TRENDS-in-MEDICINE

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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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NOTE: There are two longer-than-usual pieces in ***Quick Takes*** this week – one on **Amylyx Therapeutics' AMX-0035** and another on **Atara Biotherapeutics' ATA-188 and ATA-190**.

*Remember, nearly all items in **Quick Takes** have a link somewhere, except the calendar.*

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

✓ A lot of positive trials were reported, including:

- INCYTE and NOVARTIS' Jakafi (ruxolitinib) in a confirmatory Phase III trial in steroid-refractory GvHD.
- PFIZER's abrocitinib in a Phase III trial in moderate-to-severe atopic dermatitis.
- REATA PHARMACEUTICALS' omaveloxolone (RTA-408) in a Phase II trial in Friedreich's ataxia.
- ROCHE's Rituxan (rituximab) in a Phase III trial in moderate-to-severe pemphigus vulgaris.
- TAIHO ONCOLOGY's Lonsurf (trifluridine + tipiracil) in a pre-specified subgroup analysis of a Phase III trial in metastatic gastric cancer patients with or without prior gastrectomy.
- UCB's bimekizumab in a Phase III trial in moderate-to-severe psoriasis.

✓ But there was also one notable negative Phase III trial: LILLY's pegilodecakin failed to prolong survival in second-line metastatic pancreatic cancer.

✓ ICER found two cardiovascular drugs cost-effective but budget busters: **Johnson & Johnson and Bayer's Xarelto** (rivaroxaban) and **Amarin Pharmaceuticals' Vascepa** (icosapent ethyl).

✓ PHILIPS' Stellarex – Two low-dose ***paclitaxel***-eluting drug-coated balloons were approved by the FDA.

SHORT TAKES

■ ALEXION PHARMACEUTICALS is buying **Achillion Pharmaceuticals** for $930 million, which will give it danicopan, a treatment for use in combination with a Complement 5 inhibitor to treat paroxysmal nocturnal hemoglobinuria (PNH).

■ BLUEPRINT MEDICINES' BLU-782 – The exclusive worldwide development and commercialization rights to this oral ALK2 inhibitor were licensed to **Ipsen/Clementia Pharmaceuticals** as a treatment for fibrodysplasia ossificans progressiva (FOP).

- BRIDGEBIO PHARMA isn't buying Eidos Therapeutics after all because Eidos turned down a third offer.

- CLEVELAND DIAGNOSTICS' IsoPSA Assay for diagnosing prostate cancer was granted breakthrough device status by the FDA.

- COSMO PHARMACEUTICALS' Aemcolo (rifamycin) – The U.S. rights to this FDA-approved antibiotic for treating traveler's diarrhea were licensed to **RedHill Biopharma**.

- Diabetes – In a 10-year, parallel-arm French cohort study of islet cell transplantation in 28 Type 1 diabetics, to be published in November in ***Diabetes Care***, 28% met the primary endpoint – insulin independence with HbA_{1c} ≤6.5%.

- EDITAS MEDICINE is collaborating with **Asklepios BioPharmaceutical** on research and development of *in vivo* delivery of genome editing medicines for neurological diseases.

- ENTERPRISE THERAPEUTICS' ETD-002 – The company got up to $7 million in funding from the Cystic Fibrosis Foundation to support Phase II development of this calcium-activated chloride ion channel modulator, a TMEM16A potentiator.

- FEMTOGENIX's Pyridinobenzodiazepine (PDD) ADC payload platform – Data presented at the World ADC meeting in San Diego showed that the company's antibody drug conjugates containing DNA-binding therapeutic payloads using the PDD platform have a "favorable" toxicity profile and potent efficacy.

- FLEXION THERAPEUTICS' Zilretta (triamcinolone acetonide extended-release injectable) – The FDA indefinitely postponed a decision on a supplemental new drug application (sNDA) for Zilretta to allow repeat administration for treating osteoarthritis knee pain. However, the company said the FDA indicated it expects to complete its review in the coming weeks and has not asked for any additional clinical data.

- GE HEALTHCARE got a $224 million order from NYC Health + Hospitals for medical imaging technology upgrades at its 11 hospitals over the next 10 years – MRI, CT, nuclear cameras, x-ray machines, catheterization labs, PET/PETCT, and fluoroscopy.

- IMMUTEP's eftilagimod alpha (IMP-321) – The results of the 24-patient, open-label Phase I TACTI-mel trial, presented at the World Immunotherapy Congress in Basel, Switzerland, showed synergy between this Lag3 and Merck MSD's Keytruda (pembrolizumab), an anti-PD-1 – in metastatic melanoma.

