Trends-in-Medicine

Quick Takes

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

SHORT TAKES

- **AMGEN's Prolia (denosumab)** – was approved for osteoporosis in Europe and the U.S., but the U.K.'s National Institute for Health and Clinical Excellence (NICE) has not decided whether to make it available through the National Health Service (NHS).
- **ASTRAZENECA's Axanum, combination of Nexium (esomeprazole + aspirin)** – The FDA rejected it, asking for more data, but the company is still hoping for European approval.
- **BAXTER's GammaGard Liquid** – was withdrawn from the market after an increasing number of reports of allergic reactions associated with 2 lots of GammaGard, which is used to treat primary immunodeficiency disorders associated with defects in humoral immunity.
- **Cardiologists** – A MedAxiom survey of >150 cardiology practices found that 60% either have already fully integrated with a hospital or are considering it. Only 28% said they are not currently considering consolidation or will never consider it.
- **COVIDIEN** – announced that it is buying medical device maker ev3 Inc., which will expand its position in the endovascular market.
- **EISAI's eribulin** – breast cancer treatment was granted FDA priority-review, with a decision expected by September 30, 2010.
- **IVUS vs. OCT** – According to the results of a CRTonline survey, 67% of cardiologists do not think optical coherence tomography (OCT) will replace intravascular ultrasound (IVUS), but a third do. (**www.crtonline.org**)
- **POLY IMPLANT PROTHÈSE's (PIP's) silicone breast implants** – The biocompatibility tests being conducted on the fraudulent silicone this French manufacturer used in its now-banned breast implants are expected to be completed by the end of June or early July 2010.

- **NOVOGEN's phenoxodiol –** This plant-derived multiple signal transduction regulator (MSTR) failed to significantly improve overall survival or progression-free survival in a Phase III study in recurrent ovarian cancer, though there were no safety concerns. The company is still hopeful about a second-generation agent, triphendiol.
- **OREXIGEN THERAPEUTICS' Contrave (naltrexone + bupropion) –** The FDA has accepted the NDA, which means the Agency now has three obesity drugs in the final stages of review. No date for an FDA advisory committee has been set yet for Contrave or Arena Pharmaceuticals' lorcaserin, but Vivus's Qnexa (phentermine + topiramate) will be reviewed by the Endocrinologic and Metabolic Drugs Advisory Committee on July 15, 2010.

NEWS IN BRIEF

Drug Enforcement Administration (DEA) – will permit e-prescribing of controlled substances

DEA issued an interim final rule that will, for the first time, allow for electronic prescribing of controlled substances. However, it will be at least 6 months before the rule is implemented. The inability to do e-prescribing of controlled substances has been cited as a major barrier to physician adoption of e-prescribing, so this decision could be good for companies offering e-prescribing solutions.

European drug price cuts – hard for pharmas to swallow

One of the Greek government's austerity moves was a cut in pharmaceutical drug prices by an average of 25%. Spain and Ireland also are cutting prices; there are reports that Germany, Italy, and France may do so as well; and the specter was raised of additional price controls in the U.K. In addition, the European Medicines Agency may require new drugs prove their efficacy is better than existing drugs.

Some pharmas already are finding that they can't absorb these price increases. Danish pharmaceutical company, Leo Pharma, for instance, said that, reluctantly, next month it will begin withdrawing 18 of 29 of its products from the Greek market. Leo Pharma said, "A price reduction on our products of up to 37% will have severe consequences on our total business, including long-term investments in research and development to the benefit of patients worldwide. Since the Greek prices on our products are reference point for prices in a number of European countries, we risk that prices in, for example, Spain, Portugal, Italy, Romania, Turkey, Czech, Hungary, etc., will also be subject to severe reductions if we do not act."

European Heart Failure Congress 2010, Berlin, Germany – promising results from 4 studies

1. CARDIAC CONCEPTS' RespiCardia – phrenic nerve stimulation helps sleep apnea

Results of a Polish and U.S. feasibility study indicate that stimulation of the phrenal nerve could potentially treat central sleep apnea (CSA). Dr. William Abraham from Ohio State University, one of the principal investigators, reported on 13 optimally-treated heart failure patients with documented CSA who were studied during two consecutive nights of sleep. The first night (without intervention) was compared to the second night during which the phrenic nerve was stimulated via a temporary transvenous lead implant.

The study found transvenous phrenic nerve stimulation was safe and well tolerated in this short study, and patients had statistically significant benefits: a 91% reduction in central apneas, a 55% improvement in oxygenation levels, a 51% decrease in night arousals, and a 49% reduction in apnea hypophea, an indicator of CSA severity.

CSA activates the sympathetic nervous system which results in intrathoracic pressure increases, arrhythmia, and myocardial ischemia, making it one of the most potent predictors of mortality in heart failure. About 75% of heart failure patients have a sleep disorder – half of these with CSA and half with obstructive sleep apnea (OSA).

A larger, long-term study is planned.

