a 2-day hearing on ethylene oxide (EtO) sterilization of medical devices, including discussion of recommendations for reducing the risk from reprocessed duodenoscopes, and the panel warned that closing more EtO facilities without a backup plan in place for alternative medical device sterilization could create "a major medical logistical failure." One panelist suggested the FDA should ask HHS Secretary Azar to declare a public health emergency that would take precedence over state legislation causing sterilization plant closures.

FDA approvals/clearances

- AXONICS MODULATION TECHNOLOGIES' r-SNM, a sacral neurmodulation device for treating overactive bladder and urinary retention, was cleared for use.
- BEIGENE's Brukinsa (zanubrutinib), a BTK inhibitor from China, was granted accelerated approval as a second-line treatment for mantle cell lymphoma.
- CELGENE and ACCELERON's Reblozyl (luspatercept-aamt), erythroid maturation agent, was approved to reduce the frenzy of blood transfusions in adults with beta-thalassemia. The FDA warned against use by pregnant women and advised that patients should be monitored for hypertension and blood clots.

- CLARIPI's ClariCT.AI, an artificial intelligence-based CT algorithm, which reduces noise and enhances image clarity in low- and ultralow-dose CT scans using convolutional neural network technology, was cleared for use.
- CONFORMIS' Conformis Hip System, its next-general 3D-designed hip replacement system, was cleared for use.
- COOPER COMPANIES/COOPERVISION's MiSight, a contact lens for slowing progression of myopia (nearsightedness) in children age 8-12 at start of therapy, was cleared for use.
- HEARTVISTA's One Click, an artificial intelligence-assisted autonomous MRI acquisition software for cardiac ischemia exams, was cleared for use.
- HOLOGIC's 3DQuorum, a mammogram imaging technology that can reduce the number of images by 66% and cut interpretation time, was cleared for use.
- HOYA/PENTAX MEDICAL's Pentax Medical Video ED34-i10T2, a duodenoscope with a sterile disposable elevator component, was cleared for use.
- IMPULSE DYNAMICS' Optimizer Smart System, an implantable 2-lead system for delivering cardiac contractility modulation (CCM) therapy to heart failure patients, was granted premarket approval (PMA).
- NOVARTIS' Adakveo (crizanlizumab-tmca) was approved to reduce the frequency of vaso-occlusive crises (VOCs) in patients age ≥16 with sickle cell disease.
- REFLEXION HEALTH's VERA (Virtual Exercise Rehabilitation Assistant) – A new feature for this physical therapy platform – that enables it to produce form-triggered audio and visual best practice reminders – was granted 510(k) clearance.
- SHIONOGI's Fetroja (cefiderocol) was approved to treat complicated urinary tract infections (cUTIs) in adults with limited/no alternative treatment options.
- ZYDUS CADILA got tentative approval from the FDA to market a generic version of **Celgene's Otezla** (apremilast, soon to be an Amgen drug), a treatment for psoriasis, psoriatic arthritis, and oral ulcers in Behçet's disease.

FDA recalls/warnings

- CARDINAL HEALTH's Genius 2 and Genius 3 – An urgent field safety notice was issued, warning that these tympanic thermometers could be inaccurate because of a potential calibration issue.
- GREENBRIER INTERNATIONAL/DOLLAR TREE – The FDA notified the company that Dollar Tree was selling over-the-counter (OTC) drugs from Chinese contract manufacturers that had received Agency warning letters, and the stores still had recalled products on their shelves. Even worse, this was not a one-time occurrence; apparently it has been going on since 2016.
- EDWARDS LIFESCIENCES' Pascal – All lots of the guide sheath for this transcatheter aortic valve replacement (TAVR) were recalled due to a manufacturing issue that may have damaged the inner line. The company issued an urgent field safety notice that the issue could result in embolization of a segment of the inner line material, but there are no reports of patient injury.
- MEDTRONIC's Valleylab FT10 and Valleylab FX8 – The company warned that these electrosurgical generators have a cybersecurity weakness, but a software patch is available for some of the FT10 devices, and the company is working to fix other vulnerabilities.
- PHILIPS' HeartStart XL+ – These automated external defibrillators (AEDs) made before 2017 were recalled because of a risk that the rotary therapy selector switch may fail.
- Ranitidine – This week's voluntary recall due to possible NDMA contamination is Amneal Pharmaceuticals' ranitidine (tablets and syrup).
- SMITH & NEPHEW's Profix 750 Gram Mallets – The company issued a field safety corrective action to update the cleaning and sterilization guide for this mallet because the poly tip could come off during use.
- STRYKER's STAR – The company issued a safety notice about a higher-than-expected risk of polyethylene fracture (13.79%) with this total ankle replacement implant.

