TRENDS-in-MEDICINE

November 28, 2010

by Lynne Peterson

Quick Takes

…Highlights from this week's news affecting drugs and devices in development…

SHORT TAKES

- **ABBOTT LABORATORIES' atrasentan –** The company reported that atrasentan met the primary endpoint in an 89-patient Phase II trial in chronic kidney disease (CKD), reducing albuminuria vs. placebo.
- **Acute kidney injury –** The National Institutes of Health will hold a workshop on how to do clinical trials for acute kidney injury on December 2 and 3, 2010, in Bethesda MD. This will include a session on biomarkers.
- **ADVANCED CELL TECHNOLOGY** received FDA permission to begin a clinical trial of its embryonic stem cell-based treatment in patients with Stargardt disease, a rare genetic disorder that impairs central vision and can lead to blindness. The company said it plans to start the 12-patient study in early 2011.
- **APRICUS BIOSCIENCES' PrevOnco (lansoprazole delivered with NexACT technology) –** The company signed a Special Protocol Assessment (SPA) with the FDA approval and will begin a pivotal, one-year, ~218-patient Phase III trial of this drug for advanced, inoperable hepatocellular carcinoma refractory to Bayer/Onyx's Nexavar (sorafenib). PrevOnco already has orphan drug status.
- **ASTRAZENECA** is considering a spin-off of its Astra Tech division, which develops, manufactures, and markets dental implants and urology and surgical devices.
- **Biosimilars –** European regulators set new guidelines for development of biosimilar monoclonal antibodies, but they are still secret. The European Medicines Agency (EMA) hasn't published the details yet, but a document is expected to be posted on the EMA website "shortly," which is likely to mean a few weeks.
- **Blood supply –** The FDA's Blood Products Advisory Committee will discuss blood safety issues, including the risk of dengue virus infection in blood donors and murine leukemia virus-related human retroviruses, at a December 14-15 meeting.
- **BRISTOL-MYERS SQUIBB's Yervoy (ipilimumab) –** The FDA has cancelled the December 2, 2010, Oncologic Drugs Advisory Committee (ODAC) meeting on this treatment for advanced melanoma and will reschedule it after reviewing "additional data" submitted by the company.
- **Electroconvulsive therapy devices –** The FDA's Neurological Devices Advisory Committee will meet on January 27-28, 2011, to discuss possibly reclassifying these devices.

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- **HELIX BIOPHARMA's topical interferon alpha-2b –** The FDA put a clinical hold on a Phase II trial of this preventive therapy for precancerous, low-grade cervical lesions, asking for additional data on the drug's stability.
- **HOLOGIC's Selenia Dimensions**, a 3-D mammography system, got an approvable letter from the FDA. The hold-up is FDA review and inspection of the company's manufacturing facility, methods, and controls.
- **JOHNSON & JOHNSON's** latest recall is 800,000 bottles of children's Benadryl and Motrin, which the company blamed on – guess what – manufacturing problems.
- **PIERRE FABRE's Javlor (vinflunine) –** This bladder cancer treatment failed to win approval by the U.K.'s National Institute for Health and Clinical Excellence (NICE), which said that it is too expensive and that the company "didn't provide conclusive evidence of the drug's clinical effectiveness."
- **ROCHE's Herceptin (trastuzumab) –** The U.K.'s NICE has recommended Herceptin be made routinely available to certain patients with metastatic gastric cancer.
- **SONOVA HOLDING's HiRes 90K –** The company plans to pull this cochlear implant, developed by its Advanced Bionics unit, off the market after receiving reports of adverse events from two patients. Sonova said its division "is working closely with the FDA to identify the problem and institute changes to the product to ensure that the HiRes 90K has the highest quality for patients who use the device."
- **VERTEX's telaprevir** has been submitted to the FDA for approval to treat hepatitis C. The company is asking for priority review.

NEWS IN BRIEF

Alzheimer's disease – prevention trial outlook

The EMA held a meeting recently, with the FDA participating by video link, on proposals for the first therapeutic treatment and prevention trials for families with autosomal-dominant Alzheimer's disease (AD). According to a report by ***Alzheimer's Research Forum News*** (**www.alzforum.org/new/detail.asp?id=2612**) the meeting was a response to a request by scientists from the Dominantly Inherited Alzheimer Network (DIAN), which has enrolled 125 of a planned 400 members of several dozen families with autosomal-dominant AD into a comprehensive six-year biomarker study of preclinical AD. DIAN researchers want to offer study participants a treatment trial.

While EMA and FDA officials didn't make any commitments at the meeting, they did provide some insight into their thinking on several key issues, including:

- **The outcome measures.** For a trial in people with pre-symptomatic AD, Dr. Russell Katz, director of the FDA's Division of Neurology Products, said the FDA might accept a relevant biomarker that has a lot of congruent evidence, even if it is not yet formally validated, combined with a measure of subtle cognitive deficits.
- **Number of trials.** Regulators indicated that one successful trial might suffice for approval.
- **Accelerated approval.** Dr. Katz said this is not yet an option with the FDA.
- **Orphan drug.** Regulators indicated this is unlikely. Dr. Katz suggested an alternative: seeking approval for a specific subset of AD patients.
- **Placebo control.** Patients are reluctant to enter these trials in AD, but both the EMA and the FDA insisted on placebo controls.