- INCYTE and NOVARTIS' Jakafi (ruxolitinib), a JAK1/2 inhibitor, met the primary endpoint in the confirmatory open-label, 310-patient Phase III REACH2 trial in steroid-refractory acute graft-versus-host disease (GvHD), significantly improving overall response rate at Day 28 vs. best available therapy.

- INVIBIO BIOMATERIAL SOLUTIONS' Juvora – A 3-year Portuguese study, presented at the European Association for Osseointegration (EAO) meeting in Lisbon, found that this PEEK polymer-based dental disc was associated with three-times less bone loss vs. a metal prosthesis.

- ION BEAM APPLICATIONS (IBA) signed a long-term agreement with the Azrieli Centre for Neuro-Radiochemistry at Canada's **Centre for Addiction and Mental Health** to facilitate PET radiopharmaceutical identification, development, and testing of applications in neurology and oncology.

- LIFE IMAGE partnered with **Graticule** to improve clinical trial data and help pharmaceutical and biotech companies accelerate drug development and postmarket safety, effectiveness, and label expansion.

- NOVARTIS/SANDOZ ended its digital therapeutics partnership with **Pear Therapeutics**.

- NOVIGENIX is collaborating with **RadioMedix** on development of an immune-transcriptomic-based diagnostic test for RadioMedix's alpha and beta peptide receptor radionuclide therapy for patients with neuroendocrine tumors.

- PHILIPS is expanding its partnership with **Spencer Health Solutions**, planning to take Spencer's medication adherence/telehealth services to Europe.

- REATA PHARMACEUTICALS' omaveloxolone (RTA-408), an Nrf2 activator, met the primary endpoint in the 103-patient Part II of the Phase II MOXIe trial in Friedreich's ataxia, significantly improving the mFARS score at Week 48 vs. placebo in patients with no pre-existing musculoskeletal foot deformity.

- RELMADA THERAPEUTICS' REL-1017 (dextromethadone) – Both doses (25 mg and 50 mg) of this oral NMDA antagonist (that works on the same binding site as ketamine) met the primary endpoint in the double-blind, 62-patient Phase II REL-1017-202 trial in treatment-resistant depression, significantly improving scores on MADRS, CGI-S, CGI-I, and SDQ vs. placebo.

- SEASPINE is collaborating with **restor3D** on 3D-printed interbody devices for spine surgery.

- SHIONOGI's Fetroja (cefiderocol lyophilized powder, S-649266) – The FDA's Antimicrobial Drugs Advisory Committee voted 14-2 that there is substantial evidence of efficacy and safety for this IV antibiotic in treating complicated urinary tract infections, including pyelonephritis. The PDUFA date is November 14, 2019.

- SPRING BANK PHARMACEUTICALS' inarigivir (SB-9000) – In interim top-line 12-week results from the first cohort on the ongoing 42-patient Phase II ACHIEVE trial of Gilead Sciences' Vemlidy (tenofovir alafenamide) ± a 50 mg dose of this dinucleotide in hepatitis B, 7 of 30 patients in the low-dose (50 mg) arm were HBsAg responders and met the primary endpoint of a ≥0.5 $\log_{10}$ IU/mL reduction in HBsAg vs. 3 of 12 patients in the Vemlidy alone arm. Excluding patients with signs of an ALT flare prior to entering the study, 5 of the remaining 28 low-dose patients were HBsAg responders.

- SYROS PHARMA's SY-1365 – Development of this IV CDK7 inhibitor was discontinued, and the company will focus instead on SY-5609, an oral CDK7 inhibitor for solid tumors.

- TAIHO ONCOLOGY's Lonsurf (trifluridine + tipiracil) – A pre-specified subgroup analysis of prior gastrectomy patients from the Phase III TAGS trial in ≥3-line metastatic gastric or gastroesophageal junction adenocarcinoma, published in ***JAMA Oncology***, showed that the treatment was tolerable and prolonged overall survival vs. placebo regardless of prior gastrectomy, with safety comparable to patients who had not had a gastrectomy.

- TAKEDA sold 30 prescription and over-the-counter products (for pain, gastroenterology, cardiovascular, and respiratory treatment) that are distributed in parts of the Near East, Middle East, Africa, and the Ukraine, to **Acino**, a Swiss pharma for $200 million.

- Transcatheter valves – A study, published in ***JAMA Internal Medicine***, found that deaths associated with transcatheter valve-repair procedures (both aortic and mitral valves) may be under-reported in the FDA adverse events database (MAUDE). The study found that 17.5% of deaths associated with **Edwards Lifesciences' Sapien 3** and 24.7% of deaths associated with **Abbott's MitraClip** were misclassified as "injury" or "malfunction," not deaths.

- TRIALBEE is partnering with **TriNetX** to accelerate research and development of new services to improve patient access to clinical trials.

