TRENDS-in-MEDICINE

July 14, 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…

Trends-in-Medicine
Stephen Snyder, *Publisher*
2731 N.E. Pinecrest Lakes Blvd.
Jensen Beach, FL 34957
772-285-0801
Fax 772-334-0856
www.trends-in-medicine.com
TrendsInMedicine@aol.com

Note: While ***Trends-in-Medicine*** did not attend the American Headache Society meeting in Philadelphia, there is a lot of news from that meeting in ***Quick Takes*** this week.

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

- ✓ BIOHAVEN's rimegepant met the co-primary endpoints in a pivotal Phase III trial in migraine.
- ✓ Drug prices – The Trump administration's plan for requiring pricing in TV drug commercials was blocked by a judge, and the administration withdrew its proposal to eliminate rebates to insurers and PBMs.
- ✓ EDWARDS LIFESCIENCES' Centera – This TAVR has a safety issue that led to deaths, which the company blamed on anatomical issues.
- ✓ ESRD – President Trump signed an Executive Order aimed at increasing the number of patients on home dialysis or transplant to 80% by 2025.
- ✓ ICER, in separate reports, found that neither of the two peanut allergy therapies is cost-effective and neither of the two Duchenne muscular dystrophy therapies is cost-effective.
- ✓ INTRA-CELLULAR THERAPIES' lumateperone met the primary endpoint in one Phase III trial in bipolar depression but missed it in another.
- ✓ SOL-GEL TECHNOLOGIES' Epsolay (microencapsulated benzoyl peroxide cream 5%) had positive results in two Phase III trials in rosacea.

SHORT TAKES

- Abdominal aortic aneurysm (AAA) – A Canadian study, published in ***JAMA Network Open***, found long-term survival in elective AAA patients was similar with endovascular aortic repair (EVAR) and open surgical repair, and that benefit persisted out to 1 year (94.0% vs. 91.0%) but not beyond that. EVAR's advantage in survival free from death, MI, or stroke lasted longer – out to 4 years (72.9% vs. 69.9%) but not beyond that. The researchers concluded that the superiority of EVAR may be limited to the short term because of a high reintervention rate, improvements in surgery, and too-liberal use of EVAR.
- AGILITI bought Zetta Medical Technologies, which provides medical imaging equipment services and parts.
- ALEXION PHARMACEUTICALS' Kanuma (sebelipase alfa), a treatment for lysosomal acid lipase deficiency (LAL-D), was granted a priority review voucher by the FDA.

- ALGERNON PHARMACEUTICALS' NP-120 – In a mouse study NP-120 was superior in reducing fibrosis in idiopathic pulmonary fibrosis (IPF) to both Boehringer Ingelheim's Ofev (nintedanib) and Roche/Genentech's Esbriet (pirfenidone).

- ALTIMMUNE is buying **Spitfire Pharma**, which will give it SP-1373 (renamed ALT-801), a GLP-1/glucagon receptor co-antagonist for treating non-alcoholic steatohepatitis (NASH) and obesity.

- APOTEX voluntarily withdrew 31 abbreviated new drug applications (ANDAs) from the FDA until its manufacturing issues with the Agency are resolved.

- ARCHIMED bought **EUROLyser**, an *in vitro* diagnostics company which develops point-of-care testing devices and kits for PSA, troponin I, HbA_{1c}, and more.

- AURA BIOSCIENCES licensed use of **Clearside Biomedical**'s Suprachoroidal Space Microinjector technology for use with its ocular cancer drug candidates.

- BIODESIX is collaborating with **Thermo Fisher Scientific** on a blood-based DNA sequencing analysis for liquid biopsies.

- BIOHAVEN PHARMA's rimegepant – This CGRP inhibitor met the co-primary endpoints in the pivotal, 1,186-patient Phase III migraine trial, with 19.6% pain-free at 2 hours vs. 12% with placebo and 37.6% free from the most bothersome symptom at 2 hours vs. 25.2% with placebo. The results were presented at the American Headache Society meeting in Philadelphia and simultaneously published in the ***New England Journal of Medicine***.

