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SHIP-1 BID 'ATOPIC' FOR DISCUSSION

Armada nada: Flagship COPD phase II sunk, Aquinox to set sail for gladder bladder news

By Randy Osborne, Staff Writer

Aquinox Pharmaceuticals Inc. CEO David Main told investors during a conference call that it was "impossible to know the right answer" to the question of why the phase II trial called Flagship with AQX-1125 failed in chronic obstructive pulmonary disease (COPD), but he noted the very sick patients enrolled had "lots of exacerbations" and "lots of symptoms."

Shares of the company (NASDAQ:AQXP) closed Thursday at $2.13, down $4.42, or 67.5 percent.

See Aquinox, page 3

Mild market rebound, but China's public firms still suffering losses

By Cornelia Zou, Staff Writer

HONG KONG – A dramatic plummeting in the value of publicly listed shares in Mainland China over the last month has wiped out roughly $3 trillion in wealth and raised fears of a collapse in the country's stock market, a collapse that could exacerbate slowing economic growth.

See Stocks, page 4

REGULATORY

New squamous NSCLC drug may be just around the corner

By Mari Serebrov, Regulatory Editor

Marginal. Modest. Incremental.

That's how the FDA and members of its Oncologic Drugs Advisory Committee (ODAC) described the 1.6-month improvement in overall survival (OS) Eli Lilly and Co.'s necitumumab demonstrated in a pivotal trial as a

See FDA, page 5

IN THIS ISSUE

DEALS AND M&A

Globavir moves oncology program to Sorrento, which continues cancer march with Nantworks

By Marie Powers, News Editor

Globavir Biosciences Inc. found a partner for its lead oncology program in Sorrento Therapeutics Inc., which in turn inked another in a string of deals with the oncology syndicate Nantworks LLC that is being assembled by founder Patrick Soon-Shiong.

For Los Altos, Calif.-based Globavir, the exclusive license for BC001, a preclinical hypoxia-inducible factors (HIF)-1 inhibitor designed to treat solid tumors, means its first oncology partnership and future cash flow of up to $80 million in regulatory and sales milestones, plus multitiered royalty payments on global net sales. Sorrento also assumes responsibility for development and commercialization costs. Although the companies did not disclose additional

See Globavir, page 6

NEWCO NEWS

'Sirting' for better control in type 2 diabetes, Nusirt exploits metformin pathway

By Marie Powers, News Editor

Nusirt Biopharma Inc. is a small biotech that has largely avoided the limelight, but ambitious goals to attack two major indications – type 2 diabetes and nonalcoholic steatohepatitis (NASH) – could quickly raise its profile.

Company founder and chief scientific officer Michael Zemel spent his 30-year academic career exploring the endocrine and nutritional modulation of energy metabolism and disease risk, moving in 1990 to direct the Nutrition Institute at The University of Tennessee. Through his research, Zemel concluded "there were some fundamental things happening at the cellular level" that caused cells to differentiate when they received energy, mainly in the form of glucose converted from carbohydrates, explained Joseph

See Nusirt, page 7

FINANCINGS

Anthera Pharmaceuticals Inc., of Hayward Calif., said it priced an underwritten public offering of about 3.3 million shares of its common stock at $7.50 each. The company estimated that the gross proceeds will be approximately $25 million. Anthera has granted the underwriters a 30-day option to purchase up to an additional 500,000 shares of common stock. Citigroup Global Markets Inc. and Piper Jaffray & Co. are acting as joint book-running managers. Suntrust Robinson Humphrey Inc. is acting as co-manager. Shares of Anthera (NASDAQ:ANTH) fell 87 cents, or 10.4 percent, to close Thursday at $7.47.

Cleveland Biolabs Inc., of Buffalo, N.Y., said it closed a private placement with venture investor David Davidovich for approximately 6.5 million unregistered common shares at $3.87 apiece, for $25 million in proceeds. The price per share represented a premium of 35 percent to the closing price of the company's shares (NASDAQ:CBLI) on June 23, the day before the agreement was signed.

Clovis Oncology Inc., of Boulder, Colo., said it priced an underwritten public offering of 3.5 million shares of its common stock at $78 each for gross proceeds of $275 million. The underwriters have a 30-day option to purchase up to an additional 528,846 shares of common stock. Shares of Clovis (NASDAQ:CLVS) closed Thursday at $78.20, down 83 cents.

Global Blood Therapeutics Inc., of South San Francisco, has filed an S-1 form with the SEC for an IPO of up to $115 million. According to the filing, the company is focused on developing and commercializing therapeutics to treat blood-based disorders. Its initial product candidate, GBT440, is a once-daily, oral therapy for sickle cell disease. The company intends to list on Nasdaq under the symbol GBT.

Innavirvax SA, of Evry, France, said it completed its third funding round for €3.6 million (US$4 million) to accelerate the development of VAC-3S, an immunotherapy aimed at restoring the immune system of people living with HIV. The product is in a phase IIa European study, which has recruited 86 patients with HIV. The primary endpoint is to evaluate the immune response to the administration of three different doses of VAC-3S, which will be compared in adults living with HIV-1 who are receiving antiretroviral therapy to control their viral load.

VBI Vaccines Inc., of Cambridge, Mass., has filed a shelf registration statement to raise up to $75 million. The number of shares and share price have not yet been disclosed. The company's enveloped virus-like particle (eVLP) vaccine platform allows for the design of eVLP vaccines that closely mimic the target virus. VBI's lead eVLP asset is a cytomegalovirus vaccine.

STOCK MOVERS 7/9/2015

Company	Stock in $	Change in %
Nasdaq Biotechnology	+$42.18	+1.11%
Affimed NV	+$1.54	+10.63%
Aquinox Pharmaceuticals	-$4.42	-67.48%
Atara Biotherapeutics Inc.	+$4.58	+9.38%
Novavax Inc.	+$1.20	+11.00%
Ultragenyx Pharma	+$13.63	+13.76%
Sciclone Pharmaceuticals	-$1.69	-15.05%

Biotechs showing significant stock changes Thursday

OTHER NEWS TO NOTE

Heraeus Holding GmbH, of Hanau, Germany, completed an equity investment in **Ankasa Regenerative Therapeutics Inc.,** of La Jolla, Calif. Heraeus said Ankasa's development of the stem cell growth factor, WNT3A, which helps to maintain bone growth and repair, could have strategic relevance for its subsidiary, Heraeus Medical GmbH, which develops biomaterials and medical devices for orthopedic surgery, traumatology and biosurgery. Details of the investment were not disclosed.