- UCB's bimekizumab, an IL-17A/F inhibitor, met both primary endpoints in the 570-patient Phase III BE VIVID trial in moderate-to-severe psoriasis, showing superiority to both placebo and Johnson & Johnson's Stelara (ustekinumab) at Week 16 on both PASI90 and IGA 0/1.

- Vaping update – The Centers for Disease Control and Prevention (CDC) reported that there are now 1,479 patients with confirmed EVALI (e-cigarette and vaping lung injury) across 49 states, and 33 deaths across 24 states. The average age of patients who got EVALI is 23 (range 13-75).

- XENIKOS' T-Guard, a treatment that uses toxin-conjugated monoclonal antibodies that target CD3 and CD7 molecules on T cells and NK cells to treat patients with steroid-refractory acute graft-versus-host disease post allogeneic hematopoietic stem cell transplant, was granted fast track status by the FDA.

Very early research news

- CABALETTA BIO – University of Pennsylvania researchers have developed a new type of CAR T, a chimeric autoantigen receptor (CAAR) T cell, designed to specifically eliminate B cells which are responsible for autoimmune diseases. In data presented at the American Neurological Association (ANA) meeting in St. Louis MO, the CAAR T cells appear to have efficacy in myasthenia gravis. Cabaletta plans a trial of its DSG3-CAAR-T in mucosal pemphigus vulgaris in 2020.

NEWS IN BRIEF

AMYLYX PHARMACEUTICALS' AMX-0035 (Sodium phenylbutyrate + tauroursodeoxycholic acid)

On a recent webcast, Sabrina Paganoni, MD, PhD, an ALS researcher from Massachusetts General Hospital, and Justin Klee, president/co-founder of Amylyx, reviewed the status of the 24-week Phase II CENTAUR trial (plus an open-label extension) of this combination drug in amyotrophic lateral sclerosis (ALS), saying the trial is completed and being analyzed now, with results expected by the end of November 2019, perhaps with a presentation at the International ALS Symposium in Australia in December 2019 or the American Academy of Neurology meeting in April 2020.

Dr. Paganoni explained that 1 in 400 women and 1 in 350 men get ALS in their lifetime, and at any given time ~30,000 people in the U.S. have ALS. She said it generally takes about a year to diagnose ALS after symptoms first begin, with average survival 3 years. Thus, about 6 months after diagnosis the typical patient won't be able to walk independently. She said the two FDA-approved treatments – riluzole and Mitsubishi

Tanabe Pharma's Redicava (endaravone) – have a "very modest" effect.

Klee explained that the two drugs in AMX-0035 are synergistic, at least they were in preclinical studies. And he noted that 90% of CENTAUR patients continued into an open-label extension study.

Among the other points Dr. Paganoni and Klee made were:

- The primary endpoint, change in ALSFRS-R, is determined by a questionnaire, but it is commonly used in ALS, is considered validated by the FDA, and is a clinically meaningful measure. Klee said, "We will really affect quality of life and function. Our primary endpoint is a clinically meaningful scale."
- *Asked if they expect a survival benefit*, Dr. Paganoni said, "We are following it, but we are enrolling people relatively early. We don't expect the entire group to have a large number of deaths in the trial because we are enrolling participants early, within 8 months of symptoms, and we are only following them for 6 months…Survival is not the only required endpoint. The field is really moving more toward functional-based therapies. For people with ALS, participating in a trial is essentially their only shot."
- *Asked why he is so optimistic about AMX-0035,* Klee said, "First, we are targeting mechanisms that have not been sufficiently targeted before that we think are critical in the degenerative process. Second, what is particularly exciting is that the individual drugs have both been successful in previous small ALS trials and showed potential benefit. All of our preclinical data showed the combination has a far stronger effect than either agent alone. And, third, I think this is a really well done clinical trial."
- *Asked which ALS patients would likely get AMX-0035 if the trial is positive and the FDA approves it*, Dr. Paganoni said, "My expectation is everyone will be able to get it. If the results are positive and significantly so, I would expect it to be approved for all patients."
- *Asked if there is a time point in disease progression where the drug is unlikely to be beneficial*, Dr. Paganoni said, "We will need to learn more about that in the open-label extension study to understand if there is a time point where it doesn't help…The way we prescribe approved drugs for ALS now is for the patient's lifetime because there is…no evidence the drugs stopped working at any specific time point…Over time patients are likely to lose function, but if we can slow that down and maintain important activities, there is a strong case for continuing to prescribe the drug."

ASTRAZENECA

- FluMist. Manufacturing issues mean that shipments to the U.S. of this inhaled flu vaccine will be down by about two-thirds this year.
- and DAIICHI SANKYO's trastuzumab deruxtecan (DS-8201a), an antibody-drug conjugate for treating HER2+ metastatic breast cancer, was granted priority review by the FDA.