- BIOMARIN PHARMACEUTICAL's valoctocogene roxaparvovec – After meeting with the FDA, the company said it plans to file a biologics license application (BLA) to the FDA – and to the European Medicines Agency (EMA) – for this gene therapy for severe hemophilia A in 4Q19 based on Phase I/II data without waiting for the two ongoing Phase III trials (GENEr8-1 and GENEr8-2) to complete.

- BOEHRINGER INGELHEIM's Ofev (nintedanib), added to cisplatin and Lilly's Alimta (pemetrexed), failed to improve progression-free survival (PFS) vs. cisplatin/pemetrexed alone in the Phase III part of the LUME-Meso trial in malignant pleural mesothelioma (6.8 months vs. 7 months). The results were published in ***The Lancet Respiratory Medicine***.

- BRISTOL-MYERS SQUIBB's Sprycel (dasatinib) – A study by German researchers, published in ***Science Translational Medicine***, suggests that this chronic myeloid leukemia (CML) drug may be useful in treating/preventing cytokine release syndrome in patients getting CAR T therapy. In mice, Sprycel can temporarily inactivate CAR T cells.

- CATALYST BIOSCIENCES' marzeptacog alfa – In a Phase II trial, presented at the International Society on Thrombosis and Haemostasis (ISTH) meeting in Melbourne, Australia, this subcutaneous Factor VIIa variant met the primary endpoint in a prophylaxis trial in hemophilia A or B with inhibitors, significantly reducing the annualized bleed rate. The trial also met all the key secondary endpoints.

- CELGENE expanded its collaboration with **Nimbus Therapeutics** to include Nimbus' HPK1 inhibitor program and now has the option to acquire the program while Nimbus will continue to control research and development.

- CELLECTAR BIOSCIENCES' CLR-131, an investigational treatment for relapsed/refractory diffuse large B-cell lymphoma (DLBCL), was granted fast track status by the FDA.

- CELSIUS THERAPEUTICS is partnering with **Johnson & Johnson/Janssen Biotech** on development of a therapy for inflammatory bowel disease (IBD), using Celsius' machine learning and single-cell genomics technology to identify biomarkers to predict patient response to J&J's Tremfya (guselkumab) combined with Simponi (golimumab).

- Digital health – A study by Parks Associates found that 22% of U.S. households with broadband have used a self-diagnosis app (e.g., iTriage, WebMD, Symptomate, and Ada) in the past 12 months.

- EDWARDS LIFESCIENCES' Centera – The company issued a safety notice, warning customers that it has had reports of cases in which difficulty in manipulating this transcatheter aortic valve replacement (TAVR) results in vascular injury, including death. Edwards said it believes the issue is tracking difficulty in patients with certain tortuous anatomies, recommending an alternate treatment in one situation and a stiffer guidewire in another.

- GENEREX BIOTECHNOLOGY bought **Pantheon Medical – Foot & Ankle**, a specialty orthopedic surgery device company.

- GILEAD SCIENCES signed a 10-year global research and development collaboration with **Galapagos**, which will also give Gilead rights to GLPG-1690, an autotaxin inhibitor for idiopathic pulmonary fibrosis (IPF), and an option on U.S. rights to GLPG-1972, an ADAMTS-5 inhibitor for osteo-arthritis.

- HANMI PHARMACEUTICAL's HM-12525A – **Johnson & Johnson/Janssen** returned the development rights to this anti-diabetes obesity drug to Hanmi even though two Phase II trials met the primary endpoint (weight reduction) because it did not meet J&J's goals on glucose lowering.

- HILLROM is selling its Bard-Parker line of scalpels, blades, and other surgical consumables to an affiliate of Audax Private Equity.

- HIV – A consortium, led by researchers at Scripps Research, was given a $129 million grant by the National Institutes of Health (NIH) to work on a vaccine for HIV.

- Idiopathic pulmonary fibrosis (IPF) – A retrospective study of a large insurance database (Optum), published in the *American Journal of Respiratory and Critical Care Medicine*, found that two commonly used treatments for this lung disease – **Boehringer Ingelheim's Ofev** (nintedanib) and **Roche/Genentech's Esbriet** (pirfenidone) – both decreased overall mortality equally (-23%) and decreased hospitalizations (-30%).

- JOHNSON & JOHNSON/JANSSEN's Darzalex (daratumumab) – A BLA was submitted to the FDA for a subcutaneous formulation of this anti-CD38 to treat multiple myeloma.