European Regulatory News

- *France.* Agence Nationale de Sécurité du Médicament et des Produits de Santé (ANSM) said it will maintain two fast track approval pathways for new and already known drugs even after the European Union's new clinical trial regulation goes into effect next year.
- Gout. The European Medicines Agency (EMA) issued a final guideline for development of new urate-lowering therapies and anti-inflammatory drugs to treat gout.
- ARADIGM PHARMACEUTICALS' Linhaliq (ciprofloxacin) – The company withdrew its marketing application to the EMA.
- ASTRAZENECA's Qtrilmet (dapagliflozin + saxagliptin + metformin, Qternment XR in the U.S.) – This triplet pill – a modified-release combination of an SGLT2 inhibitor, a DPP-4 inhibitor, and metformin – was approved by the European Commission to treat Type 2 diabetes.

- BIOCEPT's CEE-Sure – Both the blood collection tube, which is designed to stop cell clumping and prevent clogging of microfluidics devices, and the CEE-Sure sample collection shipping kit were granted CE Marks.
- BIONEER's AccuPower HCV Quantitative RT-PCR Kit, which quantifies hepatitis C virus viral RNA from blood samples, was granted a CE Mark.
- CELGENE's Revlimid (lenalidomide) – The EMA's Committee for Medicinal Products for Human Use (CHMP) recommended expanded approval to include treatment in combination with Roche's Rituxan (rituximab) in adults with previously treated follicular lymphoma.
- D&A PHARMA's Hopveus (sodium oxybate) – CHMP agreed to re-examine its negative opinion of this treatment for alcohol dependence.
- JAZZ PHARMACEUTICALS' Sunosi (solriamfetol) – CHMP recommended approval to treat excessive daytime sleepiness in patients with narcolepsy.
- JOHNSON & JOHNSON's Opsumit (macitentan) – The company withdrew its expanded use application for this.
- KIADIS PHARMA's Luxceptar (viable T cells) – The company withdrew its marketing application.
- MERCK MSD's Ervebo [Ebola Zaire Vaccine (rVSVΔ-ZEBOV-GP live)] was approved by the European Commission. The World Health Organization (WHO) also prequalified the vaccine, which means it meets WHO's standards for quality, safety, and efficacy.
- NOVARTIS
  - Isturisa (osilodrostat) – CHMP recommended approval to treat Cushing's syndrome.
  - Mayzent (siponimod) – CHMP recommended approval to treat adults with active secondary progressive multiple sclerosis (that is, patients with relapses or imaging features of inflammatory activity).
- PAIGE's Paige Insight, a digital pathology viewer, and **Paige Prostate**, an artificial intelligence-based module, were granted CE Marks for use in prostate cancer diagnosis.
- PFIZER's Xeljanz (tofacitinib) – CHMP concluded that this JAK inhibitor can increase the risk of pulmonary embolism or deep vein thrombosis (DVT) in patients already at high risk, recommending that the drug be used with caution in all patents at high risk of blood clots. CHMP also said the maintenance dose of 10 mg BID should not be used in patients with ulcerative colitis who are at high risk of blood clots unless there is no suitable alternative treatment. And CHMP recommended against using the drug in patients age >65 unless there is no alternative.
- RIGEL PHARMACEUTICALS' Tavlesse (fostamatinib) – CHMP recommended approval to treat primary immune thrombocytopenia.
- ROCHE
  - Kadcyla (trastuzumab emtansine) – CHMP recommended expanded approval for adjuvant treatment of HER2+ early breast cancer with residual invasive disease after neoadjuvant treatment.
  - Polivy (polatuzumab vedotin) – CHMP recommended conditional approval to treat relapsed/refractory diffuse large B-cell lymphoma.
- SANOFI/GENZYME's Lemtrada (alemtuzumab) – CHMP recommended restricting use of this multiple sclerosis drug due to rare but serious side effects, including death, and recommended new measures to identify and manage the serious side effects.

U.K.'s National Institute for Health and Care Excellence (NICE) News

- GW PHARMA – NICE recommended use of two cannabis-based drugs:
  - Epidyolex (cannabidiol) for the treatment of seizures in patients with Lennox Gastaut syndrome (LGS) or Dravet syndrome.
  - Sativex (nabiximols) for spasticity due to multiple sclerosis.

Regulatory news from other countries

- *China.* BEIGENE's tislelizumab (BGB-A317) – The Center for Drug Evaluation completed its technical review of this PD-1 inhibitor and recommended the National Medical Products Administration approval.