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Aquinox

Continued from page 1

"As part of the top line we received the [pharmacokinetic data]," Main said. "We know that the patients that were on the treatment arm [and] received the drug had the same plasma levels as the patients receiving the same dose of drug in prior trials. We got good drug exposure, so our expectation is that there is probably more likely something to do with the refractoriness of this disease" at the stage patients were tested, he said.

Last month, the lead candidate from the firm's SH2-containing inositol-5'-phosphatase-1 (SHIP-1) program narrowly missed statistical significance in the phase II trial called Leadership in bladder pain syndrome/interstitial cystitis (BPS/IC), but the data were good enough for Vancouver, British Columbia-based Aquinox to move ahead with development of AQX-1125 in that indication. Stephen Shrewsbury, chief medical officer (CMO), said at the time that "pain scores seemed pretty well matched between the groups. I think had the trial [enrolled] a few more patients or perhaps gone on for a few weeks longer we might have actually hit" the statistical significance bar.

Such was not the case for Flagship, though, which randomized 400 patients to get either AQX-1125 or placebo. AQX-1125 on top of standard of care did not improve COPD exacerbation symptoms, nor did it reduce the medically treated exacerbation rate as compared to placebo on top of standard-of-care therapy.

"We have examined the parameters of the trial and are confident that these results were not due to any observed imbalance in the treatment arms or due to the design or execution of the trial," CMO Shrewsbury said of the Flagship experiment. Patients treated with 200-mg oral, once-daily AQX-1125 (same dose and frequency as in the Leadership trial) for 12 weeks tracked their results by using a patient-reported outcomes tool called EXACT, a rough acronym for "the Exacerbations of Chronic Pulmonary Disease Tool," a diary with 14 items.

Patients in the Leadership study, too, were required to report daily on pain in an electronic or e-diary. The patients in that more successful trial were randomized following a screening period of nine to 21 days during which they had to demonstrate an average minimum pain score of five on a numerical rating scale (NRS) for short of zero to 10, with 10 being severe pain. They had to have at least a mean score of five over a minimum of seven for the last nine days prior to randomization. As with EXACT, the NRS scale is one of several standard endpoints used in trials; pain is the most common endpoint for current BPS/IC trials, too, with 21 of 48 current BPS/IC trials registered on clinicaltrials.gov listing pain as the primary endpoint, Shrewsbury noted.

Yet to report is the Kinship phase II trial with AQX-1125 for atopic dermatitis, with top-line results expected in the first quarter of next year.

The idea behind binding and activating SHIP-1 is to enhance the enzyme's inflammation reduction activity. SHIP-1 is mainly found in immune cells and functions by restoring balance after inflammatory responses, dialing down the activation state of immune cells, along with the recruitment and migration to sites of inflammation. SHIP-1 operates in the PI3 kinase pathway. In June, before either of the phase II trials reported data, Cowen and Co. analyst Ritu Baral expressed confidence. "We think Aquinox's SHIP-1 platform is the basis for a promising portfolio of the potential drugs for epithelial inflammatory diseases (e.g., COPD, BPS/IC)," since SHIP-1 plays a key role in the immune system. She predicted both experiments would succeed, and forecast $1.8 billion in COPD peak sales.

Of the Flagship trial, Shrewsbury said Aquinox "will complete secondary analyses, [but] these are unlikely to alter our conclusions, though they may help explain the absence of an effect in this population." CEO Main, asked if AQX-1125 is kaput in COPD, said "the better use of our resources and energies are on BPS/IC," adding that "we will continue to think about COPD and other respiratory diseases, but if we were to specifically talk about COPD, we would probably conclude that [in] a future trial we would want to think about earlier intervention in the disease." COPD, he said, "is not going to be on the near-term horizon."

Jefferies analyst Biren Amin wrote in a June research report that "an increase in the treatment period beyond six weeks in addition to sample size could increase the odds of success" in future BPS/IC experiments. Amin, during the conference call Thursday on Flagship, wanted to know if the company had collected biomarker data that might provide clues to the drug's activity in COPD. Shrewsbury said researchers had not, but "we will be selecting biopsy samples in our Kinship trial in atopic dermatitis and we'll obviously be discussing those at some point in the future."

Aquinox went public in the first quarter of last year, pricing its offering at $11, the midpoint of the proposed range, and bumping up the number of shares sold by half a million to 4.2 million for gross proceeds of about $46.2 million. (See *BioWorld Today*, March 10, 2014.) **//**

REGULATORY FRONT

The **Biotechnology Industry Organization** (BIO) issued a statements opposing an amendment to the 21st Century Cures Initiative legislation filed by Rep. Dave Brat (R-Va.) that would convert the mandatory funding for the NIH to discretionary funding. "NIH funding over the past decade has failed to keep pace with the biomedical research inflation and, as a result, the success rate of meritorious research proposals has fallen dramatically, which has a long-lasting impact on the development of breakthrough treatments and cures for patients suffering from life-threatening and debilitating disease," said BIO President and CEO Jim Greenwood. He called consistent and sustainable growth in NIH funding "critical" to the industry. The **Pharmaceutical Research and Manufacturers of America** (PhRMA) also opposes the amendment. Both BIO and PhRMA, however, continue to support the 21st Century Cures legislation.

Stocks

Continued from page 1

A marketwide rebound of almost 6 percent July 9 could mark the beginning of a turnaround, but it did little to offset weeks of sharp losses.

Panicky investors, many of them individuals who had been encouraged to invest on margin by a loosening of rules earlier this year, have fled the market en masse since the middle of June. The losses have been steep and the drop is the biggest since the launch of the Shanghai stock market in 1992.

"The sharp drop is not caused by the performances of the companies but the general market trend right now," Zou Peng, an analyst at China International Capital Corp., told *BioWorld Today*.

The fear that has led investors to sell off is not linked to any one sector or event but rather with the market as a whole, said Zou.

The sell-off was then exacerbated by margin calls on leveraged investing. Earlier this year, Chinese regulators opened the door for individual investors to borrow money from stock brokers to invest in shares.

Shares were also buoyed by the Shanghai Hong Kong Stock Connect scheme, which opened Shanghai's stock market to Hong Kong investors. A similar program is in the works for Shenzhen.

The various moves led to a stellar performance by Chinese bourses. The Shanghai Composite Index rose about 60 percent from Dec. 31 to its June 12 peak of 5,178.