- KOGENT licensed an investigational wireless device, developed by researchers at Texas A&M University, that provides direct illumination for surgeries.

- NAVITAS LIFE SCIENCES is collaborating with **ThoughtSphere**, which will power Navitas' digital and clinical analytics cloud-based clinical data, SaaS OneClinical.

- NORITSU AMERICA bought **R&F Imaging Systems**, a sales and service company for medical imaging equipment.

- SANGAMO THERAPEUTICS and PFIZER's SB-525 – Data on 8 patients from the Phase I/II ALTA trial in hemophilia A, presented at ISTH, showed that 2 of the 4 patients at the highest dose (30 trillion vectors per kg) rapidly achieved normal and sustained levels of Factor VIII with the Factor as long as 24 weeks, with no bleeding events and no need for Factor treatment. The other 2 patients had Factor VIII activity kinetics consistent with the first two patients.

- SANOFI's isatuximab – The FDA accepted the BLA for this anti-CD38 for treating relapsed/refractory multiple myeloma.

- SKYHAWK THERAPEUTICS expanded its collaboration with **Biogen** to develop small molecule RNA splicing modifiers using Skyhawk's SkySTAR technology, to treat multiple sclerosis, spinal muscular atrophy, and other neurological disorders. Biogen got an exclusive license for the intellectual property for any drugs developed.

- SOL-GEL TECHNOLOGIES' Epsolay (microencapsulated benzoyl peroxide cream 5%) – The company reported positive results from two Phase III trials (SGT-54-01 and SGT-54-02) in papulopustular rosacea, significantly improving both co-primary endpoints – clear/almost clear on IGA and reduction in inflammatory lesion count at Week 12.

- TAKEDA's Adynovate (pegylated anti-hemophilic Factor, recombinant) – Updated results from the Phase IIIb/IV PROPEL trial were presented at ISTH, showing that using PK-guided dosing led to Factor VIII trough levels of 8%-12% in hemophilia A patients, with a reduction in average total annual bleed rate (ABR) and reduced average spontaneous joint ABR.

- TELEFLEX's UroLift – A 1,413-patient real-world, retrospective study, published in the *Journal of Endourology*, found that this implant significantly reduced urinary tract symptoms from benign prostatic hyperplasia at 2 years. Symptoms were significantly improved at all follow-up time points.

- TITAN PHARMACEUTICALS' Probuphine (buprenorphine implant) for opioid use disorder will be distributed (mostly but not exclusively in the U.S.) by CVS Health/CVS Caremark.

- TRANSENTERIX's AutoLap – The company is selling some of the rights to this image-based laparoscope positioning system to **Great Belief International**.

- TYME TECHNOLOGIES' racemetyrosine (SM-88) – Updated results on 38 of the 49 patients enrolled in the ongoing, open-label Phase II Tyme-88-PANC trial in advanced pancreatic cancer, presented at the ESMO World Congress on Gastrointestinal Cancer 2019 in Barcelona, Spain, showed a median survival of 6.4 months (vs. historic survival of 2-2.5 months).

- VIIV HEALTHCARE's Dovato (dolutegravir + lamivudine) – This 2-drug combination met the primary endpoint in the Phase III TANGO trial, showing non-inferiority to a 3-drug combination, Gilead Sciences' Vemlidy (tenofovir alafenamide), in suppressing the HIV virus over 48 weeks.

Animal health news

- ELANCO ANIMAL HEALTH – **Bayer** reportedly has approached Elanco for a possible deal to off-load its animal health unit.

Very early research news

- HIV – A mouse study, published in *Nature Communications*, found that, using a combination of CRISPR gene editing and a long-acting antiretroviral therapy, eliminated HIV (in the mice).

■ MERCK MSD's Cavatak – A 15-patient U.K. study, published in the journal ***Clinical Cancer Research***, suggests this therapeutic vaccine may have utility in bladder cancer.

