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SEVEN PHASE III TRIALS COMPLETED

Nymox heads toward filings, again, after long-term fexapotide win in BPH

By Marie Powers, News Editor

Although the development program for fexapotide (NX-1207) was encumbered by previous failure and threatened to go into extra innings – Nymox Pharmaceutical Corp. completed seven U.S. phase III trials, by its count – the company appeared to round third base and head for home after reporting success in the long-term repeated injection group from the phase III program for its lead candidate, designed to treat benign prostatic hyperplasia (BPH) and localized prostate cancer.

Details were scant, but the company maintained that long-term outcomes in 344

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STRATTERA BLACK-BOXING MATCH

Stimulating data in ADHD: Supernus NCE to 'fill gap' in soon-generic therapies?

By Randy Osborne, Staff Writer

In the wake of Alcobra Ltd.'s FDA-mandated clinical hold on the phase III study with metadoxine extended release in adults with attention deficit hyperactivity disorder (ADHD), Supernus Pharmaceuticals Inc. – which chalked up positive data Tuesday in a phase IIb trial

[See Supernus, page 4](#)

BIOSIMILARS

India ready to become major biosimilars player

By T.V. Padma, Staff Writer

NEW DELHI – India is very well placed to tap into the biosimilars opportunities expected in the next 15 years, with its domestic market poised to grow to \$40 billion by 2030, against a backdrop of an expected \$240 billion growth in the global market, according to a newly released white paper on India's potential in the sector.

Several large Indian companies have invested in biosimilars and have the capability for in-house product development, observes the paper by Hyderabad-based Sathguru Management

[See Biosimilars, page 5](#)

THE BIOWORLD BIOME

Takes two taus to tango, but they don't tangle

By Anette Breindl, Senior Science Editor

Researchers were able to reverse memory deficits in a mouse model of Alzheimer's disease by preventing cleavage of the protein tau by the enzyme caspase-2.

"There's a soluble aspect of tau that disrupts synaptic function, and we have identified a key player in why that occurs – the caspase-2 cleavage of tau," said Karen Ashe, a professor of neurology and neuroscience at the University of Minnesota, summarizing the results for *BioWorld Today*.

"Reducing caspase-2 caused synapses to repair themselves," which suggests that targeting the process Ashe and her team have identified might offer advantages over current strategies, which are by and large aimed at "preventing further decline."

Amyloid beta plaques and tau tangles are two anatomical hallmarks of AD. But

[See Alzheimer's, page 6](#)

JAPAN

Daiichi Sankyo pushes oncology efforts for aging Japan population

By Richard Smart, Staff Writer

TOKYO – Japan's Daiichi Sankyo Co. Ltd. is making progress in the oncology field, a key sector for social well-being as the global population grows older.

"The oncology pipeline of Daiichi Sankyo continues to grow and currently includes more than 20 small molecules and monoclonal antibodies with novel targets in both solid and hematological cancers," company official Jennifer Brennan told *BioWorld Today*.

Daiichi Sankyo has also entered a strategic collaboration with Agonox Inc., a privately held American biotech company that has previously partnered with Medimmune LLC, the global biologics arm of London-based AstraZeneca plc, on its OX40 agonist.

Agonox will collaborate with the Japanese company on the development

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REGULATORY FRONT

The **FDA** gave the all-clear Tuesday to **Janssen Pharmaceuticals Inc.**'s Xarelto (rivaroxaban) as a safe and effective alternative to warfarin in patients with atrial fibrillation (AF). The agency reached that verdict after completing a variety of analyses to assess the impact a faulty monitoring device had on results from the ROCKET-AF clinical trial that were used to demonstrate Xarelto's safety and efficacy in AF patients. The Alere Inratio device, which was used to monitor warfarin therapy in the trial's control group, was recalled in July due to the potential to generate inaccurate results.