That performance led to warnings that a bubble was forming and could burst at any time. The burst came just days later.

The volatility has been intense, with single-day drops of as much as 8 percent and many companies dropping by the maximum 10 percent in a single day. For example, the Shanghai Composite Index slid 5.9 percent to 3,507.192 on July 8.

And biotech companies have not been immune to the drops.

"It has affected all sectors, not just [the] health care sector," said Ocean Pan, analyst at GF Holdings Hong Kong.

Almost all listed companies have been hit, including biotech and medtech.

Tasly Pharmaceutical Group Co. Ltd. (SH:600535) dropped from a high of ¥55.57 (US$8.95) on June 15 down to ¥38.46 on July 8 before bouncing back to ¥42.31 Thursday.

Walvax Biotechnology (SH:300142) has been spared the carnage. The company had suspended trading on June 16 pending a shareholder deal announcement.

Vaccine maker Chongqing Zhifei Biological Products (CH:300122), which is listed in Shenzhen, was trading at ¥44.80 on June 11 but closed at ¥19.80 Thursday, down by half in less than a month.

Shanghai Fosun Pharmaceutical Group (SH:600196) dropped from ¥35.99 on June 10 to ¥21.87 on July 8 before bouncing back to ¥24.3 Thursday.

STOPPING THE BLEEDING

In an effort to contain the slide, the government has introduced a raft of measures that could have an impact on company performance in the long term.

One such measure is a ban on sales of shares by shareholders with stakes greater than 5 percent in any one company. Another is a ban on new IPOs on both the Shanghai and Shenzhen stock exchanges that took effect on July 4 and is open-ended. The aim of the ban is to prevent investors from selling shares of companies that are currently listed to invest in new offerings. The ban has had a definite effect on the IPO pipeline for the rest of the year.

Other measures have seen the China Securities Regulatory Commission (CSRC) put plans in place to buy shares of large companies, mostly state-owned, which have benefited disproportionately. Other companies have resorted to halting trading to stem the bloodletting.

"The rout will have a negative influence on IPOs," said Pan. "Hong Kong IPOs will be influenced as well since the overall environment is not good."

And the rout has extended to Hong Kong, where the Hang Seng Index dropped 14 percent from 27,404 on June 24 to 23,516 on July 8, when it dropped by almost 6 percent in a single day before rising by 5 percent on July 9 to 24,392. The drop on July 8 was the largest in a single day since 2008.

Some Hong Kong-listed companies have seen wild swings in their share values.

Sinopharm Holdings Co. Ltd. (HK:1099), China's biggest pharmaceutical and medical device enterprise in China, dropped from a high of HK$31 (US$3.99) to HK$29.55 on July 8. Sinopharm closed July 9 at HK$30.65.

Another biopharma listed in Hong Kong is Shenyang-based 3Sbio Inc. (HK:1530), which went public last month. Shares dropped to HK$8.25 from a high of HK$10.56 on June 23.

Struck by the rout even harder, another traditional Chinese medicine company, Guangzhou Baiyunshan Pharmaceutical Holdings Co. Ltd. (HK:00874), dropped HK$2.45, from HK$22.85 to HK$20.40, almost an 11 percent fall on July 8. It bounced back to HK$23.75 on July 9.

Luye Pharma (HK:02186) closed at HK$7.66 on July 7 and dropped 4.4 percent to HK$7.32 before bouncing back on July 9 to HK$7.72.

Meanwhile, Chinese regulators say they will support the market, and the People's Bank of China said July 8 it would provide "ample liquidity" to the country's stock market.

On Thursday, the overall market rose sharply but a lot of companies remain suspended and it is difficult to say whether sentiment has turned. **//**

FDA

Continued from page 1

first-line treatment for squamous non-small-cell lung cancer (NSCLC).

But that improvement could be enough to make necitumumab the first new drug in a few decades to be approved for the disease, which has no cure and few treatment options.

While ODAC wasn't asked to vote on an approval recommendation at its meeting Thursday, most of the panelists voiced support for the anti-EGFR monoclonal antibody, citing the need for a targeted treatment and Lilly's commitment to risk management and further exploration of the science behind the disease and the drug.

In wrapping up the meeting, Richard Pazdur, director of the FDA's Office of Hematology and Oncology Products, said an approval decision on the fast-tracked biologic is possible before its PDUFA date.

Researchers have made considerable strides over the past decade in understanding NSCLC, which accounts for about 85 percent of all lung cancers. One of the lessons learned is that squamous and nonsquamous NSCLC are two different diseases and what works in one can be harmful in another, the FDA's Gideon Blumenthal said.

The differences were apparent in Lilly's development of necitumumab, which was tested in both diseases. The INSPIRE trial, in which necitumumab was given along with pemetrexed and cisplatin to treat nonsquamous NSCLC, was closed prematurely at the request of the data monitoring committee due to an imbalance in the number of deaths attributed to potential thromboembolic events (TEs) and deaths of all causes in the study arm compared with the control arm. The data at the time of the closure showed no OS improvement. (See *BioWorld Today*, July 9, 2015.)

However, in the SQUIRE trial, which evaluated necitumumab along with chemo drugs gemcitabine and cisplatin in squamous NSCLC, the median OS was 11.5 months in the investigational arm compared with 9.9 months in patients receiving only the two chemo drugs. The median progression-free survival was 5.7 months in the necitumumab arm compared with 5.5 months in the control arm and the overall response rate was 31 percent vs. 29 percent.

IN SEARCH OF A BIOMARKER

Because of the higher-than-expected incidence of TE events, Lilly searched for a biomarker that could be used to identify patients likely to benefit from the drug. The obvious place to start was the EGFR H-score. But investigators found that the EGFR protein expression was high in more than 95 percent of the 1,093 patients enrolled in the SQUIRE trial, said Katie Sugarman, Lilly's regulatory lead for oncology. Because so few patients didn't have the marker, the FDA agreed the number was too small to draw a conclusion.

The Indianapolis-based drugmaker has continued to look for other potential biomarkers, including HER2, HER3 and FGFRI. The company also is focused on steps to mitigate the risks, which could improve the prognosis for patients. For instance, Sugarman said in conducting the international SQUIRE study, Lilly learned that it needed to be more proactive in educating physicians about the need to regularly monitor for low magnesium levels as there could be a link to those levels and the serious adverse events that were seen.