NEWS IN BRIEF

AMGEN and NOVARTIS

■ **Aimovig (erenumab).** There was mixed news for this CGRP inhibitor for migraine treatment at the American Headache Society meeting. Among the numerous studies presented were:

- Sustained efficacy and long-term safety in the 4-year results of a 5-year, open-label extension study.
- A study of 375 patients prescribed Aimovig that found 72%-76% of patients did not have a response at Month 1, reinforcing the need to wait for Month 3 to determine efficacy.
- A 415-patient study of initial non-responders that found that by Month 3, 44% of the patients had responded, and by Month 6, 65% responded, again showing the drug should be taken at least 3 months and perhaps longer before deciding it doesn't work.
- A study that showed efficacy in allodynia.
- A study that showed combining Aimovig with Allergan's Botox (onabotulinumtoxinA) was more effective with the 140 mg dose than the 70 mg dose (-11.5 migraine days vs. -3.1 migraine days) at Day 60.
- Insurance coverage remains a problem. A study found that of 113,675 patients prescribed Aimovig in a 9-month period, ending January 31, 2019, only 35% had it covered by insurance.

■ **Umibecestat (CNP-520).** Two pivotal Phase II/IIII trials of this BACE1 inhibitor were terminated after an interim analysis found that Alzheimer's patients taking the drug had a ***worsening*** rate of cognitive decline. Banner Alzheimer's Institute also had been participating in the studies.

Duchenne muscular dystrophy (DMD)

A report on DMD drugs by the Institute for Clinical and Economic Review (ICER) used updated pricing estimates that are significantly higher and, no surprise, the therapies are even less cost-effective now. The report found:

- There isn't persuasive evidence that exon-skipping therapies improve outcomes that matter to patients.
- Both Emflaza (a corticosteroid) and Exondys 51 modestly increase dystrophin levels but the clinical significance of this is "uncertain."

ICER Analysis of Cost-Effectiveness of DMD Therapies (*based on a 40 kg patient*)

Measurement	Cost per mg	Original annual treatment cost	Updated annual treatment cost
Prednisone	$0.05	$550	$550
PTC Therapeutics' Emflaza (deflazacort)	$6.19	$62,900	$81,400
Sarepta Therapeutics' Exondys 51 (eteplirsen)	$16.00	$892,000	$1,002,000

- Exondys 51 would be over-priced even if it restored DMD patients to perfect health for an additional 40 years.
- Emflaza has greater benefits than prednisone, but it is too expensive in the U.S., where it is 50-times higher than in other countries.

Ebola update

■ Research by the Centers for Disease Control and Prevention (CDC), published in ***Lancet Infectious Diseases***, showed that two of the investigational Ebola therapies being tested in the Democratic Republic of the Congo – **Gilead Sciences' remdesivir** (GS-5734) and **Mapp Biopharmaceutical's ZMapp** – look very promising in laboratory studies.

■ **MERCK's rVSV-ZEBOV.** Data from the World Health Organization (WHO) showed that this vaccine has had a 97.5% efficacy rate vs. people not immunized.

INTRA-CELLULAR THERAPIES' lumateperone

Two Phase III trials in bipolar depression had mixed results with this atypical antipsychotic.

- **Study 404.** Lumateperone met the primary endpoint, showing a significant reduction in the MADRS score vs. placebo. Secondary endpoints also were met.
- **Study 401.** Lumateperone missed the primary endpoint (also reduction in MADRS score), which was blamed on a higher than expected placebo response (-20.7 points with 42 mg, -18.9 points with 28 mg, and -19.7 points with control).

LILLY's Emgality (galcanezumab-gnlm)

■ Post hoc analyses of three Phase III chronic and episodic migraine trials, presented at the American Headache Society meeting, showed this CGRP inhibitor:

- Significantly more patients had a reduction in disability vs. placebo on MIDAS – 20.3% vs. 13.9% of patients had little/no disability at Month 3 in the REGAIN trial.
- A pooled analysis of the EVOLVE-1 and EVOLVE-2 trials found that 66.1% of patients with moderate-to-very severe disability, shifted to little/no disability at Month 6 vs. placebo (44.0% vs. 26.5%).

- Emgality led to improvement in all 7 items of the MSQ-RFR.

