Trends-in-Medicine

Quick Takes

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

SHORT TAKES

- **AMYLIN's Bydureon (exenatide long-acting) –** Amylin said it has responded to an FDA request for manufacturing information and a risk evaluation and mitigation strategy (REMS) for this once-weekly version of the injectable diabetes drug, Byetta (exenatide), and is awaiting a new target date for an FDA decision on approval.
- **CARDIOVASCULAR SYSTEMS** received an unconditional Investigational Device Exemption (IDE) from the FDA and will start a pivotal trial to evaluate the Diamondback 360° coronary artery plaque removal system.
- **CUBIST's ecallantide (CB-500929) –** After reviewing Phase I/II clinical trial data, the company decided to stop developing this therapy for blood loss during cardiopulmonary bypass surgery and said it will terminate its development and commercialization agreement for ecallantide with **Dyax**.
- **EDWARDS LIFESCIENCES –** The first Japanese trial of transcatheter aortic heart valves has begun with the Sapien XT, which already has a CE Mark.
- **EV3** has enrolled 287 patients in the DURABILITY-II trial to evaluate the EverFlex stent.
- **EVOTEC –** The German Federal Ministry of Education and Research will fund Phase I clinical trials of the company's H_3 receptor antagonists for improved cognition, alertness, and attention.
- **FOREST LABORATORIES** said it is dropping out of a $340 million deal to develop and commercialize **Phenomix**'s dutogliptin for Type 2 diabetes despite optimistic results from a Phase III trial reported by Phenomix.
- **MEDTRONIC** has signed a definitive agreement to acquire **ATS Medical**, a company focused on heart valve and cardiac ablation therapies, for $370 million.
- **NYCOMED/FOREST LABORATORIES' Daxas (foflumilast) –** The European Medicines Agency recommended approval for Daxas as add-on therapy to bronchodilator treatment in patients with chronic obstructive pulmonary disease (COPD). An FDA advisory committee voted 10-5 to recommend against approval of Daxas on April 7, 2010.

- **TAKEDA's azilsartan (TAK-491) –** The company filed for FDA approval of this antihypertensive, which it hopes will replace candesartan (marketed as Blopress by Takeda and as Atacand by AstraZeneca) when the Blopress patent expires in 2012.
- **TRACON's TRC-105 –** The National Cancer Institute has initiated a Phase I/II trial of this monoclonal antibody in patients with castration-resistant prostate cancer (CRPC).

NEWS IN BRIEF

ASTHMATX's Alair Bronchial Thermoplasty System – gets FDA clearance

Alair was cleared by the FDA for use in adults with severe and persistent asthma that is not well controlled with inhaled corticosteroids and long-acting beta agonists. This is the first radiofrequency (RF) device cleared to treat severe/persistent asthma. It has a catheter with an electrode tip that delivers RF energy directly to the airways, with a controller unit generating and controlling the energy. The RF energy heats the lung tissue in a controlled manner, reducing the thickness of smooth muscle in the airways and improving a patient's ability to breathe. One treatment is not sufficient; patients will require multiple sessions targeting different areas in the lungs.

The Alair system is designed to reduce the number of severe asthma attacks on a long-term basis. However, there is a risk of immediate asthma attacks during the course of the treatment. The FDA is requiring a five-year post-approval study of the long-term safety and effectiveness, so Asthmatx plans to follow many of the patients in the pivotal trial plus another 300 new from several medical centers in the U.S.

BOSTON SCIENTIFIC – court rejects huge Guidant settlement as insufficient

A U.S. Federal District Court judge rejected a $296 million settlement that the U.S. Department of Justice reached with Boston Scientific for a four-year-old investigation which determined that Guidant, then an independent company, made false statements to the FDA regarding modifications to its Ventak Prizm and Contak Renewal implantable cardioverter defibrillators (ICDs). The devices were found to have caused the deaths of at least seven patients. The rejected settlement would have been the largest monetary criminal penalty for violating federal laws relating to medical technology.

In his decision, District Judge Donovan Frank wrote that the settlement was "not in the best interests of justice" and sent company and Justice Department officials back to the drawing board. The judge suggested that in addition to a settlement amount, restitution be made through a payment to Medicare or a charity. The judge also recommended probation for the company, perhaps in the form of community service, in an effort to hold it accountable.

DENDREON's Provenge (sipuleucel-T) – approved for prostate cancer

Billed as the first cancer "vaccine," this autologous cellular immunotherapy received FDA approval for advanced metastatic prostate cancer in men who do not respond to hormone therapy. Although a BLA (Biologic License Application) was filed in 2006, the FDA delayed approval, asking Dendreon for additional information.

That new data in 512 patients showed a modest survival advantage of 4.1 months: median survival after treatment of 25.8 months vs. 21.7 months for placebo. Dr. Karen Mitchum, acting director of the FDA's Center for Biologics Evaluation and Research, said, "The availability of Provenge provides a new treatment option for men with advanced prostate cancer, who currently have limited effective therapies available."