ODAC Chairwoman Deborah Armstrong agreed that managing the toxicities of the drug could improve the OS. She encouraged Lilly to be frank in the labeling about the population that doesn't benefit from the drug, including those 70 and older, who appeared to do better in the control arm of the SQUIRE trial than on the study drug.

Howard Fingert, ODAC's industry representative, commended Lilly for its commitment to go beyond drug marketing to focus on the ongoing science and risk management of drug development, both of which are dynamic processes. With so many trials being global in scope, he said finding biomarkers is critical as they can supersede geographic differences.

The FDA staff and most of the ODAC panelists concluded that necitumumab's modest benefit in squamous NSCLC outweighed its risks. Several of them noted that the risks were consistent with the adverse events observed with other anti-EGFR antibodies and the incremental OS improvement was in line with that of other cancer drugs approved by the FDA.

PATIENT PERSPECTIVE

During the public hearing session, Scott Santarella, president and CEO of the Addario Lung Cancer Foundation, challenged the notion that 1.6 months is marginal. Even one more hour, day, week or month in the life of lung cancer patients translates into another milestone they can enjoy with their loved ones, he said.

Hildy Grossman, a nine-year lung cancer survivor and president/founder of Upstage Lung Cancer, reminded the committee that medical breakthroughs are made in incremental steps and stressed that weighing the benefits and risks should be the patient's choice.

Squamous NSCLC strikes mostly men who are or were smokers and who are likely to have other diseases such as diabetes or heart problems.

While targeted therapies have been approved for nonsquamous NSCLC, patients with squamous tumors – about a third of all NSCLC patients – are mostly treated with gemcitabine and cisplatin. As a result, their five-year survival rate is less than 5 percent.

That population "has sort of been left behind in the NSCLC" drug development, Armstrong acknowledged.

Panelist Louis Diehl, an oncologist and professor at Duke University, noted that the approval of necitumumab would mean he would have to discuss a lot of issues with individual patients before prescribing the drug. "I would like to have that discussion," he said. //

Globavir

Continued from page 1

details of the partnership, Globavir said Sorrento participated as an equity investor in a previous financing round.

BC001 is the only one of Globavir's oncology assets that was not derived from its drug discovery platform, which has spawned a number of other immuno-oncology candidates. Instead, the drug emerged from predecessor company Biocycive Inc., which Globavir CEO Shalabh Gupta founded at the end of 2010 to focus on the development of small-molecule drugs targeting oncology indications.

"This particular drug is one we had been working on from 2011 to 2014," when discussions with Sorrento began, Gupta said.

Gupta was acquainted with Henry Ji, Sorrento's president and CEO, and George Uy, the company's executive vice president and chief commercial officer, and appreciated that both men "had a very deep understanding of the science of how this drug can work," he explained. "They understood the value proposition."

BC001 targets HIF1a-p300 interaction, upstream of the activation of multiple oncogenic targets. Currently, no FDA-approved agents target HIF, which helps to differentiate the asset in the growing immuno-oncology space, according to Globavir. Preclinical data presented last year at the American Association for Cancer Research meeting in San Diego suggested that, against various cancer cell lines, BC001 decreased cell growth, with EC50 values in the nanomolar range. In breast cancer and renal cell carcinoma models, BC001 (1 mg/kg) suppressed tumor growth compared with control.

Globavir believes BC001 could potentially become a standard-of-care therapy for cancer patients who fail to respond or develop resistance to conventional VEGF inhibitors, such as Avastin (bevacizumab, Roche AG), which could transform it into a drug with a very large market, Gupta suggested.

"The Sorrento management team understood that proposition very well," he said, adding that Sorrento has the infrastructure to move BC001 to human trials, which are expected to begin next year.

Globavir's lead compound, GBV006, is an undisclosed combination of known drugs that could potentially be advanced through the 505(b)(2) pathway to treat hemorrhagic fevers, including dengue, West Nile and Ebola. Discovery of the potential value of GBV006 in infectious diseases was made at Stanford University School of Medicine, and Globavir holds the worldwide exclusive license to develop and market the compound, which is designed to target several stages of the viral life cycle. (See *BioWorld Today*, Aug. 20, 2014.)

The company has been in discussion with the FDA about the design of a phase Ib/IIa study for the drug and expects to file an investigational new drug application by year-end, Gupta said.

However, "we have an oncology background, and we want to stay in oncology – especially immuno-oncology," Gupta told *BioWorld Today*. "To that end, we're utilizing our drug discovery platform, which we've also been working on for several years. We want to develop new, proprietary 505(b)(2) drugs in immuno-oncology, utilizing small molecules."

The field of immuno-oncology has a great need for small-molecule development, he maintained, since most players are focused on monoclonal antibodies. Globavir's discovery platform uses computational algorithms and other resources to sort databases of approved drugs and chemical scaffolds to determine which compounds might be repurposed. For assets that can be advanced through the 505(b)(2) pathway, the company has the potential to move from concept to human trials in less than two years, according to Gupta.

The BC001 deal frees up internal resources to advance the remainder of the pipeline while providing cash flow on the back end. In the meantime, Globavir is in discussions for additional partnerships for oncology candidates, which include programmed cell death protein 1, or PD-1, cytotoxic T-lymphocyte antigen 4, or CTLA-4, and Tryptophan 2,3-dioxygenase, or TDO, inhibitors.

"Some of these assets are what you might call low-hanging fruit, as we understand the particular mechanisms of action and the targets are very well known," Gupta said. "If we find the right partner in the near term, we want to be able to partner them."

Globavir plans to advance some of the assets on its own, although it might entertain partnerships with co-promotion or joint development rights.

"We're looking at all of these options because we have a broad pipeline," Gupta said. "It would be different if we had only one drug."

Gupta declined to provide the amount of cash held by the company but said Globavir has no imminent plans for a financing round.

GLOBAVIR ASSET BACKS INTO SORRENTO, NANTWORKS VENTURE

Partner Sorrento further solidified its own run through oncology drug development with yet another deal with Nantworks. This time, San Diego-based Sorrento established a joint venture with Nantworks subsidiary Nantbioscience Inc., to develop small molecules against targets that have proved elusive for biopharmas.

Sorrento will contribute lead inhibitors of the proto-oncogenes c-Myc, the newly licensed master metabolism regulator HIF-1a and an inducer of the tumor suppressor cytokine TRAIL to the joint venture, which will be 60 percent owned by Nantbioscience and 40 percent by Sorrento. The companies will commit $100 million to the program, which they dubbed "Moonshot," in the same proportions.