- The results of the >20,000-people OVERCOME study of both migraines and people without migraine found that more needs to be done about awareness and under-standing of the disease.
  - Of the 2,000 people without migraine who were surveyed:
    - ✓ >40% thought migraineurs use the condition as an excuse to avoid work, family, or school commitments and/or exaggerate their symptoms.
    - ✓ 36% believed that miigraine attacks are caused by the person's own unhealthy behaviors.
    - ✓ 29% believe migraineurs make things difficult for their co-workers.
    - ✓ The more migraineurs they knew, the ***more*** negative their beliefs were about those with the disease.
  - Of the 8,844 patients with ≥4 migraine days/month, >60% sought care within the last 12 months, and 33.6% of these went to a hospital emergency room or urgent care clinic, and <5% of these patients were prescribe a migraine preventive medication.

MERCK MSD

- Diabetes. Researchers from the University of Utah, in collaboration with Merck Research Laboratories, reported in the journal ***Science*** that a mouse study found ceramides (a kind of fatty lipid) can reverse insulin resistance and fatty liver in mice. Now they are looking for drugs that do the same thing in Type 2 diabetes.

- **Keytruda (pembrolizumab).** Submitted six supplemental BLAs (sBLAs) to the FDA – for 400 mg (given in a 30-minute infusion) Q6W – in melanoma, Hodgkin's lymphoma, primary mediastinal large B-cell lymphoma, gastric cancer, hepatocellular carcinoma, and Merkel cell carcinoma. The PDUFA date is February 18, 2020.

NOVARTIS

- **Entresto (sacubitril + valsartan).** A research letter, published in ***JAMA Cardiology***, opined that the cost of this heart failure drug is a potential barrier to use by Medicare beneficiaries, even though it is covered by all Part D plans, pointing out that their annual cost for this drug can be $1,685. An accompanying editorial said doctors, broadly, should be more aware of out-of-pocket costs to patients for drugs.

- TNO-155. Novartis is partnering with **Mirati Therapeutics** to combine this SHP2 inhibitor with Mirati's MRTX-849 in advanced solid tumors with KRAS G12C mutations.

Peanut allergy

ICER issued its final report on peanut allergy therapies, and the conclusions were:

- Neither **Aimmune's AR-101** nor **DBV Technologies' Viaskin Peanut** is superior to strict peanut avoidance.
- AR-101 appears more effective than Viaskin Peanut but has more side effects.
- There is uncertainty about the long-term effects of either therapy.
- To be cost-effective, the price would have to be ≤$4,200/year for AR-101 and ≤$6,500 for Viaskin Peanut.
- Treatment with AR-101 results in a 0.75 incremental quality-adjusted life year (QALY) and a 0.26 QALY for Viaskin Peanut.
- Eligible patients that could be treated without exceeding ICER's budget impact threshold ($991 million) – 41% for AR-101 and 71% for Viaskin Peanut.

ROCHE/GENENTECH's Hemlibra (emicizumab-kxwh)

Data on this hemophilia A drug, presented at ISTH, included:

- A pooled analysis of data on 400 patients from four HAVEN trials, showing that >92% of patients had no treated spontaneous bleeds and >87% of patients had no treated joint bleeds after Week 25.
- Updated results from the HAVEN-3 and HAVEN-4 trials, showing that Hemlibra's improvement in quality of life was clinically meaningful vs. other Factor VIII treatment.
- An analysis of HAVEN trials which suggested that additional Factor treatment may not be needed for patients on Hemlibra who undergo minor surgery.
- An interim analysis of 88 patients from the Phase IIIb STASEY trial again showed the safety of Hemlibra in patients age ≥12 with Factor VIII inhibitors, with no cases of thrombotic microangiopathy or thrombotic events and no new safety signals.

TEVA's Ajovy (fremanezumab-vfrm)

Among the data presented at the American Headache Society meeting on this CGRP inhibitor for migraine prevention were:

- The results of the FOCUS trial, which found there were clinically meaningful responses to Ajovy in patients who had

had inadequate response to 2-4 classes of migraine prevention medications.

- The results of a web-based survey after a 1-year extension study, which found high patient satisfaction with Ajovy.

uniQure

The company reported updated data from two gene therapies in trials in hemophilia B, both of which were presented at ISTH:

- **AMT-061.** At 36 weeks, all 3 patients from the ongoing, open-label, single-dose, single-arm Phase IIb trial of this AAV5-based gene therapy – who had low levels of AAV5 antibodies at entry but were allowed in the trial anyway – had sustained increase in Factor IX activity
- **AMT-060**
  - Longer-term (3.5-year) follow-up on 10 patients who got this first-generation gene therapy had sustained increased in Factor IX activity and improvement in their disease state (less use of Factor IX replacement therapy and less decreased bleeding frequency).
  - All 5 patients in Cohort 2 continue to be free of routine Factor IX replacement therapy.