ASPIRE PRODUCTS' Expiratory Muscle Strength Training (EMST) device – new therapy for PD

A randomized, sham-controlled, 4-week, 60-patient study published in the journal ***Neurology*** found that this home-based, hand-held device that strengthens the muscles involved in swallowing can address a serious symptom of Parkinson's disease (PD). University of Florida researchers reported that one-third of the healthy volunteers who used the device improved their ability to swallow vs. 14% of control patients. This is important because the most common cause of death in PD is pneumonia caused by inhaling foreign material, such as food, during swallowing. PD patients also often have difficulty sensing material in their airways and coughing hard enough to expel it. EMST also may have utility in multiple sclerosis.

BIOGEN IDEC/ELAN's Tysabri (natalizumab) – more PML, rate rising

Five more cases of progressive multifocal leukoencephalopathy (PML) were reported in multiple sclerosis (MS) patients treated with Tysabri, bringing the total to 75. The company now estimates the rate at 0.96 per 1,000. When the first few cases of PML occurred, Tysabri was taken off the market. The FDA's decision to allow Tysabri back onto the market was based on the rate being <1 per 1,000 patients. For patients who have taken Tysabri for ≥18 months, the rate is currently 1.71 per 1,000 patients. The FDA currently has the safety of Tysabri under review, but there is no date for any FDA decision.

BOSTON SCIENTIFIC – buying percutaneous valve company

Boston Scientific is buying Sadra Medical, which is developing the Lotus repositionable and retrievable transcatheter aortic valve. Boston Scientific is paying $450 million ($225 million upfront and up to $225 million more when certain milestones are met) for a basically unproven technology.

Sadra has completed a 12-patient feasibility study in Germany, using an 18 Fr delivery system. Three of those patients were not implanted due to procedural deaths in two patients. Of the nine patients who actually got a Lotus valve, one died at 30 days, one had a major stroke, and one had an MI. Sadra expects to start a registration trial in Europe in 1Q11 with its 23 mm valve and in 3Q11 with its 27 mm valve. Sadra is hoping for a CE Mark in 2012. It is unlikely a U.S. pivotal trial could start before a CE Mark is obtained.

In comparison, Medtronic paid $700 million for CoreValve, which has a successful valve on the European market and just began a pivotal U.S. trial. Boston Scientific already had a stake in Sadra, and, according to former CEO James Tobin, Boston Scientific was helping Sadra resolve "some delivery system issues."

GENERAL ELECTRIC and TOSHIBA – CT scanners exonerated

The FDA said GE Healthcare and Toshiba America Medical Systems are ***not*** to blame for the overexposure of hundreds of patients to CT-induced radiation resulting from brain perfusion scans. The FDA investigated GE and Toshiba CT scanners at six hospitals (385 patients) and found no violations of either laws or regulations by the two companies. According to the FDA, both GE's and Toshiba's protocols provided "reasonable and appropriate image quality and dose."

The FDA also sent a letter to the Medical Imaging Technology Alliance (MITA) outlining steps that manufacturers could take to improve safety and lower the risk of future patients' overexposure to radiation, including:

- More information and training to purchasers on safe and effective parameters for different scans.
- Instruction on the proper use of automated exposure controls and when manual parameter settings would be better.
- An alert system that automatically informs CT operators when parameters are set at levels that would cause injury to a patient.
- Creation of a manual with CT dose-related information.
- Specific manufacturer recommendations for scanning parameters and settings for all scanning sequences as well as estimates and explanations of dose values for each scan.

Insurance firms – ordered to spend more on patient care

As of January 1, 2011, insurers covering large groups must spend at least 85% of every dollar on medical care or "activities that improve healthcare quality." For small group and individual plans, it is 80%. That means only 15%-20% of spending can go for administrative items such as salaries, bonuses, and marketing.

Department of Health and Human Services (HHS) Secretary Kathleen Sebelius said some insurers spend <60% of revenue on medical care, "While some administrative costs are certainly necessary, we believe that they have gotten out of hand. And that's going to change in 2011."

However, what constitutes spending on medical care was defined to include: spending to lower infection and mortality rates, reduce hospital readmissions, and reduce medical errors; spending to create medical home models; and spending for certain investments in health information technology.

JOHNSON & JOHNSON/CORDIS's Nevo – delayed

Enrollment was suspended in a key European trial of this cardiac stent, which elutes sirolimus from reservoirs sealed with a biodegradable polymer. The NEVO-II trial comparing Nevo to Abbott's everolimus-eluting Xience stent was stopped due to an issue with the balloon catheter.

J&J said it will not launch Nevo in any markets until it restarts the NEVO-II trial. J&J submitted Nevo to European regulators in late 1Q10 based on the RES-I trial, which found Nevo superior to Boston Scientific's paclitaxel-eluting Taxus Liberté stent.