The joint venture follows the acquisition in May by Nantworks Inc. of the rights to Sorrento's Cynviloq, a nanoparticle-based paclitaxel cytotoxic therapeutic that was renamed Nant-paclitaxel, and the formation of Nantibody, a Nantworks joint venture specifically focused on immunotherapeutics.

See Globavir, page 9

Nusirt

Continued from page 1

Cook Jr., president and executive chairman of Nusirt's board.

"When energy arrives at the cell, the cell has to decide what to do with it," Cook said. "Does it make protein? Does it store the energy somewhere? Does it send it somewhere else? All of those decisions, at the cellular level, are some of the mysteries but also the beauties of our biology."

Zemel's thesis was that an unknown mechanism controlled that gatekeeping function. And, from his work in nutrition, Zemel recognized that people who exercised were less prone to gain weight. Zemel put his observations to the test and concluded, along the way, that the simple amino acid, leucine, was instrumental in helping cells determine how to use, store or redirect energy to other tissues.

Zemel's first inclination was to develop a series of nutraceutical products based around leucine – commonly found in meat, beans, milk and other foods – but company officials quickly recognized a bigger opportunity in applying his understanding of leucine to drug development. Thus, Nusirt's technology platform combines leucine with medicines that target metabolic diseases that can be addressed by activating the sirtuin1/AMP kinase (Sirt1/AMPK) signaling pathway.

Since that pathway is common to the blockbuster diabetes drug metformin, it didn't take rocket science to deduce the potential opportunity from combining the drugs, using leucine to amplify the effect and reduce the dose of metformin needed to achieve equivalent glucose control. Results of the company's preclinical research, published in the July 2015 issue of *Metabolism*, showed that combining leucine and subtherapeutic doses of metformin activated the Sirt1/AMPK pathway and resulted in improved glycemic control and insulin sensitivity, offering comparable or improved ability to reduce hyperglycemia, improve blood glucose response to insulin and reduce fasting blood glucose and insulin levels compared to full-dose metformin.

The company replicated the findings both in a model organism (*C. elegans*) and in diet-induced, insulin-resistant mice.

Nusirt, based in Nashville, Tenn., has a phase IIa trial under way to evaluate whether the preclinical results can be matched in humans. The company is testing whether the combination of Nusirt technology and three separate low doses of metformin can effectively control glucose levels compared with full doses of metformin alone. The study is fully enrolled, and Nusirt expects to report findings early in the third quarter.

If the data meet the test, with no adverse events, the company hopes to move directly into larger studies that could be treated as pivotal trials by the FDA and support a new drug application using the 505(b)(2) pathway, which the agency previously indicated it will support, according to Cook.

Nusirt hasn't determined whether it will seek to conduct the next set of studies independently or choose a partner first.

"It's highly likely that we'll engage a partner in some portion of our development," Cook said. "Our current business plan does not call for us to develop a commercial presence around the world. That's a very extensive undertaking, and it's hard to justify it on the back of a single product. So at least for the rest of the world, it's highly likely that the commercial activities and maybe some portion of the development activities will largely be conducted by someone else."

'TYPE 2 DIABETES IS A CONTINUUM OF LIFE'

For the foreseeable future, companies pursuing therapies for type 2 diabetes are consigned to seeking iterative improvements to help patients manage day-to-day glucose control and prevent complications associated with the disease, according to Cook.

"Unfortunately, I don't see anything that is a true cure for type 2 diabetes," he told *BioWorld Today*. "Maybe there's some hope for type 1 if we can figure out a way to do an extracorporeal pancreas or a better way to implant beta cells."

On the other hand, "type 2 diabetes is a continuum of life, starting with overweight, going to obesity, then pre-diabetes, then diabetes, then insulin-dependent diabetes," Cook pointed out. "This is really a net sum game. If you consume energy, you've got to use it or it's going to get stored or excreted. Until we figure out a way to reduce weight in the population, we have a real battle on our hands in fixing this disease."

Most of the drug candidates introduced into the diabetes space in recent years don't truly mediate the underlying mechanism of the disease, he maintained, ticking off a list that included agents such as dipeptidyl peptidase-4 inhibitors, sodium-glucose co-transporter 2 inhibitors and GLP-1 receptor agonists.

"We end up with drugs that lower glucose but don't really cure the disease," he said. "Even metformin, as good as it is, does increase the insulin sensitivity of the body but doesn't fix the fundamental disease."

Treating pre-diabetes, even through mechanisms that mediate appetite and increase satiety, offers an attractive opportunity for drug developers, but reimbursement is a major issue.

"Payers are very reluctant to open the coffers to pay for pre-diabetes," Cook conceded, noting that one of the biggest questions is how to define an acceptable clinical endpoint. However, "the reality is that this is the direction where we're going to have to go," he added.

Metformin is likely used off-label now to treat pre-diabetes, he pointed out, noting that the American Diabetes Association's 2015 guidelines expressly called for the use of metformin to help prevent diabetes in certain populations. Nusirt sees more opportunities for approved drugs in that population, particularly in combination with diet and exercise regimens.

In addition to its type 2 diabetes candidate, the company is advancing a follow-on compound in NASH. The second compound uses the Nusirt technology to combine leucine, low-

See Nusirt, page 8

Nusirt

Continued from page 7

dose metformin and a low dose of PDE5 inhibitor sildenafil, the active ingredient in Viagra. Preclinical data suggested the combination restored diseased livers in animal models "to an almost naïve state," Cook said.

Nusirt proposed an investigational new drug application and held an initial meeting with the FDA to discuss the combination in NASH, and Cook is optimistic the company will move its candidate into the clinic in the fourth quarter.

In May, Nusirt raised a $6 million series C, with $2 million of the round allocated so far, bringing the company's total funding to "considerably less than $20 million," Cook said. Although the C round is designed to see the company through completion of the diabetes study and the start of the first NASH trial, "we expect to be considering other funding options later this year," he added. //

Coming Monday in *BioWorld Insight*

BIOTECHS POSITION THEMSELVES IN TOMORROW'S TECHNOLOGIES TODAY

One of the hot new areas of endeavor is gene therapy, which is expected to have a significant impact on the development of new innovative therapies during the next decade. As a result it comes as no surprise that both premier biotech companies and big pharma firms are getting into the space through strategic partnerships that will help strengthen their pipelines down the road. There have been several deals inked already this year with more predicted to follow. In addition, emerging gene therapy companies are taking advantage of the rising tide of investors' enthusiasm in that area to raise capital and also make the transition to the public arena.