REGULATORY NEWS

Regulatory tidbits

- Contraceptives. The FDA released new draft guidance for determining efficacy and safety in clinical trials of hormonal contraceptives. Among the changes: broader age recommended (younger and older, both), includes obese women, not using a placebo control (so, open-label, single-arm trials would be all right).
- Drug ads. A federal judge stopped the Trump administration rule that would have required drug companies to put the monthly price of their drugs in television commercials if the list price was >$35/month. The judge said the administration did not have the regulatory authority to require that.
- Drug rebates. The Trump administration withdrew a drug cost reduction proposal that would have required rebates in Medicare and Medicaid to go to beneficiaries instead of insurers and pharmacy benefit managers (PBMs).
- Hospices. The Department of Health and Human Services' Office of Inspector General (OIG) released two reports which showed that from 2012-2016, 87% of hospices were cited for deficiencies, and 20% had problems serious enough to pose a health risk. CMS issued a statement saying that the Agency "has zero tolerance for abuse and mistreatment of any patient."
- IDEs. The FDA issued final guidance on use of investigational devices in live cases that are broadcast.
- Manufacturing. The FDA and the European Union have fully implemented a mutual recognition agreement for inspections of manufacturing sites for certain drugs, allowing the FDA to rely on EMA inspections and the EMA to rely on FDA inspections.
- Population PK. The FDA revised its 1999 draft guidance on the data and model requirements for population pharmacokinetics analyses submitted as part of new drug applications (NDAs) and biologic license applications (BLAs).
- Tariffs. The Office of the U.S. Trade Representative granted some U.S. companies – including some products by Medtronic and Varian Medical Systems – relief from the 25% import tariffs for Chinese products, and the exception was effective retroactively from July 6, 2018.

Acute flaccid myelitis (AFM)

The CDC still doesn't know what causes this polio-like illness, but in preparation for an expected uptick in late summer and early fall 2019, the CDC is urging clinicians to "help with early recognition…promote specimen collection for testing, and immediate reporting of suspected AFM cases to health departments."

So far in 2019 there have been 11 confirmed cases of AFM across 8 states.

According to CDC numbers for 2018:

- There were 233 confirmed cases in 41 states.
- 92% of confirmed cases had respiratory symptoms or fever.
- 42% of confirmed cases had upper limb involvement.
- The median time from limb weakness to hospitalization was 1 day
- The time from weakness to MRI was 2 days. MRI can distinguish AFM from other diseases characterized by weakness.
- Cases were reported to the CDC a median of 18 days from onset of limb weakness (range 18-36).

End-stage renal disease (ESRD)

President Trump signed an Executive Order aimed at improving care of ESRD patients. The three key targets are:

1. Reduce the number of patients that develop ESRD by 25% by 2030.
2. Have 80% of new dialysis patients on home dialysis or receiving a transplant by 2025 (it is 12% now).
3. Double the number of kidneys available for transplant by 2030.

FDA's Center for Drug Evaluation and Research (CDER)

In an interview with SVB Leerink analyst Geoffrey Porges, CDER director Janet Woodcock, MD, said:

- The FDA still prefers placebo-controlled trials, but understands the issues so is "supportive of non-inferiority and other trial protocols, such as dose comparisons and delayed start trials."
- The FDA really likes basket trials and remains committed to them.
- Trial failures are most often due to use of invalidated biomarker endpoints, post hoc analyses, and/or continuing development of drugs based on subgroup analyses of failed trials.
- She is frustrated with the handling of immuno-oncology studies.
- The focus on patient-reported outcomes is likely to change the endpoints the FDA will accept.
- The FDA is likely at least to keep up the pace of drug approvals, not slow them down.