The U.K.'s **Medicines and Healthcare products Regulatory Agency** (MHRA) signed a memorandum of understanding with Switzerland's regulatory agency, **Swissmedic**, to foster a shared approach to complex challenges and promote each other's regulatory frameworks, requirements and processes. The agreement is expected to provide a basis for increasing shared initiatives and creating a foundation for easier information-sharing between the two regulators, according to the MHRA. Failure to test batches of finished drugs sent to the U.S. landed **Yangzhou Hengyuan Daily Chemical Plastic Co. Ltd.**, of Yangzhou, China, on the **FDA's** import alert list and earned it a warning letter. The agency collected samples of the company's product at the port of entry and found that the drug didn't contain the specified API. Consequently, the FDA denied entry of the shipment and notified the U.S. customer, which filed a complaint with the Chinese company. Upon further investigation, Hengyuan discovered that the wrong ingredient had been added to the batch, according to the letter. During an FDA inspection of the Yangzhou facility, company officials acknowledged that the firm did not test all batches of finished drug product prior to release.

Rather than addressing quality control and manufacturing shortcomings found at its plant during an **FDA** inspection a few months ago, **Delarange Cosmetics & Healthcare BV**, of Zeewolde, the Netherlands, told the agency that it had informed its client that it would no longer produce drugs for

the U.S. market. That response drew an FDA warning letter specifying the problems at the plant that would have to be corrected should the company change its mind. The letter noted out that the company uses the same equipment to process drugs and other products. Because workers don't adequately clean the equipment between products, there's a risk that drugs could be contaminated with potentially toxic chemicals, the agency said. Other citations involved the lack of a quality unit to review and approve the release of drugs and the absence of final specifications release testing of the drugs.

Wallace Cameron International Ltd., of Wishaw, Scotland, received an **FDA** warning letter for continuing to import drugs into the U.S. even though it hasn't registered its establishment or listed its drugs with the agency for 2016. The FDA said it notified the drug company of its overdue registration and listing in March, but the firm has taken no steps to comply. The Sept. 29 warning letter, posted to the agency website Tuesday, gave the company 15 days to correct the violation and provide an explanation of each step being taken to prevent a recurrence, along with supporting documentation.

OTHER NEWS TO NOTE

Adex Therapeutics SA, of Geneva, said it started a study of ADX88178, a metabotropic subtype 4 receptor positive allosteric modulator, in a nonhuman primate model of cocaine self-administration. The study, being conducted through the company's ongoing research collaboration with the National Institute of Drug Abuse, will measure the effect of acute treatment with ADX88178 on intravenous (I.V.) cocaine self-administration in rhesus monkeys that self-administer varying doses of cocaine. The study will initially seek to determine effects of the compound on 0.4 mg/kg cocaine discrimination. Following that, a dose-ranging study will aim to determine which dose is most effective against I.V. 0.03 mg/kg/injection cocaine reinforcement in individual monkeys. Once the most effective dose is identified for each individual, the compound will be tested against a full cocaine dose-effect curve (0.001-0.1 mg/kg/injection, I.V.).

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Nymox

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patients who were given a single repeat fexapotide treatment after initial blinded treatment with fexapotide or placebo and followed for two to 6.5 years (mean 4.2 years) after initial treatment showed long-term statistically significant symptomatic improvement – measured as mean improvement of 6.5 points in the American Urological Association BPH Symptom Score – compared to phase III patients who received placebo alone ($p < 0.001$).

Nymox said the data analysis included all treatment failures. Repeat injection was determined to be safe, with no significant drug-related toxicities or side effects reported in the study.

Based on the findings, the Hasbrouck Heights, N.J.-based firm said it plans to file for regulatory approval within the next two quarters. Nymox said it will report additional analyses and results “when available in the near future” and present the data at unspecified medical and urological meetings while seeking to publish the findings in peer-reviewed medical journals.

Company officials did not respond to inquiries from *BioWorld Today*.

In development for more than a decade, fexapotide has been tested in nearly 1,000 men with enlarged prostates across seven years of placebo-controlled, double-blind U.S. studies, according to the company, which financed the entire development program. Among the studies were two prospective, randomized, multicenter, double-blind trials of fexapotide as a single injection along with two U.S. repeat injection trials and three blinded long-term extension studies. Nymox also completed several phase III safety and clinical pharmacology studies – 15 in all, according to Cortellis data.