MEDTRONIC – acquiring Ardian

Ardian's claim to fame – and what made it an acquisition target – is its catheter-based radiofrequency (RF) kidney denervation system for resistant hypertension. Data indicate that this therapy works, and it is a simple procedure to do. Ardian has a CE Mark and is expected to be launched in Europe in early 2011. It is very exciting technology.

The company hopes to initiate a pivotal U.S. trial in 1H11. The question isn't whether doctors will use it if it gets

approved; it's whether doctors who don't routinely deal with either the kidney or hypertension will try to do it.

REGENERON/BAYER's VEGF Trap-Eye – non-inferiority, but is that enough?

VEGF Trap-Eye met the primary endpoint in two Phase III trials in wet age-related macular degeneration (AMD), showing non-inferiority to Roche/Genentech's Lucentis (ranibizumab). In a 1,217-patient North American study conducted by Regeneron, 96% of VEGF Trap-Eye patients maintained their vision vs. 94% with Lucentis. Similar results were reported for a 1,240-patient trial conducted by Bayer in Europe, Asia Pacific, Japan, and Latin America. Additionally, injections every other month were as effective as monthly injections. *So, what is the advantage of VEGF Trap-Eye over Lucentis or Roche/Genentech's even less expensive Avastin (bevacizumab), which is widely used off-label for AMD?*

REGULATORY NEWS

FDA official retires under a cloud

Terry Vermillion, head of the FDA's Office of Criminal Investigations, said he will retire after being accused of misconduct by a whistleblower, who alleged that Vermillion had ordered changes to FDA documents to make the FDA look better. Congressional investigators have criticized Vermillion's department for months, and earlier this year the Government Accountability Office (GAO) said the FDA should exercise more oversight over Vermillion's department, which has 230 staffers. Sen. Charles Grassley (R-IA), who requested the GAO investigation, said, "I hope that with new leadership this office will contribute more to the FDA's overall mission of protecting public safety."

Upcoming FDA Advisory Committees and Other Regulatory Meetings of Interest (*items in RED are new since last week*)		
Date	**Topic**	**Committee/Event**
	November 2010	
November 30	**GlaxoSmithKline/Valeant's ezogabine** for epilepsy	PDUFA date
November 30	Discussion of **pediatric development of four oncology products** that were either recently approved by FDA or, are in late-stage development for an adult oncology indication: Pfizer's crizotinib, Allos Therapeutics' Folotyn (pralatrexate), Amgen's Xgeva (denosumab), and Eisai's Halaven (eribulin)	Pediatric Oncology Subcommittee of the FDA's Oncologic Drugs Advisory Committee
	December 2010	
December 1	**GlaxoSmithKline's Avodart** (dutasteride) and **Merck's Proscar** (finasteride) for prostate cancer	FDA's Oncologic Drugs Advisory Committee (ODAC)
December 2	**AstraZeneca/iPR Pharmaceuticals' Zictifa** (vandetanib) for thyroid cancer	FDA's Oncologic Drugs Advisory Committee (ODAC)
December 2	**Oceana Therapeutics' Solesta** (dextranomer in gel of stabilized non-animal hyaluronate) for fecal incontinence	FDA's Gastroenterology and Urology Devices Advisory Committee
December 2-3	Workshop on how to do **clinical trials for acute kidney injury,** including a session on biomarkers	National Institutes of Health
December 3	**Allergan's Lap-Band,** expanded indication	FDA's Gastroenterology and Urology Devices Advisory Committee
December 7	**Orexigen Therapeutics' Contrave** (naltrexone + bupropion), a diet drug	FDA's Endocrinologic and Metabolic Drugs Advisory Committee
December 9	**GSK/Human Genome Sciences' Benlysta** (belimumab) for lupus	PDUFA date
December 14-15	Risk of dengue virus infection in blood donors, murine leukemia virus-related human retroviruses, and an update on **blood safety issues**	FDA's Blood Products Advisory Committee
December 15-16	**Automated external defibrillator** safety and development	FDA public hearing
December 16	**AstraZeneca's Brilinta** (ticagrelor), an anticoagulant	PDUFA date
December 29	**Mannkind's Afresa** (inhaled insulin)	PDUFA date
	January 2011	
January 7	**Endo Pharmaceuticals' Opana TRF** (oxymorphone ER) for pain	PDUFA date
January 27-28	Discussion of **possible reclassification of electroconvulsive therapy devices**	FDA's Neurological Devices Advisory Committee
January 31	**Orexigen Therapeutics' Contrave** (naltrexone + bupropion), a diet drug	PDUFA date
	Other future meetings	
March 7, 2011	**Salix Pharmaceuticals' Xifaxan** (rifaximin) for non-constipation IBS	PDUFA date
March 26, 2011	**Bristol-Myers Squibb's Yervoy** (ipilimumab) for advanced melanoma	PDUFA date (***Will this be delayed because the December 2, 2010, FDA Advisory Committee was cancelled?***)
Date TBA, 2011	Review of **accelerated drug approval process**	FDA's Oncologic Drugs Advisory Committee (ODAC)
Summer 2011	Report on **FDA 510(k) reform**	Institute of Medicine