Trends-in-Medicine

Quick Takes

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Trends-in-Medicine
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April 18, 2010

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

SHORT TAKES

- **IRIDEX** has expanded its reach into ophthalmology with the acquisition of RetinaLabs, a retinal instrumentation company.
- **JOHNSON & JOHNSON/CORDIS** has started the open-label, non-randomized INNOVATION trial of its Incraft stent for abdominal aortic aneurysms (AAAs).
- **Svelte Medical Systems** – Robert Croce, former head of Johnson & Johnson's Cordis subsidiary, has joined the board of directors of this privately-held stent development company.

NEWS IN BRIEF

AVANIR's Zenvia (quinidine + dextromethorphan) – reduces involuntary laughing, crying

Clinical trial data showed that this combination of a generic anti-arrhythmic and a generic cough suppressant reduced the instances of involuntary laughing or crying in patients prone to pseudobulbar effect because of traumatic brain injury, multiple sclerosis (MS), or amyotrophic lateral sclerosis (ALS). In the study, 253 patients took Zenvia for 12 weeks, and they scored an average of 2.7 points better on a 35-point scale assessing involuntary laughing or crying vs. patients who did not receive the drug. There are currently no FDA approved therapies for pseudobulbar effect.

BIOGEN IDEC/ELAN's Tysabri (natalizumab) – trials start for PML screening tool

Clinical trials involving 9,000 people will start this year to test a screening tool that aims to predict the likelihood that MS patients taking Tysabri will develop progressive multifocal leukoencephalopathy (PML), a fatal brain condition linked to the drug. The assay determines whether a patient has antibodies to the JC virus which causes PML, and if they do, the immunosuppressive action of Tysabri may activate it. According to researchers, the risk of PML is about 1:500 for patients exposed to the virus but is much lower among those not exposed. The clinical trials will determine the rates of false positives and negatives obtained with the assay and will try to determine how many patients become infected with the JC virus over time. According to ***Bloomberg***, a company spokesperson said the screening tool could be marketed in 2011 if the trials show low rates of false positive test results.

Tysabri was taken off the market in 2005 because of three cases of PML, but the FDA allowed it back on the market in 2006 with a very strict risk management program and with the understanding that the incidence of PML would be ≤1:1,000. To date, there have been 42 cases of PML reported with Tysabri.

BOSTON SCIENTIFIC – two defibrillators back on market but investor lawsuit filed

The FDA cleared manufacturing changes to the Cognis CRT-Ds and Teligen ICDs that Boston Scientific originally failed to report, allowing the company to make those devices available to doctors and patients again. However, the older Confient, Livian, Prizm, Renewal, and Vitality devices are still awaiting clearance, and ***The Wall Street Journal*** reported that the company has identified some additional manufacturing changes that should have been reported to the FDA. All of the defibrillators have been unavailable since mid-March when Boston Scientific informed the FDA that it had failed to obtain clearance for manufacturing changes.

Meanwhile, a U.S. institutional investor in Massachusetts is seeking a class action suit against Boston Scientific's cardiac rhythm management business because the company allegedly failed to disclose to investors unethical business practices its sales force used to market devices. In December 2009, Boston Scientific paid a fine and agreed to disclose any payments made to physicians as part of a settlement to a U.S. Department of Justice investigation. The suit seeks class action for all investors who purchased Boston Scientific shares between April 20, 2009, and March 12, 2010.

American Association for Cancer Research (AACR) meeting – breaking news from

AACR is meeting this week in Washington DC. Some early results being reported from the meeting include:

1. **Vaccine for breast cancer – some small progress.** When delivered by dendritic cells, a cancer-testis antigen, Brother of the Regulator of Imprinted Sites (BORIS), shows strong and effective antitumor cellular immune responses in a breast cancer mouse model. Researchers reported that 18.75% of mice remained tumor free and 50% remained free of metastases after treatment. Although encouraging, a vaccine based on BORIS doesn't completely inhibit tumor growth or eliminate metastases and should be combined with strategies to reduce tumor-associated immune suppression, researchers said.