ATARA BIOTHERAPEUTICS

Several doctors who treat and do research in multiple sclerosis (MS) were interviewed at the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS) meeting in September in Stockholm, Sweden, about two **Atara Biotherapeutics**' allogeneic T-cell immunotherapies that target specific Epstein-Barr virus (EBV) antigens:

- ATA-188, an ***off-the-shelf*** allogeneic T-cell immunotherapy
- ATA-190, an ***autologous*** allogeneic T-cell immunotherapy

Initial ***safety*** results from an ongoing open-label, dose-escalating Phase I trial of ATA-188 in progressive MS were presented in a poster at the European Academy of Neurology (EAN) meeting in Oslo, Norway, in late June 2019. The data showed that the therapy was well tolerated, with no dose-limiting toxicities and no Grade ≥3 treatment-emergent adverse events.

At ECTRIMS, initial efficacy data and updated safety results from that Phase I trial were presented in a poster. The measures at 3, 6, and 12 months were EDSS, the Fatigue Severity Score, the MS Impact Scale-29, the Timed 25-Foot Walk (T25FW), the 9-Hole Peg Test, MSWS-12, and visual acuity. Clinical improvement was defined as clinically significant or greater improvement on ≥2 of those scales sustained over ≥2 consecutive time points.

- The updated ***safety*** results showed that all 4 dose cohorts were well tolerated, with no cytokine release syndrome, graft-versus-host disease, or dose-limiting toxicities.
- The ***efficacy*** data at 6 months showed:
  - 4 of 6 patients in Cohort 1 had a clinical decline at 6 months that was maintained at 12 months.
  - All 6 patients in Cohort 2 met the criteria for clinical improvement or partial clinical improvement.

Data on Cohorts 3 and 4 are expected in 2020, with a randomized, double-blind Phase Ib trial planned once the dose is selected.

Comments about the outlook for ATA-188 and how attacking EBV, also known as human herpesvirus 4, may impact the course of MS included:

- **Causation**
  - *Tobias Derfuss, MD, a neurologist, treasurer of ECTRIMS, and director of the outpatient clinic at University Hospital, Basel, Switzerland:*
    - ✓ "The people at Atara have developed a therapy against these Epstein-Barr-infected cells that are also involved in Epstein-Barr virus-related tumors. The whole idea is based on the idea that EBV is the causative agent in MS, which I don't think has been established."
    - ✓ "There is a connection between Epstein-Barr virus and MS, and, of course, if you have infectious mononucleosis, the risk of MS is doubled. Certain antibody concentrations also increase your risk, but how the link works [isn't understood]."
    - ✓ "We know that MS is involved in a person's genome and that it requires an environmental trigger, but whether the Epstein-Barr virus is a causal link is not known."
  - *Mar Tintoré, MD, PhD, a neurologist from Vall d'Hebron University Hospital and Research Institute in Barcelona, Spain, and secretary of ECTRIMS:*
    - ✓ "It is possible that Epstein-Barr virus has something to do with starting this immune-mediated abnormality. But there are children with MS who more commonly are negative for Epstein-Barr."
    - ✓ "Epstein-Barr is probably not the only virus that may play a role. However, this is a good initiative because we have to approach all aspects of this disease. It is a good approach, but, of course, there is no guarantee that this approach will be successful. We have to be flexible and to look to different approaches in this disease. I think these attempts are worth trying."
- **Immune response.** Does the infection change the way the immune system responds to the infections? Dr. Derfuss said, "I don't think this has been explained."
- **Eradication.** Dr. Derfuss said, "The problem is that to get rid of Epstein-Barr virus is very difficult because the infection stays in the B cells. This might be another approach to get at the infection, but it is very much experimental at this point because, frankly, we don't really know at this point if they are connected."
- **Testing.** Dr. Derfuss said, "I do not test patients for Epstein-Barr virus infection because almost everyone is positive, and it wouldn't really help us in the diagnosis. Most often people are infected with EBV and do not have any symptoms of the infection."

The bottom line: Interesting approach and interesting data, but very early.

Cardiovascular (CV) drugs – a final ICER report

The Institute for Clinical and Economic Review (ICER) issued a final report on two CV drugs, saying they both met cost-effectiveness as add-on therapies. However, ICER noted that the U.S. healthcare system can't afford to cover as many patients as are eligible:

- **JOHNSON & JOHNSON and BAYER's Xarelto (rivaroxaban).** While 30% of eligible patients might get this Factor Xa inhibitor, ICER predicted that only 6% of patients could be treated without this being a budget buster.
- **AMARIN PHARMA's Vascepa (icosapent ethyl).** ICER expects this to be even more popular with a "majority" of eligible patients wanting it, but only 4% could be treated without being a budget buster.