2. CardioMEMS Champion device – reduces heart failure hospitalizations

The 550-patient Phase III CHAMPION trial compared patient management according to data from the CardioMEMS pulmonary artery pressure measurement device, Champion, vs. a control group managed with traditional information (weight gain). By six months, the treatment group was being hospitalized 30% less frequently than the control group, with an annualized risk reduction of 38%, suggesting a progressive improvement over time. Mean pulmonary artery pressure was also substantially reduced with CardioMEMS. There were no device failures and a very low number of device complications.

Phase III CHAMPION Trial Results

Measurement	CardioMEMS	Control	p-value
Primary endpoint: Heart failure hospitalizations at 6 months	83	120	<0.0001 (30% risk reduction)
Heart failure hospitalizations at 15 months	154	254	<0.0001 (38% risk reduction)
Pulmonary artery pressure at 6 months	---	---	0.008
Days alive outside the hospital at 6 months	177.1	154.9	0.024
Quality of life by Minnesota Living with Heart Failure Questionnaire	45	51	0.024

Powered by wireless radiofrequencies (no batteries!) from the external electronic monitor, the CardioMEMS device is a paperclip-sized pressure sensor that uses a catheter-based delivery system, involving right heart catheterization, to introduce the sensor into the pulmonary artery. It then transmits real-time pressure data to an external electric monitor. The device detects and alerts the doctor to rises in arterial pressure, the most direct indicator of worsening heart failure.

Dr. Abraham, a co-principal investigator of the study, called it "the first major breakthrough in the management of heart failure in nearly a decade," adding, "For the first time, instead of managing symptoms or weight gain the device allows us to directly manage patient's pulmonary pressures."

3. CELLADON's Mydicar (enzyme replacement therapy) – improves heart failure outcomes and symptoms

Six-month Phase II data from the randomized CUPID trial showed that this therapy significantly improved outcomes and symptoms in advanced heart failure patients.

Phase II CUPID Trial Results

Measurement	Mydicar	Control
Primary endpoint: Composite of clinical outcomes, exercise tolerance, heart failure symptoms, biomarker and cardiac function	---	---
Quality of life by Minnesota Living with Heart Failure Questionnaire	- 10.3	+ 3.5
6MWD	+ 1 meter	- 87 meters
NT-ProBNP	- 13.5 pg/mL	+ 5,540 pg/mL
Left ventricular end-systolic volume	- 9 mL	+ 18.2 mL
High dose results		
Reduction in cardiovascular events (death, LVAD, cardiac transplant, worsening heart failure, heart failure hospitalizations)	Significantly better with Mydicar (p=0.04)	
Length of hospital stay	0.2 days	2.1 days

4. Galenica's Ferinject (IV ferric carboxymaltose) – boosts iron levels and improves renal function

The FDA rejected this IV iron therapy (under the name Injectafer in the U.S.) for safety reasons, but the data keep mounting that IV iron is beneficial.

A post hoc analysis of the FAIR-HF trial which was presented at the European heart failure meeting showed that treating iron deficiency in chronic heart failure (CHF) patients was associated with improved renal function. The original Phase III study results, presented at the American Heart Association meeting in 2009, demonstrated that iron deficient CHF patients who received intravenous Ferinject had significant improvement in symptoms, six-minute walk distance, NYHA Class, and quality of life. The key finding of that study was that iron deficiency is not necessarily related to anemia, and boosting iron levels has benefits irrespective of anemia status.

A new subanalysis of FAIR-HF found improvement in the estimated glomerular filtration rate (eGFR) vs. placebo (p=0.017 at Week 24). The treatment effect was independent of the baseline level of renal function, age, gender, CHF severity, diabetes, or anemia.

Dr. Piotr Ponikowski of Poland estimated that at least 35%-40% of CHF patients have iron deficiency, "Many patients with CHF have renal dysfunction which is strongly related to poor health outcomes. None of the therapies currently recommended for CHF patients has a favorable effect on renal function. Thus, there is great interest in treatments which may have renoprotective properties…But as yet we don't have any clear ideas about the mechanism of how iron would be improving renal function."

JAVELIN PHARMACEUTICALS – trying to force Hospira to buy it

Javelin has filed a lawsuit against Hospira in an attempt to force Hospira to acquire it as planned. On May 23, 2010, Javelin announced that some batches of its injectable pain therapy, Dyloject (diclofenac injection) was contaminated with a white particulate matter, and all batches had been recalled in the U.K. Dyloject is not yet approved in the U.S., but it has been submitted to the FDA for approval, with a decision expected in October 2010. Hospira extended its tender offer to June 16, 2010, but Javelin wants Hospira to buy it at the April price (before the recall). Javelin asked for an expedited review of its complaint because it had just $1.1 million in cash on hand as of the end of 1Q10.

MEDIMMUNE's motavizumab – FDA panel recommended against approval

Citing concerns about safety, including an increased risk of non-fatal hypersensitivity skin reactions, the Antiviral Drugs Advisory Committee voted not to recommend approval of this experimental drug to prevent serious respiratory syncytial virus (RSV) in infants. MedImmune said it will continue to work with the FDA to overcome the committee's concerns. MedImmune hopes to replace its older RSV drug, Synagis, with motavizumab.

