TRENDS-in-MEDICINE

June 17, 2012

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
772-334-7409
Fax 772-334-0856
www.trends-in-medicine.com
TrendsInMedicine@aol.com

NOTE: Subscribe to ***Trends-in-Medicine*** for a report on **Ophthotech's Fovista** for wet age-related macular degeneration (AMD) and for full coverage of the FDA's Circulatory System Devices Advisory Committee meeting on an expanded indication for **Edwards Lifesciences' Sapien** percutaneous aortic valve to include some operable patients.

SHORT TAKES

- **AMGEN's Sensipar (cinacalcet)** missed the primary endpoint in a Phase III trial testing whether the drug could reduce mortality and heart failure in chronic kidney disease patients on dialysis.
- **AMPIO PHARMACEUTICALS' Optina (danazol) –** The company reported that a 32-patient study in diabetic macular edema was positive, with Optina significantly more effective than placebo, regardless of the patient's body mass index (BMI). The company plans a pre-IND meeting with the FDA in July 2012.
- **ASTRAZENECA's Seroquel (quetiapine) –** The Pentagon removed this antipsychotic, which has been used to treat post-traumatic stress disorder (PTSD), from its approved formulary list.
- **AVANIR PHARMACEUTICALS' AVP-923 –** The FDA gave the company the green light for a Phase II study of AVP-923 as a treatment for agitation and other behavioral disturbance in Alzheimer's disease patients, and the company hopes to start the proof-of-concept trial in 3Q12.
- **BOSTON SCIENTIFIC** completed its acquisition of **Cameron Health**, which has a sub-cutaneous ICD under review by the FDA.
- **CELLCEUTIX's Prurisol (KM-133) –** The company said it secured Section 505(b)(2) status from the FDA for this psoriasis treatment, allowing it to go to Phase II development.
- **CSL BEHRING's rIX-FP**, a recombinant fusion protein linking coagulation Factor IX with recombinant albumin to prevent and treat bleeding episodes in patients with hemophilia B, was granted orphan drug status by the FDA.
- **Electrophysiology –** Cardiostim and the European Society of Cardiology/European Heart Rhythm Association's EUROPACE will hold their annual meetings jointly for four years, starting in June 2014.
- **FIBROCELL SCIENCE** is selling its majority stake in **Agera Laboratories**, a skin-care company, to **Rohto Pharmaceutical Co.**

- **GENZYME's Lemtrada (alemtuzumab)** was submitted to the FDA and to the European Medicines Agency (EMA) to treat multiple sclerosis.

- **GILEAD SCIENCES' Truvada PrEP** – The company said the FDA has extended its review of this HIV therapy to help prevent the transmission of HIV to healthy people. The new PDUFA date is September 14, 2012.

- **GLAXOSMITHKLINE** is buying the marketing rights for **Basilea Pharmaceutica AG's Toctino** (alitretinoin), a hand eczema drug, which will be handled by GSK's **Stiefel** unit.

- **JAK inhibitors** – A study published in ***Cancer Discovery***, a journal of the American Association for Cancer Research, found that a substantial proportion of NK/T-cell lymphomas – an aggressive lymphoma that is prevalent in Asia, where it accounts for nearly 50% of T-cell lymphomas in some areas – harbor JAK3 mutations, and they suggested that patients with these lymphomas might benefit from treatment with a JAK inhibitor.

- **MEDTRONIC's MiniMed** – The company has submitted a premarket application (PMA) for this continuous glucose monitoring device with an automatic low glucose suspension feature.

- **RAPTOR PHARMACEUTICAL's RP-103 (delayed-release cysteamine)** – The company said the FDA accepted its filing of this BID treatment for nephropathic cystinosis.

- **RECOR MEDICAL's Paradise** – The company reported 6–month follow-up data on eight patients with resistant hypertension treated with this renal denervation system. The data showed that systolic blood pressure was reduced by ~33 mmHg. This system differs from other renal denervation systems because it uses ultrasound instead of radio-frequency energy.