MIGRAINE DRUGS TARGETING CGRP COULD GET REALLY PROFITABLE

CGRP stands for calcitonin gene-related peptide but it could double for "could get really profitable" if drug companies targeting CGRP and its associated receptor are successful; Evercore ISI analyst Umer Raffat said he thinks the market to treat migraines with CGRP drugs could reach $8 billion to $10 billion. Allergan plc has licensed a pair of oral receptor antagonists from Merck & Co. Inc. for $250 million plus potential development and commercial milestone payments and tiered double-digit royalties. Meanwhile, Alder Biopharmaceuticals Inc., Eli Lilly and Co., Amgen Inc. and Teva Pharmaceutical Industries Ltd. are pushing their antibody-based treatments through the clinic.

PARTNERING DEALS CONTINUE AT STRONG PACE IN SECOND QUARTER

The land grab for assets continued at a torrid pace in the second quarter as pharma and biotech companies opened their bulging wallets to help strengthen their pipelines and position themselves in future emerging technologies. *BioWorld Insight* dives into the current deals universe and highlights some of the key transactions.

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OTHER NEWS TO NOTE

Benitec Biopharma Ltd., of Sydney, acquired full rights to the preclinical ddRNAi-based hepatitis B virus therapeutic program, Hepbarna, from **Biomics Biotechnologies Co. Ltd.**, of Nantong, China. The companies previously conducted the program as a joint venture. Benitec will pay Biomics A$2.5 million (US$1.86 million) up front with an additional A$3.5 million upon commercialization of the program. Biomics also will receive a single-digit royalty on net sales.

Cellectis SA, of Paris, said it achieved a milestone under its collaboration agreement with **Les Laboratoires Servier**, also of Paris, in the preclinical development of two next-generation candidates to treat solid tumors. Cellectis said the milestone triggered a payment but did not disclose the amount. (See *BioWorld Today*, April 2, 2014.)

Depomed Inc., of Newark, Calif., said the Patent Trial and Appeal Board of the U.S. Patent and Trademark Office issued its final decision in the inter partes review proceedings (IPRs) initiated by **Purdue Pharma LP**, of Stamford, Conn., against two Depomed patents (U.S. Patent Nos. 6,340,475 and 6,635,280), confirming the patentability of each of the 25 claims subject to the IPRs. Depomed said it will now continue its patent infringement case against Purdue, which alleges infringements of the patents by Purdue's reformulated Oxycontin (oxycodone HCl extended-release tablets). Depomed is currently being pursued in a hostile takeover bid by **Horizon Pharma plc**, of Dublin, which made an all-stock offer valuing Depomed at about $3 billion. (See *BioWorld Today*, July 8, 2015.)

IN THE CLINIC

Anika Therapeutics,Inc., of Bedford, Mass., reported positive results from the Cingal 13-02 study evaluating the safety of a repeat injection of Cingal for symptomatic relief of osteoarthritis (OA) of the knee. Cingal combines the company's cross-linked sodium hyaluronate (marketed as the single-injection viscosupplement Monovisc) with an FDA-approved steroid, triamcinolone hexacetonide. Earlier this year, Anika announced positive results from Cingal 13-01, a randomized, double-blind, placebo-controlled phase III study, which demonstrated the efficacy and safety of a single injection of Cingal for treatment of OA knee pain.

Globavir

Continued from page 6

As part of that deal, Nantpharma acquired Sorrento subsidiary Igdrasol Inc. for $90 million up front plus the potential for more than $600 million in regulatory milestone payments and $600 million more if sales targets are hit. Sorrento also will collect transfer pricing payments from unit sales and holds an option to co-develop and/or co-market Cynviloq, which could be the subject of a new drug application by year-end, via the 505(b)(2) pathway. (See *BioWorld Today*, May 18, 2015.)

Sorrento confirmed in an 8-K filed Thursday with the SEC that the sale of its interests in Igdrasol and Cynviloq to Nantpharma was completed.

In December 2014, Sorrento also committed $2 million and Soon-Shiong ponied up the remainder in a $50 million class A stock sale by Conkwest Inc., which isn't formally affiliated with the Nantworks conglomerate but lists Soon-Shiong as executive chairman and CEO. Conkwest, based in Cardiff-by-the-Sea, Calif., also is a partner in the immuno-oncology hunt. The goal is to integrate Conkwest's natural killer cell lines with fully human antibody libraries from Sorrento and take advantage of Nantworks' Nantomics proteomics platform. That strategy also embodies a cell production method and technology that allows for gene transfer without the need for lentivirus insertion. (See *BioWorld Today*, Dec. 26, 2014, and Jan. 16, 2015.)

In March, Nantworks and Sorrento expanded their collaboration, with a deal to discover and develop cancer immunotherapies derived from Sorrento's G-MAB library against Nantworks-identified neoepitopes of tumor-specific antigens drawn from its body of genomic and proteomic data. That arrangement called for another Nantworks subsidiary, Nantcell LLC, to pay Sorrento $10 million in cash and to provide a $100 million share of Nantcell equity and an unspecified share of profits from the partnership in exchange for an exclusive license to any antibodies or immunotherapies produced during the collaboration. (See *BioWorld Today*, March 17, 2015.)

The luster of immuno-oncology has helped Sorrento's shares (NASDAQ:SRNE), which are trading near their 52-week high. On Thursday, the stock gained 69 cents to close at $16.70. //

OTHER NEWS TO NOTE

Epizyme Inc., of Cambridge, Mass., said it amended and restated its agreement with Summit, N.J.-based **Celgene Corp.** to extend their research collaboration for at least three additional years. Under the collaboration, Celgene will have the option to license histone methyltransferase, or HMT, inhibitors being developed by Epizyme against three predefined targets. Revised terms call for Epizyme to receive a $10 million extension fee in return for an option to individually license global rights for two of the targets and ex-U.S. rights for the third target, and Celgene may exercise those options at the time of investigational new drug application filing for an additional pre-specified license payment. Epizyme will fund development for each candidate through phase I trials and may earn total potential milestones of up to $610 million on the three targets, including up to $75 million in development milestones and license fees, $365 million in regulatory milestones and $170 million in sales milestones, plus royalties up to the low double digits on worldwide sales. The firms have been working together since 2012. (See *BioWorld Today*, April 26, 2012.)