FDA approvals/clearances

- ABBOTT's Alinity s System for screening blood and plasma was approved by the FDA.
- AZURITY PHARMACEUTICALS' Katerzia (amlodipine benzoate), an oral liquid suspension formulation of calcium channel blocker, was approved to treat hypertension in patients age ≥6.
- CENTERLINE BIOMEDICAL's Intra-Operative Positioning System, which provides 3D visualization during endovascular procedures by using electromagnetic tracking and anatomical mapping algorithms, was granted 510(k) clearance.
- CONTIPI MEDICAL's ProVate, a disposable, non-invasive device for treating women with pelvic organ prolapse, was approved.
- ICOTEC's VADERone, a pedicle screw system for use after minimally-invasive and open spine surgery, was granted 510(k) clearance.

FDA recalls/warnings

- ACLARIS THERAPEUTICS' Eskata (topical hydrogen peroxide) – The company received an untitled letter from the FDA's Office of Prescription Drug Promotion (OPDP) that cited a video for this treatment for seborrheic keratoses that OPDP said didn't have sufficient risk information and made misleading statements about the efficacy.
- AKORN received a warning letter about "inadequate" investigation of faulty batches, failure to exercise controls over data, and "poor aseptic behavior" at its plant in Somerset, NJ.
- ALEXION PHARMACEUTICALS' Ultomiris (ravulizumab) was approved by the European Commission to treat adults with paroxysmal nocturnal hemoglobinuria who are clinically stable after treatment with Soliris (eculizumab) for ≥6 months and who have clinical symptoms of high disease activity.
- BIOCON received a Form 483 for problems at its plant in Malaysia.
- HAMILTON MEDICAL's Hamilton-G5 Ventilators were recalled due to the potential for sporadic error messages, causing the ventilator to stop and enter "ambient state."
- MEDTRONIC's MiniMed 600-series insulin pumps (620G, 630G, 640G, and 670G) – The FDA warned (a Class II recall) patients that the keypad buttons on these devices can temporarily become "unresponsive" when air pressure changes quickly (e.g., during airplane takeoffs and landings).

European Regulatory News

- Anti-androgen drugs. The EMA's Pharmacovigilance Assessment Committee (PRAC) is reviewing drugs containing cyproterone (anti-androgens), looking at the risk of meningioma, after a French study suggested the risk though very low, may be increased in people on high doses for a long time.
- *Germany.* REGENERON PHARMACEUTICALS and SANOFI's Praluent (alirocumab) – A German court rule in favor of Amgen, finding that this PCSK9 inhibitor infringes on an Amgen patent and granted an injunction against sales of Praluent in Germany.
- ICAD's ProFound AI, an advanced artificial intelligence technology and solution for 2D mammography for use in detecting breast cancer in women with dense or calcified breasts, was granted a CE Mark.

- NEUROLIEF's Relivion, a non-invasive neuromodulation digital therapy for treating migraines, was granted a CE Mark.

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

- ABBVIE and BOEHRINGER INGELHEIM's Skyrizi (risankizumab) – NICE recommended use of this IL-23 inhibitor to treat severe plaque psoriasis.
- ALNYLAM's Onpattro (patisiran) – NICE reversed its earlier decision and is now recommending use of this RNAi therapeutic to treat hereditary transthyretin-mediated amyloidosis (hATTR amyloidosis).
- ASTRAZENECA's Farxiga (dapagliflozin) – NICE recommended use of this SGLT2 inhibitor to treat Type 1 diabetes.

Regulatory news from other countries

- *China.*

- EISAI PHARMACEUTICAL is partnering with Dundee University on development of new oncology drugs. Eisai get the marketing rights to PROTACs, drugs that use a cell's natural disposal system to get rid of proteins that cause cancer.
- FOSUN PHARMACEUTICAL bought GlaxoSmithKline's plant in Suzhou, China, and the rights to make generic Epivir (lamivudine) to treat hepatitis B.

- *Japan.* FORTY SEVEN's 5F9 – The company signed a regional license agreement with **Ono Pharmaceutical** for development, manufacturing, and commercialization of this anti-CD47 for all therapeutic uses in Japan, South Korea, Taiwan, and some other countries in Southeast Asia.