2. **ANTISENSE PHARMA's trabedersen – appears to increase survival in glioblastoma.** A Phase IIb clinical trial showed that trabedersen, a TGF-β2 inhibitor, may be a treatment option for high-grade glioblastoma. The trial tested intra-tumor administration of 10 µM or 80 µM doses in 145 patients with recurrent or refractory glioblastomas and after 24 months found that 83.3% of patients receiving the lower dose survived vs. 53.3% of those receiving the higher dose and 41.7% of patients having conventional chemotherapy. Duration of response was 29.1 months vs. 8 months for standard chemotherapy. The median overall survival benefit with lower dose trabedersen was 17.4 months more than standard chemotherapy. A Phase III clinical trial, SAPPHIRE, is currently enrolling patients.

3. **AMGEN's Vectibix (panitumumab) – Roche technology helps predict response.** Amgen researchers reported that they used Roche 454 pyrosequencing technology in a Phase III clinical trial to simultaneously look for nine genes that may predict whether a patient will respond to Vectibix. They assessed single tumor samples from 288 patients randomized to receive Vectibix with best supportive care or supportive care alone for metastatic colorectal cancer and found that 109 tumors had more than one mutation, and 20 tumors had more than one mutation in a single gene. Vectibix significantly improved progression-free survival in 124 patients with KRAS wild-type tumors but had no effect on those with KRAS mutant tumors. Researchers found that Vectibix also improved survival in patients with NRAS wild-type, BRAF wild-type, and BRAF mutant tumors.

4. **RADIOMEDIX imaging agent – detects cancer stem cells.** A new radiolabeled hedgehog imaging agent can detect the presence of cancer stem cells that indicate a tumor is likely to recur after treatment. Company researchers used the imaging agent in a pilot study in patients with breast cancer and found significantly increased binding to breast cancer cell receptors in tumor cultures enriched with breast cancer stem cells. This is the first study to show that radiolabeled hedgehog can differentiate cancer stem cells from the entire tumor population and may be useful in identifying more aggressive disease. Additional research is underway and includes further assessment of the radiolabeled hedgehog to identify cancer stem cells with positron emission tomography (PET).

CAMBRIDGE HEART – cleared to market module measuring risk for sudden cardiac death

Cambridge Heart reported it has received FDA clearance to market the Microvolt T-Wave Alternans (MTWA) OEM module, a non-invasive device that integrates with Cardiac Science's Q-Stress systems to assess a patient's risk of sudden cardiac death. The module can measure small rhythm irregularities during a regular stress test. The MTWA will be marketed to existing customers as an upgrade and to new customers as an optional add-on.

CATALYST's vigabatrin – new source of trial funding

The National Institute on Drug Abuse (NIDA) will provide $10 million in funding for a second trial of vigabatrin in cocaine and methamphetamine addiction involving about 200

patients. Catalyst will contribute $2.8 million toward the cost of the trial. A previous trial was unsuccessful, but Catalyst said that there were not enough patients enrolled, and an independent panel thought there was encouraging evidence that vigabatrin helps patients break their addiction.

FDA phases out CFC asthma and COPD inhalers

The FDA has announced the phase out schedule for inhalers containing ozone-depleting chlorofluorocarbons (CFCs) as propellants. The last dates devices for the manufacture, sale, or dispensation are:

- June 14, 2010, for Boehringer Ingelheim's Alupent Inhalation Aerosol (metaproterenol) and King's Tilade Inhaler (nedocromil).
- December 31, 2010, for Abbott's Azmacort Inhalation Aerosol (triamcinolone) and King's Intal Inhaler (cromolyn).
- June 30, 2011, for Forest's Aerobid Inhaler System (flunisolide)
- December 31, 2013, Boehringer Ingelheim's Combivent Inhalation Aerosol (albuterol + ipratropium) and Graceway's Maxair Autohaler (pirbuterol).

The FDA is urging asthma and COPD patients using these medications to discuss with their healthcare professional switching to currently available alternatives. The phase-out is required by the Clean Air Act, in accordance with U.S. obligations under the Montreal Protocol on Substances that Deplete the Ozone layer.