Genmab A/S, of Copenhagen, Denmark, said it completed the rolling submission of the biologics license application (BLA) for daratumumab as a treatment for patients with multiple myeloma who have received at least three prior lines of therapy, including both a proteasome inhibitor (PI) and an immunomodulatory agent (IMiD) or who are double refractory to a PI and an IMiD. The drug, a human IgG1k monoclonal antibody, was granted breakthrough therapy designation in that population earlier this year. Completion of the submission triggers a $15 million milestone payment from partner Janssen, a unit of New Brunswick, N.J.-based **Johnson & Johnson**. The companies have requested priority review for the BLA.

Iox Therapeutics Ltd., of Winnersh, UK, was launched as a spinout company of Isis Innovation, the University of Oxford's technology commercialization company, and Ludwig Cancer Research (LCR) to develop a cancer immunotherapy discovered through a collaboration between LCR and Vincenzo Cerundolo, the director of the MRC Human Immunology Unit within the University of Oxford's Weatherall Institute of Molecular Medicine. Work will center on discoveries of synthetic lipid compounds that activate iNKT cells, believed to play a role in antitumor immune responses, which could prove efficacious in combination with other immunotherapies.

Monopar Therapeutics LLC, of Lake Forest, Ill., reached agreement with Cancer Research UK and Cancer Research Technology to move Monopar's antibody treatment, HuATN-658, into the clinic in patients with advanced solid tumors. HuATN-658 is designed to target the cell surface protein uPAR, which is found in high levels in some of the most deadly cancers. Under the terms, Cancer Research UK's Centre for Drug Development will finance and complete preclinical development of HuATN-658 and conduct a phase I trial. Upon completion, Monopar has the right to acquire the clinical trial data.

Porton Biopharma Ltd., of Salisbury, UK, was spun out of Public Health England's clinical drug development and production capability into a standalone, state-owned biopharmaceutical limited company that has been approved by the Secretary of State for Health. The company manufactures the leukemia drug Erwinase as well as the only UK-licensed anthrax vaccine.

OTHER NEWS TO NOTE

Regen Biopharma Inc., of San Diego, said it dosed mice lacking an immune system in a safety and tolerability study of Hemaxellerate, its aplastic anemia cell therapy candidate. The purpose of the study is to evaluate whether administration of more than 10-fold the proposed clinical dose of cells in mice on a per-weight basis will cause any adverse effects on the experimental mice.

Synthetic Biologics Inc., of Rockville, Md., said in an SEC filing that its subsidiary Putney Drug Corp. and the Regents of the University of California entered an amendment to their 2005 license agreement and an amendment to the 2010 clinical trial agreement, granting Putney licenses under additional patent rights and other UC intellectual property, including related know-how, not currently licensed, related to the use of Estriol (and related compounds) for the treatment, prevention or palliation of any autoimmune disease, condition or indication, including, multiple sclerosis.

The Medicines Co., of Parsippany, N.J., said it inked a deal with Sandoz Inc., a unit of Basel, Switzerland-based **Novartis AG**, for the distribution of an authorized generic of Angiomax (bivalirudin) in the U.S. The antithromin product is indicated in patients undergoing percutaneous coronary intervention.

Tillotts Pharma AG, of Rheinfelden, Switzerland, part of the Zeria Group, said it agreed to acquire global rights for Entocort (budesonide) from **Astraeneca plc**, of London, excluding U.S. rights, which will remain with Astrazeneca. Entocort is a locally acting glucocorticosteroid, currently approved in more than 40 countries for the treatment of Crohn's disease and, in some markets, ulcerative colitis. Under the terms, Tillotts will make an up-front payment of $215 million. The transaction does not include transfer of any Astrazeneca employees or facilities.

Tocagen Inc., of San Diego, said the FDA granted fast track designation to its lead immuno-oncology product, Toca 511 & Toca FC, for the treatment of recurrent high-grade glioma, which includes glioblastoma and anaplastic astrocytoma. The treatment will enter a registrational study called Toca 5 later this year in patients with recurrent glioblastoma or anaplastic astrocytoma.

IN THE CLINIC

Dynavax Technologies Corp., of Berkeley, Calif., said the independent data and safety monitoring board (DSMB) for HBV-23, the ongoing phase III study of Heplisav-B, Dynavax's adult hepatitis B vaccine, completed its third pre-specified review and recommended that the study continue unchanged. The third DSMB review included safety data for all enrolled subjects collected through the data cut-off in June. Top-line results are expected to be released by early 2016.

Epizyme Inc., of Cambridge, Mass., said it dosed the first patient in a phase II trial of lead candidate tazemetostat (EPZ-6438) in patients with relapsed or refractory non-Hodgkin lymphoma. The five-arm study will enroll up to 150 patients with germinal center diffuse large B-cell lymphoma (DLBCL) or follicular lymphoma, stratified into those expressing mutant EZH2 and those expressing wild-type EZH2, as well as patients with nongerminal center DLBCL. A second planned phase II trial of tazemetostat in adult patients with INI1-deficient solid tumors is expected to initiate later in 2015, and a phase I study in pediatric patients with INI1-deficient solid tumors is also expected to start later this year.

Gradalis Inc., of Dallas, started a phase IIb study with its personalized cancer vaccine, Vigil, in the treatment of patients with Ewing's sarcoma family of tumors, or ESFT, disease, deemed to be refractory or intolerant to at least two prior lines of chemotherapy, who will be randomized 1-to-1 to receive either Vigil vaccine administered by standard intradermal injection once monthly for up to 12 months or a standard-of-care intravenous chemotherapy regimen of gemcitabine combined with docetaxel. The primary objective is to determine the one-year survival rate of patients treated with Vigil vs. gemcitabine/docetaxel. With Vigil, a patient's tumor cells are engineered to elicit a systemic T-cell-directed immune response when administered to the patient through intradermal injections, the company said.

Janssen Research & Development LLC, of Spring House, Pa., a unit of Johnson & Johnson, said data published in *The New England Journal of Medicine* from its phase IIb trial showed up to 86 percent of patients with moderate to severe plaque psoriasis receiving guselkumab (CNTO 1959) achieved a Physician's Global Assessment score of cleared psoriasis or minimal psoriasis at week 16, the study's primary endpoint. The X-plore study showed significantly higher levels of efficacy for all guselkumab doses at week 16 when compared with the placebo group, and responses were maintained through week 40 of the study. The trial also included an active comparator arm, which showed several guselkumab dosage regimens provided better response rates compared with the anti-tumor necrosis factor-alpha agent, Humira (adalimumab, Abbvie Inc). Guselkumab is a human monoclonal antibody that targets the protein interleukin-23.