- **ST. JUDE MEDICAL's Durata** – The hope was that the implantable cardioverter defibrillator (ICD) lead problems with St. Jude's **Riata** would not occur with the newer Durata lead, but the FDA has had at least one voluntary report from a physician of an externalized wire with Durata – the same issue that plagued Riata. *This could be a one-time event or the tip of a new iceberg.*

- **Statins** – A study published in the ***Archives of Internal Medicine*** linked statins to reduced energy levels. The study examined energy levels and fatigue in 1,016 patients and found that patients on either **Merck's Zocor** (simvastatin) or **Bristol-Myers Squibb's Pravachol** (pravastatin) were much more likely to have energy loss vs. placebo, but the negative effect appeared worse with Zocor.

- **Thiazolidinediones (TZDs)** – A study published in the ***Archives of Internal Medicine*** found another problem with this beleaguered class of oral Type 2 diabetes drugs – i.e., **GlaxoSmithKline's Avandia** (rosiglitazone) and **Takeda's Actos** (pioglitazone) – reporting they may increase the risk of diabetic macular edema (DME).

- **TOKAI PHARMACEUTICALS' galeterone (TOK-001)** – The FDA granted fast track status to this investigational treatment for metastatic castration-resistant prostate cancer (mCRPC).

NEWS IN BRIEF

Atrial fibrillation – new risk scoring system prompts new guidelines

Goodbye, CHADS2. Hello, CHA2DS2-VASc and HAS-BLED. Researchers at Cardiostim in Nice, France, said these two new scores together are much better at predicting stroke risk in AFib patients.

The researchers said the CHA2DS2-VASc score outperformed other stroke risk scores, including CHADS2, in identifying very low-risk patients who do not need any antithrombotic therapy. And in some of the validations, the CHA2DS2-VASc score outperformed CHADS2 in predicting those who will get a subsequent stroke.

In the past, patients with a CHADS2 score of 0 were considered to be at low risk of stroke. But when these patients were rescored using CHA2DS2-VASc, the patients thought to be low risk had stroke rates from 0.8%-3.2% per year if not anticoagulated. A net clinical benefit analysis balancing ischemic stroke against intracranial bleeding based on a dataset of more than 180,000 patients with AFib in Sweden found that patients with a CHA2DS2-VASc score >1 had a positive net clinical benefit when they were anticoagulated.

The findings were irrespective of bleeding risk, which was assessed by the HAS-BLED score, which researchers said outperforms other scores (both new and old) in predicting bleeding risk.

An update to European Society of Cardiology (ESC) guidelines for AFib is expected to be launched at the ESC meeting in Munich in August 2012.

Breast cancer – gene pattern tied to chemo resistance

A Vanderbilt-led study published in ***Nature Medicine*** identified a gene pattern that may explain why chemotherapy

prior to surgery isn't effective against some tumors and suggests new therapy options for patients with specific subtypes of breast cancer. Only ~30% of breast cancer patients have a pathological complete response (pCR) with chemotherapy prior to surgery.

The researchers found that low concentrations of dual-specificity protein phosphatase 4 (DUSP4) is strongly correlated with faster tumor cell growth following neoadjuvant chemotherapy. Low DUSP4 was also correlated with basal-like breast cancer (BLBC). When DUSP4 was present, chemotherapy was effective against the cancer, but when it was deleted, there was a much lower response to chemotherapy. Researchers said this suggests that DUSP4 expression in residual resected breast tumors is a potential biomarker for drug resistance and a high likelihood of tumor recurrence. They also hypothesized that DUSP4 may be a potential biomarker for response to MEK inhibitors.

This might breathe new life into **Array BioPharma** and **AstraZeneca**'s selumetinib (AZD-6244), which missed the primary endpoint in an 87-patient Phase II trial in KRAS mutant non-small cell lung cancer. The researchers speculated that docetaxel + selumetinib might prove effective in patients with DUSP-deficient basal-like breast cancer.

EDWARDS LIFESCIENCES

- **Sapien THV – positive FDA advisory committee.** The FDA's Circulatory System Devices Advisory Committee voted overwhelmingly to recommend that the label for this transcatheter aortic valve replacement system be expanded to include ***operable*** patients who have ≥15% risk of mortality for open heart aortic valve replacement (AVR). It is already approved for ***inoperable*** patients. The panel voted 10-2 that the valve is safe, 12-0 that it is effective, and 11-0 (with 1 abstention) that the benefits outweigh the risks.
- **GLX platform –** The FDA issued a conditional investigational device exemption approval so the company can start a 500-700-patient safety and efficacy study of this platform for tissue treatment with its **Carpentier-Edwards Perimount Magna Ease Aortic Valve**, a surgical tissue valve.