Still, two years ago, Nymox hit headwinds after top-line data from a pair of phase III studies, NEXUS-1 and NEXUS-2, missed their primary endpoints – an outcome the company blamed on a stronger placebo response than seen in previous experiments. (See *BioWorld Today*, Nov. 4, 2014.)

At the time, CEO Paul Averback said on a conference call, “We had never encountered any problems before and we didn’t want to further complicate our studies, because they took long enough to do. Nobody has ever successfully enrolled 1,000 people for an injectable [year-long] prostate study where you had to do placebos before, and the more barriers you put in the more difficulty there would have been to enroll such a large number of people in the U.S.”

In April 2015, the company initiated additional analyses of the studies, and in July 2015, Nymox said phase III long-term extension studies of fexapotide in BPH met the pre-specified primary endpoint of statistically significant improvement in long-term symptomatic benefit over placebo. Nymox also said at that time that it planned to proceed with regulatory filings.

A month later, Nymox reported that it received formal approvals to change its domicile to the Bahamas.

In August of this year, Nymox reported findings from a phase III long-term cancer incidence analysis in which subjects received fexapotide or placebo to treat BPH symptoms and were followed for up to seven years (median of five years) following treatment. The study analyzed cases of prostate cancer that were subsequently diagnosed.

The expected rate of new prostate cancer cases in the U.S. general male population of middle-age and elderly men was in the range of 5 percent to 20 percent after seven years, according to Nymox. But data from the fexapotide study, which enrolled a similar population of middle age and elderly men with BPH, suggested a subsequent prostate cancer incidence of just 1.3 percent among those treated with the study drug, which Nymox called a statistically significant difference, without providing additional details.

Nymox also reported in August that a long-term, blinded, placebo crossover group study showed an 82 percent to 95 percent reduction in the number of patients who required surgery after they crossed over to fexapotide treatment compared to patients who crossed over to conventional, approved BPH treatments ($p < 0.0001$). In that study, long-term outcomes were determined in 391 patients who were given double-blind placebo injections, followed by crossover to other treatments at the discretion of each patient. The number of blinded placebo patients who subsequently received surgical treatment for BPH symptoms during the following two to three years was then prospectively analyzed.

As of June 30, Nymox reported cash and receivables, including tax credits receivable, of approximately \$327,000, compared with approximately \$653,000 as of Dec. 31, 2015.

On Tuesday, investors gave the company a vote of confidence, lifting shares (NASDAQ:NYMIX) in heavy trading by 41 cents, or 12.5 percent, to close at \$3.69. //

OTHER NEWS TO NOTE

Atara Biotherapeutics Inc., of South San Francisco, said the EMA issued a positive opinion for orphan drug designation for the company’s CMV-CTL cytomegalovirus (CMV)-specific cytotoxic T lymphocytes product candidate for the treatment of CMV infection in patients with impaired cell-mediated immunity. CMV-CTL utilizes a technology in which T cells are collected from the blood of third-party donors and then exposed to CMV antigens. The resulting activated T cells are then expanded, characterized and stored for future therapeutic use in an appropriate partially human leukocyte antigen, or HLA, matched patient, providing an allogeneic, cellular therapeutic option for patients.

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Supernus

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with [SPN-812](#) – finds itself in what CEO Jack Khattar called a “horse race” with [Sunovion Pharmaceuticals Inc.](#), recently the bearer of positive data from a pivotal trial with [dasotraline](#) in children ages 6 to 12.

[Viloxazine hydrochloride](#), the nonstimulant active ingredient in SPN-812, is considered a new chemical entity because it’s never been developed in the U.S. market, though it is available outside the U.S. as an antidepressant.

“We are building a strong intellectual property portfolio, with expirations that we expect to be in the 2029-2033 time frame” in ADHD, Khattar said during a conference call with investors. “As far as our plans on the antidepressant [side go], actually that is SPN-809, which you will see in our pipeline. We have always had that, as far as future plans go, to develop that product as an antidepressant. It hasn’t been a top, top priority. However, we actually have been making significant progress in moving SPN-809 [through] our pipeline by doing all the work we’ve been doing on SPN-812, because clearly it is the same molecule: viloxazine. We’ve done a significant amount of work on the active pharmaceutical ingredient synthesis, on the formulations, on all the preclinical work. All that will apply to SPN-809 as well – mind you, obviously, in a different indication.