Provenge is not a true vaccine, which would be used to ***prevent*** the onset of a cancer. Instead, it stimulates the immune system of men with the disease, and treatment is tailored to each patient. Immune cells are removed from the patient's blood and undergo leukapheresis to bind Provenge to cell proteins before returning the enhanced immune cells to the patient's system, where they are more effective in attacking tumor cells.

A course of treatment will cost ~$93,000. The question is how much that will limit use.

Companies with other cancer vaccines in the pipeline – e.g., Celldex/Pfizer's brain cancer vaccine; Geron's acute myelogenous leukemia (AML) vaccine, which is in mid-stage development; and GlaxoSmithKline's product for treatment of non-small cell lung cancer (NSCLC) and skin cancers – may benefit from the Provenge approval.

FDA revamps medical device advisory committees

In an effort aiming for "improved discussion and flow of information," the FDA will institute changes in the way advisory committees review and discuss data during public hearings on medical devices being reviewed for premarket approval. The changes took effect May 1, 2010. The increasing number of medical device advisory panel meetings in recent years is cited as creating "challenges" for the Center for Devices and Radiological Health (CDRH), which runs the medical device advisory committee proceedings. There were 10 such meetings addressing 14 topics in 2008, 17 meetings on 20 topics in 2009, and the number of meetings and topics in 2010 is expected to surpass those in 2009.

The FDA said the changes "address staffing issues, voting procedures, and other items related to information presentation and flow of discussion." The most striking changes are:

- **Vote topics.** Advisory committee members will no longer vote on the approvability of premarket approval applications (PMAs) or on the conditions of approval as

in the past. Instead, panel members will vote only on the safety and efficacy of a device and on the device's risk: benefit. CDRH director Dr. Jeffrey Shuren said, "By making this change in voting procedure, panel members will address key scientific issues during their discussions, which will be reflected in their votes. The change will also allow panel members to address issues related to their area of expertise instead of regulatory issues that may be unfamiliar to them."

- **FDA reviewer comments.** Although historically, FDA reviewers' presentations to advisory committees included their comments on device approvability, such comments will no longer be allowed. The FDA's presentations to panel members will continue to include reviews of the Agency's data analysis.
- **FDA reviewer opinions.** Previously, FDA reviewers presented a unified consensus analysis of supporting data to the panels. Now, FDA reviewers also will present their range of scientific opinion on the data and analysis.
- **Interruptions.** Panel members will be instructed to provide their scientific opinions and recommendations to the questions the FDA asks of them without interruption. One hour will be allotted beforehand for panel deliberations, during which panel members may ask questions of the FDA and the device sponsor. The FDA said, "We believe focusing the amount of time the sponsor may respond to questions will allow for a more robust discussion among the experts and provide CDRH with information needed to reach a decision regarding the issue before the panel."
- **Voting method.** Panels will vote by ballot instead of a show of hands to "allow each panel member to cast his or her vote without immediate influence by other votes." Votes will then be publicly tallied, and panel members will be identified by their vote.

HANA BIOSCIENCES' Marqibo (vincristine sulfate lipisomes injection) – "rolling" NDA gets FDA okay

In a pre-application meeting, the FDA agreed to review sections of the NDA for Marqibo for the treatment of relapsed or refractory acute lymphoblastic leukemia (ALL) as the company submits them. Normally, information tied to an NDA is submitted and reviewed by the Agency all at once. Marqibo was previously granted both orphan drug and fast-track designations by the FDA.

H1N1 Vaccine – complications being investigated

The Department of Health and Human Services' National Vaccine Advisory Committee is investigating whether there is a link between the H1N1 vaccine and an increased incidence of Guillain-Barré syndrome, Bell's palsy, and thrombocytopenia. Preliminary analyses of data collected from five of the many networks that are monitoring the 80 million Americans who received the vaccine showed there may be a weak connection between the vaccine and these disorders, but if so, officials estimate only one person in 1 million vaccinated is affected. The committee will conduct additional data analyses to try and determine if the preliminary results are valid. An increase in cases of Guillain-Barré syndrome is of the most interest because in 1976 a vaccine made for a different H1N1 influenza strain was connected with a small increase in patients acquiring the condition.

ICAGEN's ICA-105665 – additional Phase II trials move forward

The FDA has approved two additional Phase IIa trials using higher doses of ICA-105665, which is in development for epilepsy and pain indications. An initial Phase IIa trial using a top dose of 400 mg in photosensitive patients with epilepsy showed good response and a lack of a maximum tolerated dose (MTD). One of the additional trials will evaluate higher doses in photosensitive patients with epilepsy, and another will evaluate ascending doses in healthy volunteers. Icagen expects these trials to be completed in 2H10. If they are successful, Icagen plans a Phase IIb study in patients with treatment-resistant, partial-onset epilepsy to measure efficacy for reduction in seizure frequency.