Hospital survey

Among the findings in L.E.K.'s Annual Hospital Survey were:

- Healthcare information technology is a consistent and growing priority.
- Administrators gained influence over purchase decisions.
- Telehealth is expanding.
- Care delivery is shifting to a greater use of data and analytics.
- Increased focus on services lines and development of centers of excellence.

LILLY

- Is closing its neuroscience research center in the U.K. by the end of 2020, with neuroscience research moving to the U.S. Lilly insisted the decision is not related to Brexit.
- Pegilodecakin, which Lilly acquired with the purchase of **Armo BioSciences**, (added to FOLFOX) missed the primary endpoint in the Phase III SEQUOIA trial in second-line metastatic pancreatic cancer, failing to significantly prolong overall survival vs. FOLFOX alone.

Opioids

A study of 3,000 opioid overdose deaths in Massachusetts from 2013-2015, published in ***Public Health Reports***, found that prescription opioids were generally ***not*** involved in the overdoses. Instead, the study found:

- Commonly, the medication that people were prescribed was not the one involved in the overdose.
- Multiple drugs were involved in most of the overdoses: heroin in 61%, fentanyl in 45%.
- Prescription opioids alone were detected in only 16.5% of the overdoses.
- Only 1.3% of the people who died had a prescription for the opioid that killed them.
- Only 6% of those who died with oxycodone in their system had an active prescription for oxycodone, which means that 94% were taking oxycodone that was either diverted or leftover from an earlier prescription.
- Methadone and buprenorphine (e.g., Indivior's Suboxone) were found in 3% of the deaths.

PFIZER

- Abrocitinib, a JAK1 inhibitor, met both co-primary endpoints in the 387-patient, 12-week Phase III JADE MONO-1 trial in moderate-to-severe atopic dermatitis. The data, presented at the European Academy of Dermatology and Venereology (EADV) meeting in Madrid, showed that significantly more abrocitinib patients achieved IGA 0/1 and a ≥2 point improvement vs. placebo, and significantly more abrocitinib patients achieved EASI75 or better vs. placebo. All key secondary endpoints were also met. The most common adverse event was nausea – 20.1% of patients on the high dose (200 mg).
- Vincristine. Pfizer is stepping up production of this chemotherapy drug after **Teva**, the only other supplier, discontinued production, creating a shortage.

PROQR THERAPEUTICS' sepofarsen (QR-110)

- The FDA granted rare pediatric disease (RPD) designation.
- The company released positive top-line 12-month data from a Phase I/II trial of this RNA-based oligonucleotide in patients with Leber's congenital amaurosis 10 (LCA10) caused by the p.Cys998X mutation in the CEP290 gene. The data showed that the effect seen at 3 and 6 months is durable out to 12 months, with no new safety findings, though the cataract rate was 50% with the low dose (160 µg/80 µg). *What was surprising was that the company released these results by press release, not at the American Academy of Ophthalmology meeting in San Francisco, even though they had a booth there.*

ROCHE

- Dropped several early pipeline drugs:
  - Petesicatib (RG-7625), a cathepsin S antagonist
  - RG-6148, an antibody-drug conjugate for HER2+ breast cancer
  - RG-6123, for CEA-positive tumors
  - RG-6109, for acute myeloid leukemia
  - RG-6146, a small-molecule BET inhibitor
- Actemra (tocilizumab) beat azathioprine in the head-to-head, 118-patient Chinese TANGO trial in neuromyelitis optica spectrum disorder (NMOSD), presented at ANA, significantly reducing the time to first relapse, with 86% of Actemra patients relapse-free at Week 48 vs. 48.1% of azathioprine patients. Actemra also significantly reduced relapse risk.
- Rituxan (rituximab). The Phase III PEMPHIX trial in moderate-to-severe pemphigus vulgaris showed that this anti-CD20 was superior to mycophenolate mofetil (MMF) at Week 52 in achieving a complete response for 16 consecutive weeks (without the use of steroids) – 40.3% vs. 9.5%.

TANDEM DIABETES CARE

- Control-IQ. Tandem's experimental closed-loop insulin delivery system (t:slim X2 with Control-IQ pump + Dexcom's G6 continuous glucose monitor) met the primary endpoint in a 6-month, 168-patient trial in Type 1 diabetes, published in the ***New England Journal of Medicine***, with significantly more closed-loop patients in target range at 6 months vs. control (71% vs. 61%). All the secondary endpoints were met as well.
- Is partnering with **Abbott** to integrate its insulin pump with Abbott's glucose-sensing technology (FreeStyle Libre, a continuous glucose monitor, CGM).