GILEAD SCIENCES' "Quad" HIV drug – late stage trials started

Gilead is starting two trials with its four-component HIV drug which combines elvitegravir, cobicistat, emtricitabine, and tenofovir. Both 96-week studies will enroll ~700 patients. The first trial will compare the four-drug combination to Gilead's three-component agent, Atripla (efavirenz + emtricitabine + tenofovir), and the second will compare it to a combination of Abbott's Norvir (ritonavir), Bristol-Myers Squibb's Reyataz (atazanavir), and Gilead's two-drug combination Truvada (emtricitabine + tenofovir). The safety trials will compare the quadruple treatment's efficacy in reducing HIV levels with that of the other combinations.

Cobicistat (GS-9350), the newest molecule, works by increasing blood levels of anti-retroviral agents administered with it. Gilead will also conduct a trial comparing a combination of cobicistat, Truvada, and Reyataz to a combination of Norvir, Truvada, and Reyataz.

Gold nanoparticles – identify blood clot risk

Scottish researchers have used gold nanoparticles to accurately detect thrombin, a protein associated with blood clot formation, in blood. They applied strands of nucleic acids that bind with thrombin onto thin gold shells. When thrombin binding occurred in blood samples, they were able to detect it by shining laser light on the sample. Currently, thrombin detection requires a blood assay with fluorescent antibody binding. The scientists said the gold nanoparticle technology can be used to detect a variety of proteins, and they envision the eventual ability to inject the sensors into patients and measure protein concentrations by shining a light on the skin.

HEARTWARE INTERNATIONAL – expanding LVAD trial

The FDA is allowing the company to add up to 54 additional patients to the 140 already enrolled in the ADVANCE bridge-to-transplant trial of its miniaturized Ventricular Assist System for left ventricular support. The potential advantage of this device, which already has a CE Mark, is that it is designed to be implanted next to the heart, which avoids the abdominal surgery usually required to implant competing devices. Final results of ADVANCE are expected in December 2010.

HOSPIRA to acquire Javelin Pharmaceuticals

Javelin turned down an offer from Myriad Pharmaceuticals, saying the Hospira offer was better. Javelin has three pain drugs in development:

1. **Dyloject**, an injectable diclofenac for postoperative pain which is under review by the FDA and is already marketed in the U.K.
2. **Rylomine**, an intranasal morphine for acute pain which is in Phase III trials in the U.S. and Phase II trials in Europe.
3. **Ereska**, an intranasal ketamine for acute moderate-to-severe pain which is in Phase III trials in both the U.S. and Europe.

IMMUNOGEN/ROCHE – seeking expedited FDA review for breast cancer treatment

The companies plan to ask the FDA for an expedited review of T-DM1 based on interim clinical trial data showing that it reduced breast cancer tumor size better than expected. T-DM1 combines Roche's Herceptin (trastuzumab), which specifically targets cancer cells, with a derivative of a chemotherapy agent maytansine, that was found to be too toxic alone. T-DM1 was developed with the hypothesis that combining it with the targeting ability of Herceptin would limit toxicity to the cancer cells. In a previous 3-year trial in critically ill patients with metastatic breast cancer who had been treated unsuccessfully with an average of seven different therapies, T-DM1 reduced tumor size in one-third of those receiving it. Roche said it hopes to receive FDA approval in late 2010 or early 2011.

MERCK KGaA

- CEO Karl-Ludwig Kley said the purchase of **Millipore** was "worth every euro."

- The company plans to resubmit **cladribine**, an oral MS treatment, to the FDA "as soon as possible." The FDA rejected the cladribine filing last year. Merck KGaA also is optimistic that European regulators will approve cladribine for MS in 3Q10. The issue with the FDA is not clear, though speculation has been that this could be related to the high dose used in clinical trials performing ***worse*** than the low dose.
- **Stimuvax.** Merck KGaA is working with regulators to investigate why a patient getting this experimental cancer vaccine developed a brain infection.