“So we’ve been progressing 809 at the same time, basically, as we are progressing 812. Whether we will commercialize an antidepressant . . . that will probably not be the case for us,” and the program will likely be out-licensed, he said.

Meanwhile, Rockville, Md.-based Supernus is proceeding to an end-of-phase II meeting with the FDA after a positive dose-ranging experiment that tested SPN-812, also in children 6 to 12. The phase IIb trial hit the primary endpoint, demonstrating that SPN-812, a selective norepinephrine reuptake inhibitor, at daily doses of 400 mg, 300 mg and 200 mg, achieved a statistically significant improvement in the symptoms of ADHD from baseline to the end of the study, as measured by the ADHD Rating Scale-IV. The effort was a randomized, double-blind, placebo-controlled, multicenter trial, with each treatment administered orally once a day over five weeks, after a three-week titration phase. All doses tested in the trial were well-tolerated.

“Regarding which patient population [to pursue] in ADHD, you always have to do pediatric at minimum,” Khattar said. “You can’t even develop a product for adults without pediatric. Clearly, we will be going after pediatric and definitely after adult as well.”

He said the firm intends to start phase III trials next year, if talks proceed satisfyingly with the FDA.

FASTER ONSET KEY IN KIDS

Supernus has something of a hurdle as it faces the regulatory scrutiny given to Strattera (atomoxetine), from Indianapolis-based Eli Lilly and Co., which brings effects related to selective

inhibition of the pre-synaptic norepinephrine transporter to treat ADHD and therefore works similarly – and carries a black-box warning about suicidal thoughts in children and teenagers. “Given that viloxazine may be considered as a similar drug with similar kind of mechanism of action, that is a possibility” for the Supernus treatment as well, Khattar conceded.

“I don’t know yet for sure. We will see how that pans out as we develop the product and as we generate more data in the phase III trial.” But SPN-812 “doesn’t have any of the other side effects or issues [that] Strattera has, like liver damage [and] cardiac issues” such as blood-pressure fluctuations, he said. “We would still have a much cleaner side effect profile, even if we end up with a black-box warning.”

Jefferies analyst David Steinberg said SPN-812 “has the potential to fill an important ADHD market gap,” and estimated peak sales beyond \$250 million. “The limitations of stimulant therapies for ADHD [such as Vyvanse (lisdexamfetamine dimesylate, Shire plc) have been well-elucidated and [the Supernus candidate] therefore has the potential to become the leading branded nonstimulant ADHD drug (8 percent of ADHD prescriptions are nonstimulants), if successfully developed,” he wrote in a report. “Key possible benefits include a faster onset of action (efficacy as early as one to two weeks vs. about five weeks for Strattera), which is particularly important in children. And it would have no Drug Enforcement Administration scheduling constraints, which could assist uptake in what will be a largely genericized market segment later this decade.”

Intuniv (guanfacine, Shire plc) is already generic and Strattera is expected to meet the same fate next year, Steinberg noted, adding that the safety profile may ultimately save SPN-812 from a black-box warning. His peak-sales estimate “could prove conservative, as second to market Intuniv reached \$166 million during its first full year of promotion.”

Alcobra, of Tel Aviv, Israel, received formal word last week of the clinical hold on its ADHD study called MEASURE because of electrophysiological neurologic findings in previously submitted long-term animal studies with metadoxine, a selective antagonist to the 5-HT_{2B} receptor, a member of the serotonin receptor family. The FDA letter did not reference any clinical safety data observed in the MEASURE study or in previous human studies with the candidate, but U.S. regulators recommended that Alcobra schedule a meeting to discuss a plan to collect more human safety data in its development program. MEASURE is a multicenter, randomized, double-blind, placebo-controlled test of MDX (1,400 mg daily) for 10 weeks compared with placebo in adults.