REGULATORY NEWS

Regulatory tidbits

- Drug prices
  - A preliminary analysis by the Congressional Budget Office (CBO) of the House Democrats' bill to revise drug pricing (H.R.3) found that the bill, if enacted into law, could save Medicare $345 billion over 7 years, but the CBO also

predicted that over time there would be fewer new drugs introduced because spending on research and development would be cut – an estimated drop of ~8-15 fewer new drugs coming to market over the next 10 years.

- Democrats altered the bill to (1) raise to 35 from 25 the number of drugs for which the Department of Health and Human Services must negotiate prices and (2) require cost negotiations for any new drugs that are priced higher than the average median household income.

- FDA guidances. The FDA laid out its top guidance priorities for 2020, and they included: clinical decision support software, labeling recommendations for surgical staples, and device-specific Safety and Performance Based Pathway implementation.

- Generic drugs. Acting FDA Commissioner Ned Sharpless, MD, reported that generic drug approvals set a record in fiscal year 2019 (1,171 – 935 full approvals and 236 tentative approvals), up from 971 in 2018. Among the 2019 approvals were 125 first generics of drugs with no generic competition.

- STERIGENICS. Environmental officials in Georgia asked the company for additional test results before they will approve the reopening of the company's medical device sterilization plant in Atlanta, causing a delay in the reopening.

- Tariffs. A report in ***Newe Zürcher Zeitung*** claims U.S. trade representative Robert Lighthizer said the U.S. is considering imposing tariffs on pharmaceuticals from Switzerland. This would be bad news for Roche, Novartis, Merck KGaA, and Biogen.

FDA approvals/clearances

- ALEXION PHARMACEUTICALS' Ultomiris (ravulizumab-cwvz) was approved to treat atypical hemolytic uremic syndrome (aHUS) in patients age ≥1 month.

- APYX MEDICAL's Apyx Plasma/RF Handpiece, a single-use device designed to deliver radiofrequency energy or helium plasma for cutting, coagulation, and ablation of soft tissue, was granted 510(k) clearance.

- FIDMI MEDICAL's low-profile enteral feeding device, a gastrostomy tube for nutrition support that can be used for both initial placement and replacement, received 510(k) clearance.

- FOAMIX PHARMACEUTICALS' Amzeeq (minocycline foam, FMX-101) was approved as a topical treatment for moderate-to-severe acne.

- HISAMITSU PHARMACEUTICAL/NOVEN PHARMACEUTICALS' Secuado (asenapine), a transdermal patch for treating schizophrenia, was cleared for use.

- JDP THERAPEUTICS' Quzyttir (cetirizine Hcl) was approved to treat pediatric acute urticaria.

- JOHNSON & JOHNSON
  - iDesign Refractive Studio, a wavefront-guided photorefractive keratectomy (PRK) surgery for treatment of nearsightedness, was approved.
  - and Bayer's Xarelto (rivaroxaban) was granted expanded approval to help prevent venous thromboembolism (VTE) and VTE-related death during hospitalization and post-hospital discharge in acutely ill medical patients at risk for VTE and not at high risk of bleeding.

- OMEGA MEDICAL IMAGING's FluoroShield, an imaging device that reduces the radiation dosage, was cleared for use during fluorescein angiography.

- PHILIPS' Stellarex – Despite the controversy about **paclitaxel**, the FDA cleared two new, low-dose drug-coated balloons to treat both de novo and restenotic lesions in upper leg arteries.

- ROCHE's Xofluza (baloxavir marboxil) was granted expanded approval for use as a single-dose treatment for patients at high risk of flu complications.

- SKY MEDICAL TECHNOLOGY's Geko, an electrostimulation device for preventing venous thrombosis in non-surgical patients who are at risk for VTE, was granted 510(k) clearance. The device stimulates the calf muscles to increase blood flow.

FDA recalls/warnings

- CORAL PHARMACEUTICALS received a warning letter over violations of current good manufacturing practices (cGMP).

- CSL BEHRING's Humate-P (anti-hemophilic Factor/von Willebrand Factor complex, human) was recalled due to an error in packaging.

- DENTERPRISE INTERNATIONAL, a dental x-ray supplier, received a warning letter for failing to report complaints about alleged device malfunctions that led to additional radiation exposures. The FDA asked the company to retrospectively review its accidental radiation incidents and exposures.

- TORRENT PHARMACEUTICALS received a warning letter over violations of cGMP relating to production of losartan potassium tablets.

- VIATREXX BIO recalled all of its sterile injectables because of sterility concerns.