INCYTE's baricitinib (INCB-028050) – positive Phase IIb results

A Phase IIb trial reported at the European League Against Rheumatism (EULAR) found that the two highest doses of this oral JAK inhibitor were significantly more effective than placebo in rheumatoid arthritis patients on methotrexate, and the benefits were seen as early as Week 2. Adverse events included decreases in hemoglobin and white cells, and "small" increases in serum creatinine, LDL, and HDL.

Phase IIb Results with Baricitinib in RA

Measurement	Baricitinib 4 mg	Baricitinib 8 mg	Placebo
ACR20 improvement	75% (p<0.001)	78% (p<0.001)	41%
DAS28 <2.6	37% (p<0.001)	22% (p<0.001)	4%
ACR50	35% (p<0.001)	40% (p<0.001)	10%
ACR70	23% (p<0.001)	20% (p<0.001)	2%
HAQD ≥minimally clinically important	60%	67%	41%
Adverse events			
Infections	14%	14%	12%
Serious adverse events	0 *	1 patient	2 patients
Hemoglobin	– 0.15 g/dL	– 0.57 g/dL	– 0.14 g/dL
White cell counts	Down 8%	Down 22%	Down 4%

* 3 patients on 2 mg had serious adverse events

JOHNSON & JOHNSON

- The acquisition of **Synthes** was approved by the Federal Trade Commission (FTC), but J&J is required to sell its wrist fracture system, DVR, to **Biomet** because DVR and the Synthes wrist fracture system together would account for 70% of the U.S. market for those devices.
- **Zytiga (abiraterone).** The company submitted a supplemental New Drug Application (sNDA) to the FDA – and a type II variation to the EMA – for use of Zytiga with prednisone in men with mCRPC who are asymptomatic or mildly symptomatic after failure of androgen deprivation therapy and before chemotherapy.

REGULATORY NEWS

FDA keeps same leadership at OSE

Gerald Dal Pan, MD, MHS, was named the permanent director of the Office of Surveillance and Epidemiology (OSE) in the Center for Drug Evaluation and Research (CDER). Dr. Dal Pan, who joined the FDA in 2000 as a medical officer in the Division of Anesthetic Critical Care and Addiction Drug Products, ran OSE from 2005 to 2011, when it was reorganized. He has been acting director of the reorganized OSE since then. In the last five years, the OSE staff has more than doubled, from 116 to 250. Dr. Dal Pan is board-certified in internal medicine and neurology and is an epidemiologist.

FDA wants warning on drugs with albumin

The FDA has asked for public comment on its draft proposal to put a warning about the "extremely remote risk" of the transmission of viral disease on plasma-derived albumin and cultured drugs that contain albumin. The draft guidance also proposed measures to prevent the spread of variant Creutzfeldt-Jakob disease through blood and blood products. The comment period is open through September 10, 2012.

FDA approvals/clearances

- **ELEKTA's Agility**, a beam-shaping device used with linear accelerators to enable surgeons to accurately target radiation doses to tumor margins and limit the dose to healthy organs or tissue, received 510(k) clearance.
- **ETVIEW MEDICAL's Viva EB** endobronchial blocker, designed to help thoracic surgeons during lung isolation procedures, received 510(k) clearance.
- **GLAXOSMITHKLINE's MenHibrix**, a combination meningitis and *Haemophilus influenzae* type b (Hib) vaccine, was approved for administration to infants and children ages 6 weeks through 18 months.
- **KINETIC CONCEPTS' Vacuum Assisted Closure (VAC Therapy System)**, a wound-care device, was cleared for management of closed surgical incisions.
- **MEVION MEDICAL SYSTEMS' MEVION S250 Proton Therapy System**, which delivers intense proton beams to target lesions, tumors, and other conditions, was cleared.
- **SIEMENS**
  - **Somatom Perspective**, a 128-slice CT scanner aimed at critical access hospitals, community hospitals, and outpatient facilities, was cleared.
  - **syngo.PET** amyloid plaque software, which helps Siemens Biograph mCT PET/CT scans quantify beta-amyloid plaque buildup, was approved.
- **TOSHIBA's VeloCT** console upgrade was cleared.