2019 FDA Advisory Committees and Other Regulatory Dates of Interest (*items in RED are new since last week*)		
Date	**Topic**	**Committee/Event**
July 15-16	Discussion of ***in vitro* diagnostics**	FDA public workshop
July 16	Discussion of alternative approaches in clinical investigations of **new animal drugs**	FDA public workshop by the Center for Veterinary Medicine
July 17	Second of 3 public meetings on electronic submission of **adverse event reports** to FAERS	FDA public meeting
July 19	Real-world data in oncology	FDA-AACR workshop
July 23	**Biomarkers of neurotoxicity**	FDA workshop
July 25	**Boehringer Ingelheim's Ofev** (nintedanib) – expanded use to treat systemic sclerosis-associated interstitial lung disease	FDA's Arthritis Advisory Committee
July 26	Endpoints for drug development in **heart failure**	FDA public meeting
July 29-30	**Topical drug development** – evolution of science and regulatory policy	FDA public workshop
July 31	**Intra-Cellular Therapies' lumateperone** for schizophrenia	FDA's Psychopharmacologic Drugs Advisory Committee
August 3	**Daiichi Sankyo's pexidartinib** for treatment of tenosynovial giant cell tumor (TGCT)	PDUFA date
August 7	**Gilead Sciences' Descovy** (emtricitabine + tenofovir alafenamide) for PrEP	FDA's Antimicrobial Drugs Advisory Committee
August 8	Discussion of development of **antiviral drugs** to treat adenoviral infection in immunocompromised patients	FDA public workshop
August 12	Discussion of individualized **drug dosing** in the real-world	FDA public workshop
August 14	**Galt Pharmaceuticals' Orphengesic Forte** (orphenadrine citrate + caffeine + aspirin), a non-opioid painkiller	PDUFA date
August 18	**Roche's entrectinib** for NTRK fusion-positive solid tumors and ROS1+ metastatic non-small cell lung cancer (NSCLC)	PDUFA date
August 22	Final guidance on marketing clearance of **diagnostic ultrasound systems and transducers**	FDA webinar
August 29	**Nektar Therapeutics/Inheris Biopharma's NKTR-181** for low back pain	PDUFA date *Extended by the FDA from May 28*
September 3	**Celgene's fedratinib**, a JAK2 inhibitor for myelofibrosis	PDUFA date
Sept. 9-10	**Scientific computing**	FDA symposium
September 10	**Xeris Pharmaceuticals' Gvoke** (liquid glucagon autoinjection) for severe hypoglycemia	PDUFA date *Extended by the FDA from June 10*
September 10	Discussion of medical device **cybersecurity**	FDA's Patient Engagement Advisory Committee
Sept. 11-12	FDA **Science Forum**	FDA forum
September 13	**Aimmune Therapeutics' AR-101** for peanut allergy risk reduction	FDA's Allergenic Products Advisory Committee
September 17	Standards for future **opioid therapy approvals**	FDA public meeting
September 18	Implementing the FDA's **Predictive Toxicology Roadmap** – update	FDA public workshop
Sept. 24-26	**Regulatory science**	FDA global summit ***in Italy***
September 26	**Johnson & Johnson/Janssen's Darzalex** (daratumumab) in combination with VTD to treat multiple myeloma	PDUFA date
September 27	**Intra-Cellular Therapies' lumateperone** for schizophrenia	PDUFA date
September 28	**Amarin's Vascepa** (icosapent ethyl) – expanded approval to reduce cardiovascular risk in statin-managed patients with high triglycerides	PDUFA date
October 8	**Partners in Progress 2019:** Cancer patient advocates and FDA	FDA public workshop
October 19	**Alexion Pharmaceuticals' Ultomiris** (ravulizumab-cwvz) for treating atypical hemolytic uremic syndrome	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

2019 FDA Advisory Committees and Other Regulatory Dates of Interest – continued (*items in RED are new since last week*)		
Date	**Topic**	**Committee/Event**
November 2	**RedHill Biopharma's Talicia** (RHB-105) to treat *H. pylori* infection	PDUFA date
November 4	**Roche's Xofluza** (baloxavir marboxil), expanded use as a single-dose treatment for patients at high risk of flu complications	PDUFA date
November 4	How many doses of a **DNA Reactive (Ames+) drug** can be safely administered to healthy subjects	FDA workshhop
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
2020 FDA Advisory Committees and Other Regulatory Meetings and Events		
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 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
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**, an anti-CD38 for relapsed/refractory multiple myeloma	PDUFA date