MEDTRONIC/KYPHON's kyphoplasty – finally facing competition

Medtronic's key patents on kyphoplasty ('888 and '404) expired in February 2010. Two weeks later the FDA cleared CareFusion's device, AVAmax Vertebral Balloon, and a couple of weeks after that CareFusion announced it would actually launch the device. Then, in mid-April 2010 Stryker announced that it was launching its own FDA-cleared kyphoplasty product, the iVAS inflatable vertebral augmentation system. So now, Medtronic has two competitors in this space. The marketing wars should be interesting.

MERCK's dalotuzumab (MK-0646) – durable response in pancreatic cancer

A small (35-patient) Phase I trial in advanced pancreatic cancer showed that combining dalotuzumab with Lilly's Gemzar (gemcitabine) ± Genentech's Tarceva (erlotinib) produced a durable response. Radiologic studies to assess 25 evaluable patients after treatment found that six patients had a partial response, eight had stable disease, 10 continued with progressive disease, and one died. Investigators said the most notable result was that the duration of response ranged from 14 weeks in one of the six partial responders to 32-59+ weeks in the other five partial responders. A Phase II clinical trial is underway comparing the same dalotuzumab regimens studied in the Phase I trial with a control regimen using only Gemzar and Tarceva.

NOVARTIS's Sandostatin (octreotide) – efficacy in polycystic liver disease

In clinical trial results published in the ***Journal of the American Society of Nephrology***, Sandostatin decreased liver volume in patients with polycystic liver disease (PLD) caused by autosomal dominant polycystic kidney disease (ADPKD). The trial of 42 PLD patients showed that after one year of Sandostatin treatment, liver volume *decreased* by 5% vs. a 1% *increase* in volume seen among patients receiving placebo. In addition, patients treated with Sandostatin had stable kidney volumes vs. placebo patients, who had an average 8% increase in kidney volume. Larger trials are needed to determine the benefits of Sandostatin in PLD.

ROCHE/GENENTECH's Lucentis (ranibizumab) – effective with laser therapy in DME

A study by the National Eye Institute's Diabetic Retinopathy Clinical Research Network showed that Lucentis plus laser therapy preserves vision – and may even improve it – in patients with diabetic macular edema (DME), a condition in which the retinal tissues in the back of the eye swell, often leading to blindness. The study found that injections of Lucentis, combined with laser treatment (either prompt or delayed), was effective in almost half of DME patients, and the treatment effect was sustained at two years.

NEI director Dr. Frederick Ferris called Lucentis a "treatment breakthrough" that can protect and in some cases prevent DME, "Diabetic retinopathy is a research priority because more people are developing diabetes every year. It is the leading cause of vision loss in Americans…This study shows that people with diabetes can have significant gains in their vision if treated with ranibizumab. The findings show hope for treatment beyond laser and may improve the chances of healthy vision in the future…We expect that this will have a major impact. This is the first time in 25 years that we have definitive proof that a new treatment can likely lead to better results for the eye health of people with diabetes."

The standard of care for DME has been laser treatment. However, the NEI study of 691 patients (854 eyes) with Type 1 or Type 2 diabetes and macular edema in at least one eye showed that Lucentis injections in combination with laser treatment resulted in better vision than laser treatment alone.

Dr. Neil Bressler, chair of the Diabetic Retinopathy Clinical Research Network and chief of the retina division at Johns Hopkins' Wilmer Eye Institute, said that the study was conducted at more than 200 clinical sites with participation by more than 700 physicians, "Nearly 50% of eyes treated with ranibizumab with prompt or deferred laser treatment showed substantial visual improvement compared to laser alone for at least one year." He said that treated patients' vision improved by two lines of vision by the end of the study.

In the study, patients continued to receive injections as long as improvements in acuity and retinal thickness were seen. Dr. Bressler said, "When we no longer saw improvement, the treatment became optional unless there was a decline. There were eight to nine treatments on average in the first year and four to five in the second year. We know that in an individual person we can't predict how many injections they may need, but on average it doesn't need to be given monthly…We will be following these patients for a long period of time. [So far] we have followed everyone out to one year, and 50%-60% were followed to two years, and the results appear sustained. We will follow everyone for at least three years."

Fewer than 5% of eyes lost ≥2 lines through at least one year, and few patients had any eye-related complications. The study did not find any association between the injections and serious risks such as heart attack and stroke.

The study also looked at the use of a steroid, triamcinolone acetonide, vs. laser treatment. At one year, injections of the triamcinolone, combined with prompt laser treatment, resulted in a greater decrease in the thickness of the retina than laser alone. However, triamcinolone did not result in better vision for patients than laser, and patients had greater complication rates – 30% developed high eye pressure that required medication, and 60% developed cataracts that required surgery.