FDA recalls/warnings

- **ALERE's Triage BNP, Triage D-dimer, and Triage cardiology panel** – Hundreds of thousands of these tests used to detect heart attacks and to identify drugs in a patient's blood were recalled for quality control flaws.
- **FRESENIUS MEDICAL CARE** – The FDA is investigating whether the nation's largest dialysis center operator violated federal regulations by failing to inform patients of a potentially lethal risk connected to its **GranuFlo** device. In November 2011, Fresenius sent an internal memo to doctors at its dialysis centers, warning them that failure to properly use GranuFlo appeared to be contributing to a sharp increase in the risk of patients dying from sudden cardiac arrest.

  However, the FDA said Fresenius did not immediately warn ***other*** dialysis centers about the device. In fact, Fresenius reportedly didn't notify competitors until March 2012 when questioned by the FDA about it.
- **SIGMA's Spectrum Infusion Pumps** – A Class I recall of pumps manufactured before November 1, 2010, was initiated because they may fail suddenly, causing inaccurate flow that could include over-infusion resulting in serious injury or death.

European regulatory actions

- **DEXCOM's Dexcom G4**, a fourth-generation continuous glucose monitor (CGM), received a CE Mark.
- **NEUROTECH's ADNS-300**, a vagus nerve stimulator for epilepsy patients who don't respond to anti-epileptic drugs and are not suitable for brain surgery, received a CE Mark.

U.K.'s National Institute for Health and Clinical Excellence (NICE) news

- **AMGEN's Xgeva (denosumab)** – NICE changed its mind and no longer believes this treatment for bone metastases is cost-effective for prostate cancer patients. In March 2012, NICE recommended Xgeva for breast and prostate cancer patients with bone mets, but it said new data suggest it is not cost-effective compared to newer bisphosphonates.
- **ROCHE's Zelboraf (vemurafenib), a melanoma therapy** – Despite Roche's offer to cut the price, NICE issued a preliminary rejection, saying the longer-term effect on survival was uncertain because of crossover in the pivotal trial, making it impossible to determine cost-effectiveness.

Regulatory news from other countries

- ***Canada:*** **ABIOMED's Impella cVAD**, a percutaneous circulatory support device, was cleared by Health Canada.
- ***Japan:*** **SANOFI's Lyxumia (lixisenatide)**, a GLP-1 receptor agonist, was submitted to treat Type 2 diabetes.
- ***Korea:*** **MAZOR ROBOTICS' Renaissance System**, a surgical robot designed to replace the company's **Spine-Assist System**, was approved by the Korean Food and Drug Administration.
- ***New Zealand:*** **OSIRIS THERAPEUTICS' Prochymal**, a stem-cell therapy that uses healthy donor stem cells to treat children with acute graft-vs.-host disease, was approved.