PFIZER's tanezumab – pain relief in interstitial cystitis

Researchers from Wake Forest University reported at the American Urological Association meeting this month that a single injection of 200 µg/kg tanezumab, a nerve growth factor (NGF) inhibitor, significantly decreased the pain associated with interstitial cystitis vs. placebo. The results came from a 65-patient, 16-week, placebo-controlled study, which also found that the benefit increased over time. The frequency of urgency episodes declined with tanezumab while it increased with placebo.

QUANTERIX – test detects PSA at very low levels

Quanterix has developed a test that can spot very low concentrations of prostate specific antigen molecules in blood samples using a fluorescence enzyme that lights up when it ties to a PSA. The test could be used for the early detection of prostate cancer recurrence in men. However, urologists may not be interested in the test if the reception to Nanosphere's ultrasensitive PSA test, Verisens, is any indication; urologists insisted there was no need for super high levels of detection.

The Quanterix technology counts the number of PSA molecules released by the cells of the prostate gland into the blood. PSA molecules are trapped on beads and isolated individually on arrays of tiny wells. A fluorescent enzyme that is added to the array lights up when it binds to PSA, revealing the number of PSA molecules in the sample.

According to a study published in ***Nature Biotechnology***, the test is 1,700 times more sensitive than other PSA detection methods used in clinical laboratories. Researchers found that while commercial assays detected no PSA in any of the blood samples, the Quanterix assay found PSA present in very tiny levels in all samples.

ROCHE/GENENTECH's Avastin (bevacizumab) − Phase III trial halted in aggressive NHL

In an analysis of the first 720 patients in the MAIN trial, the Data Safety Monitoring Board found an unfavorable risk:benefit when Avastin was added to R-CHOP [Rituxan (rituximab) plus cyclophosphamide/doxorubicin/vincristine/prednisone] to treat aggressive non-Hodgkin's lymphoma (NHL), and the DSMB recommended the trial be stopped. Approved indications for Avastin will not be affected by these findings, and the >450 clinical trials of Avastin in ~30 different types of tumors will continue as planned.

ROCHE/GENENTECH's and GALENICA GROUP/VIFOR PHARMA's CellCept (mycophenolate mofetil) − positive Phase III results in lupus nephritis

No treatment for lupus has been approved by the FDA in 50 years, so doctors are hopeful about CellCept. In top line data from the three-year, 227-patient ALMS maintenance study, CellCept met its primary endpoint, demonstrating superiority (p=0.003) over azathioprine (AZA) in delaying treatment failure (death, serious renal damage, or disease relapse) in lupus nephritis patients who had responded to induction therapy with either CellCept or IV cyclophosphamide. No new safety signals were seen. The results will be presented at the 9th International Congress on Systemic Lupus Erythematosus (SLE) in Vancouver, Canada, June 24-27, 2010.

Sepsis – potential new treatment approach

Scientists from the University of Glasgow reported in ***Science*** on a potential new treatment for sepsis. They showed that the SphK1 enzyme is elevated during septic shock and blocking SphK1 "reduced the inflammatory signals sent out by the cells." In mice, the SphK1 blockers cut the risk of death, protected against multi-organ failure, and helped the clearance of bacterial infections.

SSRI antidepressants – increase the risk of cataracts

A study reported in the June issue of the journal ***Ophthalmology*** found that selective serotonin reuptake inhibitors (SSRIs) increase the risk of developing cataracts by ~15%, with some SSRIs worse than others. The study compared 18,784 cataract patients to 187,840 healthy controls >age 65 and found that Solvay's Luvox (fluvoxamine) increased the risk by 39%, Pfizer's Effexor (venlafaxine) by 33%, and GlaxoSmithKline's Paxil (paroxetine) by 23%.

The increased risk was only associated with current use of the medication, not prior use. What is the explanation? The authors explained that the lens of the eye has serotonin receptors, and in animal studies excess serotonin can make the lens opaque and lead to cataract formation.

U.K. news

1. Beta-interferons for MS – price not coming down

Prof. Christopher McCabe, a professor of health economics at Leeds University in the U.K., reported in the ***British Medical Journal*** that a government plan to cut the cost of beta-interferons in multiple sclerosis has fizzled. He estimated that pharmas would have to ***pay*** the National Health Services (NHS) in order for the drugs to be cost-effective.

2. Medical procedures to be cut to save money

The NHS plans to save £20 billion by 2014 by eliminating "low value" operations. The NHS reportedly plans to cut procedures such as hernias, joint replacements, ear and nose procedures, varicose veins, and cataract surgery.

FDA NEWS

When a request doesn't work, make it an order

You probably thought the long-acting beta agonist (LABA) labels had already been revised. Not so. The FDA told companies that new warning labels were needed for LABAs, particularly GSK's Serevent (salmeterol) and Advair (fluticasone propionate) and AstraZeneca's Symbicort (budesonide + formoterol). But the companies did not comply, at least not quickly enough to suit the FDA. So, the FDA has now ***mandated*** the label change, sending letters to GSK, AstraZeneca, Sepracor, and Dey Pharma.

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