Oncoceutics Inc., of Hummelstown, Pa., said enrollment was completed in a phase I dose-escalation study of lead compound ONC201. A total of 10 patients were enrolled – four at the escalating doses and six at the top dose level of 625 mg. The study has defined the recommended phase II dose, which was the primary goal, with full data to be reported once datasets are available for pharmacokinetics, pharmacodynamics and clinical observations for all patients. An efficacy-focused expansion phase into solid tumors with the highest sensitivity to ONC201, including prostate, colorectal and endometrial cancers, will begin shortly.

IN THE CLINIC

Regeneron Pharmaceuticals Inc., of Tarrytown, N.Y., and **Sanofi SA**, of Paris, said the 216-patient, phase III Odyssey Japan trial with Praluent (alirocumab) injection met its primary endpoint. At week 24, patients in the Praluent group experienced an average 64 percent greater reduction from baseline in their bad cholesterol, known as low-density lipoprotein cholesterol (LDL-C), when added to current standard of care, including statins, compared to standard of care alone ($p =/< 0.0001$). Patients were started on the lower dose of 75 mg, with the option to adjust their dose to 150 mg if they had not achieved their LDL-C goal (as defined by the Japan Atherosclerosis Society guidelines) at week eight. At week 24, 97 percent of patients in the Praluent group reached their LDL-C treatment goal, compared to 10 percent for placebo ($p < 0.0001$). Ninety-nine percent of patients treated with Praluent remained on the lower dose; two patients required adjustment to the higher dose.

Seattle Genetics Inc., of Bothell, Wash., said it started a phase II trial testing Adcetris (brentuximab vedotin), its CD30-targeted antibody-drug conjugate, in systemic lupus erythematosus. The randomized, double-blind, placebo-controlled dose-escalation trial will evaluate safety as the primary endpoint in about 40 patients with active disease. The study also will evaluate the activity and pharmacokinetics of Adcetris, which will be administered every three weeks.

Ultragenyx Pharmaceutical Inc., of Novato, Calif., reported interim data from the first 12 patients in the ongoing pediatric phase II study of its recombinant human monoclonal antibody, KRN23, against fibroblast growth factor 23 to treat X-linked hypophosphatemia (XLH). The mean rickets score for those patients, which was 1.4 at baseline using the Thacher Rickets Severity Scoring method, decreased by 58 percent, to 0.6, after 40 weeks of treatment with KRN23. Eight of 11 patients with rickets at baseline showed improvement, including three patients who no longer exhibited radiographic evidence of rickets at week 40. Of the 12 patients, six received biweekly dosing and six received monthly dosing of KRN23. The five patients with rickets at baseline in the biweekly dosing group all showed improvement, from a mean baseline rickets score of 1.5 to a mean score of 0.3 at week 40, representing an 80 percent reduction in rickets score. Half of the six patients in the monthly dosing group showed improvement, from a mean baseline score of 1.3 to a mean score of 0.8 at week 40, representing a 38 percent reduction in rickets score. No serious adverse events were reported and no discontinuations from the study occurred. Patients in the study continue to receive KRN23, and an additional 40-week analysis for 36 patients is planned for the fourth quarter. Ultragenyx is conducting the phase II study under a collaboration and license agreement with **Kyowa Hakko Kirin Co. Ltd.**, of Tokyo. Ultragenyx also said the FDA granted fast track designation to the KRN23 program in XLH. On Thursday, the company's shares (NASDAQ:RARE) hit a one-year high, closing at $112.65, for a gain of $13.63, or 13.8 percent.

The United Kingdom Cystic Fibrosis Gene Therapy Consortium (UKCFGTC) published the first data from a phase IIb, multidose trial for cystic fibrosis (CF) in which patients received aerosolized DNA plasmid-expressing cystic fibrosis transmembrane conductance receptor, or CFTR, manufactured by **VGXI Inc.**, of The Woodlands, Texas. The trial enrolled 136 patients 12 and older, who received monthly doses of the therapy or placebo for one year. Findings suggested gene therapy can have a meaningful effect on CF and benefit the lung function of patients. The UKCFGTC expects a larger study to assess higher and more frequent doses of the inhaled gene therapy.

APPOINTMENTS AND ADVANCEMENTS

Achaogen Inc., of South San Francisco, added Greg Stea to its board.

Argos Therapeutics Inc., of Durham, N.C., appointed John D. Menditto vice president of corporate communications and investor relations.

Bluebird Bio Inc., of Cambridge, Mass., named Philip Gregory chief scientific officer.

Egalet Corp., of Malvern, Pa., appointed Timothy P. Walbert board chairman.

Hemoshear LLC, of Charlottesville, Va., named Vincent E. Aurentz president. He will continue with his business development responsibilities.

Neos Therapeutics Inc., of Grand Prairie, Texas, added Paul Edick and John Schmid to its board.

Portola Pharmaceuticals Inc., of South San Francisco, appointed Tao Fu executive vice president, chief commercial and business officer.

PTC Therapeutics Inc., of South Plainfield, N.J., added Glenn D. Steele to its board.

Qu Biologics Inc., of Vancouver, British Columbia, named Jim Pankovich vice president, clinical operations and drug development.

Serenus Biotherapeutics Inc., of San Francisco and Johannesburg, added John Given, John Herlihy and Michael Boyd to its board, and named G. Kelly Martin board chairman.

Seres Therapeutics Inc., of Cambridge, Mass., added Dennis Ausiello to its board.

Shire plc, of Dublin, named Bill Mordan general counsel and corporate secretary, and added Olivier Bohuon to its board and appointed him to the science and technology committee.

Syndax Pharmaceuticals Inc., of Waltham, Mass., named Briggs W. Morrison CEO, and Michael A. Metzger president and chief operating officer.

Valeant Pharmaceuticals International Inc., of Laval, Quebec, appointed Robert L. Rosiello executive vice president and chief financial officer. Howard Schiller, former chief financial officer, will remain on the board and serve as a consultant.

Vtesse Inc., of Gaithersburg, Md., appointed Bjorn Hoffstedt and Heiko Runz to its scientific advisory board, and named Carrie Burke senior director, patient advocacy.

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