2019 FDA Advisory Committees and Other Regulatory Dates of Interest (*items in RED are new since last week*)		
Date	**Topic**	**Committee/Event**
October 14	**Flexion Therapeutics' Zilretta** (FX-006), an extended-release corticosteroid for osteoarthritis knee pain	PDUFA date **Postponed indefinitely**
October 21	**Eton Pharmaceuticals' ET-202** (phenylephrine) for low blood pressure	PDUFA date **No decision announced yet**
October 31	**Adamis Pharmaceuticals' Zimhi** (injectable higher dose naloxone) for opioid overdose	PDUFA date **No decision announced yet**
November 16	**Agile Therapeutics' Twirla** (AG200-15, 120 μg levonorgestrel + 30 μg ethinyl estradiol), a contraceptive patch	PDUFA date **Extended by the FDA to February 16, 2020**
Nov. 18-19	Discussion of **antibacterial drug development** – status and how to enhance enrollment	FDA-IDSA-NIAID and Pew joint workshop
November 20	Nomination of Stephen Hahn, MD, to be FDA Commissioner	Senate HELP Committee
November 21	Strategies to improve **health equity** amidst the opioid crisis	FDA public meeting
November 22	Discussion of **cold stored platelet products** intended for transfusion	FDA's Blood Products Advisory Committee
November 30	**Aquestive Therapeutics' Exservan** (riluzole oral film) for ALS	PDUFA date
December 4	**Celgene and Acceleron Pharma's luspatercept** for beta-thalassemia-associated anemia	PDUFA date
December 4-5	**Prescription drug labeling**	FDA conference for industry
December 5-6	**Repurposing off-patent drugs** – research and regulatory challenges	FDA workshop
December 6	**Patient-focused drug development**	FDA public workshop
Dec. 12-13	**Global bioequivalence harmonization initiative**	FDA workshop in collaboration with American Association of Pharmaceutical Scientists and European Federation for Pharmaceutical Sciences
December 15	**Avadel Pharmaceuticals' AV-001** (once-nightly sodium oxybate), a hospital product	PDUFA date *Extended by 3 months from September 15*
December 16	**Amgen's ABP-710**, a biosimilar of Johnson & Johnson's Remicade (infliximab) for moderate-to-severe rheumatoid arthritis and more	PDUFA date
December 24	**Correvio Pharma's Brinavess** (vernakalant), an antiarrhythmic for the rapid conversion of recent onset atrial fibrillation	PDUFA date
December 27	**Durect's Posimir** (bupivacaine extended-release) for post-operative pain	PDUFA date
December 28	**Amarin's Vascepa** (icosapent ethyl) – expanded approval to reduce cardiovascular risk in statin-managed patients with high triglycerides	PDUFA date *Expected extension from September 28, 2019*

2020 FDA Advisory Committees and Other Regulatory Dates of Interest (*items in RED are new since last week*)		
Date	**Topic**	**Committee/Event**
January 23	**Epizyme's tazematchetostat** for metastatic/locally-advanced epithelioid sarcoma	PDUFA date
February 4	**Alnylam Pharmaceuticals' givosiran** for acute hepatic porphyria	PDUFA date
February 16	**Agile Therapeutics' Twirla** (AG200-15, 120 μg levonorgestrel + 30 μg ethinyl estradiol), a contraceptive patch	PDUFA date **Extended by the FDA from November 16, 2019**
February 18	**Merck MSD's Keytruda** (pembrolizumab) – 6 sBLAs for a 30-minute Q6W infusion to treat melanoma, Hodgkin's lymphoma, primary mediastinal large B-cell lymphoma, gastric cancer, hepatocellular carcinoma, and Merkel cell carcinoma	PDUFA date
February 19	**Adverse event reporting** using ICH standards	FDA public meeting
February 21	**Esperion Therapeutics' bempedoic acid** monotherapy to treat hypercholesterolemia	PDUFA date
February 26	**Esperion Therapeutics' bempedoic acid in combination with ezetimibe** to treat hypercholesterolemia	PDUFA date
February 26	**Acacia Pharma's Barhemsys** (IV amisulpride) for post-operative nausea and vomiting (PONV)	PDUFA date
February 27	**BeiGene's zanubrutinib**, a BTK inhibitor for mantle cell lymphoma	PDUFA date
March 8	**Horizon Therapeutics' teprotumumab** to treat active thyroid eye disease	PDUFA date
March 9	**Intarcia Therapeutics' ITCA-650** (exenatide implant) for Type 2 diabetes	PDUFA date
March 10	**Bristol-Myers Squibb's Opdivo** (nivolumab) **+ Yervoy** (ipilimumab) for advanced hepatocellular carcinoma	PDUFA date

more - 2020 FDA Advisory Committees and Other Regulatory Dates of Interest (*items in RED are new since last week*)		
Date	**Topic**	**Committee/Event**
March 15	**Astellas and Seattle Genetics' enfortumab vendotin**, an antibody-drug conjugate for treating metastatic/locally-advanced urothelial cancer	PDUFA date
March 25	**Celgene's ozanimod** (RPC-1063) for relapsing multiple sclerosis	PDUFA date
March 26	**Heron Therapeutics' HTX-011** (bupivacaine + meloxicam) for postoperative pain	PDUFA date
April 4	**Celgene and Acceleron Pharma's luspatercept** for myelodysplastic syndrome-associated anemia	PDUFA date
April 30	**Sanofi's isatuximab** for relapsed/refractory multiple myeloma	PDUFA date
May 12-13	**Regulatory education for industry**	FDA conference
May 14	**Sunovion Pharmaceuticals' dasotraline** for moderate-to-severe binge eating disorders	PDUFA date
August 5	**DBV Technologies' Viaskin Peanut** for treating children with peanut allergy	FDA target action date
August 27	**Cassiopea's clascoterone cream 1%**, a topical androgen receptor inhibitor for acne	PDUFA date