- WONTECH's HairBoom Air, a lightweight helmet device that uses low-power laser therapy to promote hair growth, was granted 510(k) clearance.

European Regulatory News

- Medical device software – The European Commission's Medical Device Coordination Group issued guidance on qualifying medical device software under the Medical Devices Regulation and In Vitro Diagnostic Regulation.
- ABBVIE's Rinvoq (upadacitinib) – The European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) recommended approval of this JAK inhibitor to treat rheumatoid arthritis.
- BRISTOL-MYERS SQUIBB's Evotaz (atazanavir + cobicistat) – CHMP recommended two new contraindications for this HIV drug, warning against use in combination with Boehringer Ingelheim's Pradaxa (dabigatran), an anticoagulant, or Aegerion Pharmaceuticals' Lojuxta (lomitapide, Juxtapid in the U.S.), a treatment for familial hypercholesterolemia.
- D&A PHARMA's Hopveus (sodium oxybate) – CHMP recommended ***against*** approval as a treatment for alcohol dependence.
- DAIICHI SANKYO's Vanflyta (quizartinib) – CHMP recommended ***against*** approval of this Flt3 inhibitor to treat acute myeloid leukemia (AML).
- JOHNSON & JOHNSON
  - Darzalex (daratumumab) – CHMP recommended expanded approval for use in multiple myeloma.
  - Spravato (esketamine) – CHMP recommended approval of this nasal spray therapy for treatment-resistant major depressive disorder (MDD).
- LILLY's Baqsimi (glucagon) – CHMP recommended approval to treat severe hypoglycemia.
- MENARINI's Quofenix (delafloxacin) – CHMP recommended approval of this antibiotic to treat acute bacterial skin and skin structure infections.
- MERCK
  - Ervebo (rVSVΔG-ZEBOV-GP) – CHMP recommended conditional marketing authorization for this Ebola Zaire vaccine.
  - Keytruda (pembrolizumab) – CHMP recommended expanded approval for use as monotherapy in first-line metastatic/unresectable recurrent head and neck squamous cell carcinoma (HNSCC) in PD-L1+ patients.
- MUNDIPHARMA BIOLOGICS' Pegfilgrastim Mundipharma – CHMP recommended approval of this biosimilar of **Amgen's Neulasta** to reduce the duration of neutropenia and the incidence of febrile neutropenia due to chemotherapy.
- NOVARTIS' Revolade (eltrombopag) – CHMP recommended ***against*** expanding approval to included treatment of previously untreated patients with severe aplastic anemia age ≥12 ineligible for stem cell transplant.
- PARATEK PHARMACEUTICALS' Nuzyra (omadacycline) – The company withdrew its marketing application to the European Medicines Agency (EMA) for this antibiotic after the EMA indicated that it was considering approving only treatment of infections of the skin and skin structures but *not* community-acquired pneumonia.
- PTC THERAPEUTICS' Translarna (ataluren) – CHMP recommended ***against*** expanding approval to allow treatment of Duchenne muscular dystrophy (DMD) patients no longer able to walk.
- SANOFI's Toujeo (insulin glargine) – CHMP recommended expanded approval for use in adolescents and children as well as adults with diabetes.
- TEVA's ranitidine (generic Zantac) – The company recalled 10 lots of this antacid in the U.K. as a precautionary measure because of possible nitrosamine contamination.
- UCB PHARMA's Evenity (romosozumab) – After reconsideration, CHMP recommended approval of this sclerostin inhibitor to treat severe postmenopausal osteoporosis.
- VERTEX PHARMACEUTICALS' Kalydeco (ivacaftor) – CHMP recommended expanded approval that lowers the age and weight requirement for use in cystic fibrosis.

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

- BAYER and JOHNSON & JOHNSON's Xarelto (rivaroxaban) – NICE recommended use of this Factor Xa inhibitor plus aspirin to prevent atherothrombotic events in coronary artery disease (CAD) or symptomatic peripheral artery disease (PAD).
- TAKEDA's Takhzyro (lanadelumab) – NICE recommended use for preventing recurrent attacks of hereditary angioedema in patients age ≥12 but only if they are eligible for preventative C1-esterase inhibitor treatment, get the lowest dosing frequency, and the company discounts the price.

Regulatory news from other countries

- ***Canada.*** uniQure's Glybera (alipogene tiparvovec), a gene therapy for familial lipoprotein lipase deficiency (LPLD), acquired with the purchase of Amsterdam Molecular Therapeutics, was withdrawn from the market in 2017 because of lack of sales – and lack of FDA approval, though it was approved by the European Medicines Agency. At the time, at $1 million/treatment it was the most expensive drug in the world. Now, the National Research Council of Canada (NRC) plans to develop a Canadian version of Glybera since Canada has a large population of LPLD patients.
- ***Mexico.*** The Mexican Senate is considering legislation that would legalize marijuana.