OPTIMER's fidaxomicin – as effective as vancomycin in *C. difficile*

Results of a second Phase III trial comparing fidaxomicin and vancomycin for difficult-to-treat *Clostridium difficile* (*C. diff*) infection (CDI) show that fidaxomicin met the primary end-point of non-inferiority vs. vancomycin. Fidaxomicin was associated with ~50% fewer CDI recurrences. These results are very similar to those observed in a previous Phase III trial. The macrocyclic antibiotic was given to 535 CDI patients for 10 days, and global cure rates were 79.6% for fidaxomicin vs. 65.5% for vancomycin. Researchers reported no difference in adverse events between the two treatments. Optimer intends to submit a New Drug Application (NDA) to the FDA this year.

OREXIGEN's Contrave (bupropion + naltrexone) – not as effective as reported

Orexigen is updating its March 31, 2010, NDA filing with the FDA to reflect errors in study results involving the anti-obesity drug. In July 2010 investigators reported that clinical trial results showed that 75.8% of patients taking Contrave for 56 weeks lost ≥5% of their body weight and 48.2% lost ≥10%. But the updated results showed that 64.9% of patients lost ≥5% and 39.4% lost ≥10%. Orexigen said the error was due to improper weighting of some patients' results and claimed the drug still meets FDA parameters for approval.

Contrave is Orexigen's first drug, and it is expected to reach the market about the same time as two competing agents – Vivus's Qnexa (phentermine + topiramate) and Arena's lorcaserin.

PERKINELMER – buying Signature Genomic Laboratories

PerkinElmer has signed a definitive agreement to buy Signature Genomic for $90 million, and the transaction is expected to close in May 2010. The acquisition will enable PerkinElmer to strengthen its cancer diagnostics, molecular diagnostics, and genetic testing services. Signature Genomic provides molecular cytogenetic diagnostic services to test for chromosomal abnormalities in patients with unexplained physical and developmental disabilities, microarray technology for pre- and post-natal genetic testing, and leukemia diagnostics.

ROCHE – acquires Medingo

Roche signed an agreement to acquire Medingo, a subsidiary of Elron Electronics that is developing a semi-disposable micro pump insulin patch/pump. The device is intended to function as a conventional insulin pump integrated with tube-less patch pump technology allowing the user to administer insulin directly from the patch pump without a remote control along with the option of disconnecting the pump temporarily and securing the patch to the skin for transdermal insulin delivery. The pump can later be reconnected. The company expects a 2012 global launch for the device.

STERIS's System 1E – sterile but not sterile?

This liquid chemical sterilization system recently gained FDA clearance, but the FDA website says – in bold – that "the final processed devices are not sterile" after being treated in SYSTEM 1E. Thus, there is an apparent conflict, with the FDA saying (1) that the system is approved to sterilize devices but (2) that the system doesn't really sterilize them. Asked about this, an FDA official pointed to FDA guidance on liquid chemical sterilization. The key points in that guidance are:

- The FDA believes that "sterilization with liquid chemical sterilants does not convey the same sterility assurance as sterilization using thermal sterilization methods."
- Liquid chemical sterilization involves a two-part process. First, devices are treated with a chemical germicide, followed by a second step in which the processed devices are rinsed with water to remove the chemical residues.
- "There are several limitations with liquid chemical sterilization. Although the rinse water is treated to minimize any bioburden, it is not sterile. Because the rinse water is not sterile, devices rinsed with this water cannot be assured to be sterile. Furthermore, devices cannot be wrapped or adequately contained during processing in a liquid chemical sterilant. This means that there is no way to maintain sterility once devices have been processed."
- The FDA recommends: "The use of liquid chemical sterilants be limited to reprocessing only critical devices that are heat-sensitive and incompatible with traditional sterilization methods such as steam."

TERUMO – asks FDA for device exemption

Terumo has submitted an investigational device exemption (IDE) for the DuraHeart Left Ventricular Assist System, seeking approval to begin studying the device as a destination therapy for patients with advanced heart failure who are ineligible for heart transplant and long-term mechanical circulatory support. The system has received a CE Mark, a U.S. trial has enrolled 140 patients, and a clinical trial will also be conducted in Japan. The device has a centrifugal flow rotary pump with an impeller that is magnetically levitated to minimize friction and improve blood flow.

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