Asked if there were clues as to which patients would not respond to treatment, Dr. Bressler said, "Only 50% had substantial improvement, not everyone, and we haven't been able to identify yet any particular subgroup that indicates that they should not be treated. We can't predict which (patients) will or will not respond."

Asked if similar anti-vascular endothelial growth factor (VEGF) drugs, such as Roche/Genentech's Avastin (bevacizumab) would have the same results, Dr. Ferris said, "We don't know…Different anti-VEGF drugs are now on the table to see if they are effective…We expect drugs of a similar nature will have the same effect, but whether they will be equal or one better than the other is unknown. Genentech developed Lucentis because they thought that it would be more effective in getting into the retina because it is a smaller molecule. The data will help answer this, and clinicians will use both in their patients as they try to sort out which seems to be more effective." Dr. Bressler added, "It is great for the millions of people who have diabetes and unfortunately will develop macular edema. We know this class of drugs works …This is just the beginning to figure out how to improve on this treatment."

ROCHE's taspoglutide – met Phase III primary endpoint in diabetes

Results of the T-EMERGE-3 clinical trial showed that taspoglutide 10 mg and 20 mg once weekly were superior to placebo in reducing HbA_{1c} levels in patients with diabetes.

The trial included 326 patients and taspoglutide was added to treatment with both metformin and Takeda's Actos (pioglitazone). Data from five other T-EMERGE trials were previously released, and two additional Phase III trials with taspoglutide are ongoing.

SANOFI-AVENTIS/BRISTOL-MYERS SQUIBB's Plavix (clopidogrel) – more data showing PPIs reduce the effect

Adding a proton pump inhibitor (PPI) to counteract gastrointestinal bleeding associated with Plavix increased the risk of rehospitalization for myocardial infarction (MI) or a stent by 64%, according to a retrospective analysis reported in the ***Archives of Internal Medicine***. Rehospitalization for MI doubled among those taking both drugs. The study included 1,033 patients treated with Plavix + a PPI after MI or stenting who were followed for 360 days.

This is the latest in a litany of trials showing that PPIs do – or do not – dampen the antiplatelet activity of Plavix. In November 2009 the FDA issued a safety warning and a labeling revision for Plavix stating that use with one PPI, AstraZeneca's Prilosec (omeprazole), had been shown to decrease the antiplatelet effect of Plavix. This FDA action baffled some cardiologists because in September 2009 results of what was regarded as the definitive trial on the use of PPIs with platelet inhibitors, COGENT, showed that there was no difference in cardiovascular events between patients taking Plavix and a PPI vs. those taking Plavix and placebo. Furthermore, patients in the PPI group in that study experienced significantly fewer gastrointestinal side effects and bleeding events.

Then, on March 12, 2010, the FDA issued a "black box" warning for Plavix, indicating that some patients may have a genetic resistance to the antiplatelet action of the drug and recommending that healthcare professionals consider testing for genetic resistance or prescribing alternate antiplatelet therapy. *The question is: How many patients in studies showing that PPIs reduce antiplatelet activity may have been unidentified as "poor responders," for whom Plavix doesn't work as well.*

SIEMENS – revamps healthcare division

Siemens is revamping its healthcare division to concentrate on inexpensive clinical devices. The move is designed to attract business from customers that don't have the money or expertise for large medical devices such as scanners, including customers in developing markets. Healthcare sector CEO Hermann Requardt said that while large hospitals and clinics are trying to differentiate themselves with customized high-end solutions, smaller hospitals and physicians who are in private practice, "especially in emerging economies with above average growth, are primarily seeking cost-efficient and less complex equipment."

The healthcare division is one of the company's three major units, along with industry and energy. The division will consist of:

1. Imaging and therapy systems.
   - Imaging includes CT, MRI, and PET systems.
   - Therapy solutions include angiography systems, linear accelerators, particle therapy systems, and minimally invasive procedures.
2. Clinical products: x-ray and ultrasound equipment (until now run jointly with the large scale medical device business.
3. Diagnostics: equipment for analyzing blood and other bodily fluids as well as the necessary reagents.

Sales and service will be managed by the customer solutions unit. The hearing aid business will be managed independently in the healthcare division.

UCB's Neupro (rotigotine transdermal system) – FDA asks for reformulation

The FDA has asked for a reformulation of the Neupro patch for treatment of Parkinson's disease and restless leg syndrome before it can be sold again in the U.S. Neupro was recalled in 2008 when it was found that crystals formed on the patch and interfered with its transdermal efficacy. In September 2009 UCB was granted European approval to market the patch after showing that a cold-storage system reduced the crystal formation. The FDA, however, wants the Neupro patch reformulated to eliminate the possibility of crystal formation.

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