Upcoming FDA Advisory Committees and Other Regulatory Meetings of Interest (*items in RED are new since last week*)		
Date	**Topic**	**Committee/Event**
	June 2012	
June 20	**Onyx Pharmaceuticals' carfilzomib**, a treatment for relapsed and refractory multiple myeloma	FDA's Oncologic Drugs Advisory Committee (ODAC)
June 21	**Dune Medical Devices' MarginProbe System**, which uses electromagnetic waves to characterize human tissue and provides intraoperative information on a malignancy of the surface of *ex vivo* lumpectomy specimens	FDA's General and Plastic Surgery Devices Advisory Committee
June 21	**Repligen's RG-1068**, an imaging agent to help identify abnormalities in pancreatic ducts	PDUFA date
June 25	**QRxPharma's MoxDuo** (morphine + oxycodone) for pain	PDUFA date
June 27	**Arena Pharmaceuticals and Eisai's Lorqess** (lorcaserin) for obesity	PDUFA date
June 27	**Onyx Pharmaceuticals' carfilzomib**, a treatment for relapsed and refractory multiple myeloma	PDUFA date
June 27-28	Risk:benefit of **metal-on-metal hip replacement** and **resurfacing**	FDA's Orthopaedic and Rehabilitation Devices Advisory Committee
June 28	**Bristol-Myers Squibb's Eliquis** (apixaban), an anticoagulant for the prevention of stroke in Afib	PDUFA date
June 29	**Johnson & Johnson's Xarelto** (rivaroxaban) for acute coronary syndrome	PDUFA date
June 29	**Astellas Pharma's Betanis** (mirabegron) to treat overactive bladder	PDUFA date
	July 2012	
July 17	**Vivus' Qnexa** (phentermine + topiramate) for weight loss	PDUFA date (extended from April 17)
July 24	**GlaxoSmithKline's Tykerb** (lapatinib) **+ Roche's Herceptin** (trastuzumab), supplemental indication for HER2+ metastatic breast cancer	FDA's Oncologic Drugs Advisory Committee (ODAC)
July 25	Discussion of presurgical identification of clear-cell carcinoma of the kidney using an imaging test	FDA's Oncologic Drugs Advisory Committee (ODAC)
July 26	**Amarin's AMR-101** (omega-3 fish oil EPA) to treat hypertriglyceridemia	PDUFA date
July 26	**Horizon Pharma's Lodotra** (low-dose prednisone) for rheumatoid arthritis	PDUFA date
July 27	**Onyx Pharmaceuticals' carfilzomib** for multiple myeloma	PDUFA date
July 27	**Salix Pharmaceuticals and Progenics Pharmaceuticals' Relistor** (subcutaneous methylnaltrexone bromide) for chronic non-cancer pain	PDUFA date
July 30	**Regeneron's Arcalyst** (rilonacept) for gout	PDUFA date
July 30	**Almirall and Forest Laboratories' aclidinium** inhaled therapy for chronic obstructive pulmonary disease (COPD)	PDUFA date
	August 2012	
August 4	**Regeneron Pharmaceuticals** and **Sanofi's Zaltrap** (aflibercept) for colon cancer	PDUFA date
August 12	**Talon Therapeutics' Marqibo** (vincristine sulfate liposomes injection) for Philadelphia chromosome-negative acute lymphoblastic leukemia (ALL)	PDUFA date (extended from May 13)
August 21	**Pfizer's tofacitinib**, an oral JAK2 inhibitor for rheumatoid arthritis	PDUFA date
August 27	**Gilead Sciences' Quad** (emtricitabine+tenofovir+elvitegravir+cobicistat) for HIV	PDUFA date

Upcoming FDA Advisory Committees and Other Regulatory Meetings of Interest (*items in RED are new since last week*)		
Date	**Topic**	**Committee/Event**
	Other 2012	
September tba	**Vivus' Qnexa** (topiramate + phentermine) for obesity	EMA oral hearing
September 5	**Salix Pharmaceuticals' Provir** (crofelemer) for HIV-related diarrhea	PDUFA date (extended from June 5)
September 8	**Ironwood Pharmaceuticals and Forest Laboratories' linaclotide** for irritable bowel syndrome	PDUFA date
September 10	**Navidea Biopharmaceuticals' Lymphoseek**, a radioactive agent for tracing lymph nodes in cancer patients	PDUFA date (extended from June 10)
September 14	**Gilead Sciences' Truvada PrEP** HIV therapy to help prevent the transmission of HIV to healthy people	***New*** PDUFA date (extended from June 15)
September 23	**Regeneron's Eylea** (aflibercept) for central retinal vein occlusion (CRVO)	PDUFA date
October 21	**Impax Laboratories' IPX-066** for Parkinson's disease	PDUFA date
October 29	**Cornerstone Therapeutics' CRTX-080** to treat hyponatremia	PDUFA date
October 29	**Novo Nordisk's Degludec and DegludecPlus** (human recombinant basal insulin)	PDUFA date (extended from July 29)
	2013	
January 29	**Sanofi/Genzyme and Isis Pharmaceuticals' Kynamro** (mipromersen) for homozygous familiar hypercholesterolemia	PDUFA date