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 19	**Clearside Biomedical's Xipere** (triamcinolone acetonide), a suprachoroidal injection for treating macular edema associated with uveitis	PDUFA date **No decision announced yet**
October 21	**Eton Pharmaceuticals' ET-202** (phenylephrine) for low blood pressure	PDUFA date
October 24	**Melinta Therapeutics' Baxdela** (delafloxacin) for community-acquired bacterial pneumonia	PDUFA date
October 24	**GlaxoSmithKline/Tesaro's Zejula** (niraparib) – expanded approval to treat advanced fallopian tube, ovarian, or primary peritoneal cancer	PDUFA date
October 28-29	Discussion of applications and policies relating to deemed tobacco products, including **e-cigarettes** (*The Agency does not intend to communicate any new policies or interpretations at this meeting.*)	FDA's Center for Tobacco Products meeting
October 29	**AMAG Pharmaceuticals' Makena** (hydroxyprogesterone caproate) – for treating preterm birth – because the confirmatory trial failed	FDA's Bone, Reproductive, and Urologic Drugs Advisory Committee
October 30	**Agile Therapeutics' Twirla** (AG200-15, 120 mg levonorgestrel + 30 mg ethinyl estradiol), a contraceptive	FDA's Bone, Reproductive, and Urologic Drugs Advisory Committee
October 31	**Adamis Pharmaceuticals' Zimhi** (injectable higher dose naloxone) for opioid overdose	PDUFA date
October 31	ICH Global meeting on ICH E8(R1) guideline on general **considerations for clinical trials**	FDA public meeting
November 2	**RedHill Biopharma's Talicia** (RHB-105) to treat *H. pylori* infection	PDUFA date
November 4	Genetic toxicology: How many doses of a **DNA Reactive (Ames+) drug** can be safely administered to healthy subjects	FDA workshhop
November 4	Use of fecal microbiota for transplantation to treat ***Clostridium difficile*** infection not responsive to standard therapies	FDA public hearing
November 5	513(g) requests for information and custom device exemption	FDA's Center for Devices and Radiological Health workshop
November 6	Neoadjuvant treatment of **melanoma**	FDA/MRA public workshop
November 6-7	Ethylene oxide (EtO) **sterilization of medical devices**, including discussion of recommendations for reducing the risk from **reprocessed duodenoscopes**	FDA's General Hospital and Personal Use Devices Advisory Committee
November 7	**Effective drug development –** opportunities and priorities for the FDA's Office of New Drugs	FDA public meeting
November 8	Development of **chikungunya vaccines**	FDA's Vaccines and Related Biological Products Advisory Committee
November 12	Advancing development of pediatric therapeutics: **clinical trial endpoints for rare diseases**	FDA workshop by the Office of Pediatric Therapeutics
November 13	**Boehringer Ingelheim's Jardiance** (empagliflozin) - expanded approval for use in Type 1 diabetes	FDA's Endocrinologic and Metabolic Drugs Advisory Committee
Nov. 13-14	Immunological responses to **implanted metal-containing medical devices**	FDA's Immunology Devices Advisory Committee
November 14	**Amarin's Vascepa** (icosapent ethyl) – expanded approval to reduce cardiovascular risk in statin-managed patients with high triglycerides	FDA's Endocrinologic and Metabolic Drugs Advisory Committee (**corrected committee**)
November 14	**Shionogi's Fetroja** (cefiderocol lyophilized powder) for complicated urinary tract infections	PDUFA date
November 16	**Agile Therapeutics' Twirla** (AG200-15, 120 mg levonorgestrel + 30 mg ethinyl estradiol), a contraceptive	PDUFA date
Nov. 18-19	Discussion of **antibacterial drug development** – status and how to enhance enrollment	FDA-IDSA-NIAID and Pew joint workshop
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 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

2019 FDA Advisory Committees and Other Regulatory Dates of Interest – continued (*items in RED are new since last week*)		
Date	**Topic**	**Committee/Event**
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 tazemetostat** for metastatic/locally-advanced epithelioid sarcoma	PDUFA date
February 4	**Alnylam Pharmaceuticals' givosiran** for acute hepatic porphyria	PDUFA date
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 15	**Astellas and Seattle Genetics' enfortumab vendotin**, an antibody-drug conjugate for treating metastatic/locally-advanced urothelial cancer	PDUFA date
March 19	**Vertex Pharmaceuticals' tezacaftor + ivacaftor + elexacaftor** to treat cystic fibrosis	PDUFA date
March 25	**Celgene's ozanimod** (RPC-1063) for relapsing multiple sclerosis	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 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