Marlborough, Mass.-based Sunovion’s dasotraline, a dopamine and norepinephrine reuptake inhibitor, last month yielded results from the SEP360-202 phase II/III trial, a six-week, randomized, double-blind, multicenter, placebo-controlled, parallel-group, fixed-dose safety and efficacy experiment. The study evaluated once-daily dasotraline (2 mg/d and 4 mg/d dose arms) in 342 children, with a primary efficacy

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Biosimilars

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Consultants and the Associated Chambers of Commerce and Industry in India. The way the authors see it, the Indian biosimilars segment has built a strong foundation but now requires commercial strategies and a policy environment conducive to growth.

Several Indian firms – among them Dr. Reddy's Laboratories Ltd. and Aurobindo Pharma Ltd., both of Hyderabad; Biocon Ltd., of Bangalore; Zydus Cadila Healthcare and Intas Pharmaceuticals Ltd., of Ahmedabad; and others – have already made concerted investments and are poised to participate in that lucrative market.

Most of those companies are largely focused on the Indian market and rest of the world (ROW) markets as initial targets, but typically intend to expand to developed countries going forward. To achieve that expansion, collaborations will be fundamental, particularly to address the three key challenges the industry faces, according to the white paper.

First, the Indian biosimilars industry needs to accelerate the time to market. According to the paper, while the Indian industry has developed a high level of technical capability, given the time sensitivity of biosimilars, asset-level collaborations for technology access could accelerate the time to market and global competitiveness.

Second, the Indian industry needs to be more open toward risk-sharing if it wants to break into developed countries' markets. The U.S. and Europe represent the bulk of the opportunities in biosimilars. With an average investment of more than \$150 million needed per asset, a company has to shoulder a binary risk of \$600 million to \$1 billion in order to build a portfolio of around five assets.

"Risk-sharing co-investment collaborations, both with MNCs [multinational corporations] as well as with other Indian companies can help break this barrier to entry," the paper noted.

Third, the industry needs to expand its ROW markets to ensure commercial sustainability. Collaborations among Indian companies as well as with ROW companies will be critical to pool resources to expand markets, the paper said. While ROW markets are easier to access, financial sustainability will be elusive until markets expand to their true potential.

SUPPORT AND INCENTIVES

The paper also offers some recommendations on the kinds of government policy support needed. First, more nondilutive funding for development is required, as clinical validation investments for developed markets and related risks continue to be a challenge even for large Indian companies. While the investments are manageable for large companies focused on India and other ROW markets, younger technology-driven companies in India have experienced value erosion with the paucity of risk capital for clinical validation of

biopharmaceutical products, the paper said.

The Indian government has nondilutive grant funding mechanisms for initial de-risking of technology, but the funding is "negligible" given the long process in biosimilars product development and validation. The current funding mechanisms can support young ventures in the first few stages of development, but more structured funding is needed to de-risk the most capital intensive step of clinical validation for global markets in order for the Indian biosimilars industry to establish a global presence.

Second, while several Indian companies have now built strength across microbial and mammalian technology, technology access at the asset level will be important to accelerate the path to markets. According to the paper, the Indian government needs to extend its current fiscal incentives to corporate investments in technology acquisition, which is the "starting point" of risk investment for companies.

Third, while Indian regulators have been proactive in the early rollout of biosimilars guidelines, there is still a "great need" to fine-tune the regulatory processes to facilitate ease of functioning. That includes dropping several nonconsequential procedural steps such as approvals for toxicology studies, approvals for clone development/import, and approval for contract manufacturing organizations to manufacture clinical trial material.

Lastly, India needs to provide competitive fiscal incentives for attracting global investments for manufacturing, as well as incentives for the Indian industry in more aggressive product development and global commercialization programs.

"Our study highlights two key elements for the Indian industry to succeed in this competitive segment," Pushpa Vijayaraghavan, vice president of Sathguru Inc., told *BioWorld Today*. "With respect to the regulated markets, we point to the current Goliath vs. Goliath landscape and highlight the need for emerging market companies to collaborate and engage in risk-sharing co-investment models to break into the world's highest value markets.

"With respect to ROW markets, we are particularly concerned about the discouraging level of market expansion, despite the launch of biosimilars to break the affordability barriers. Here again, we urge companies to collaborate more willingly, to co-market biosimilars, intensify the momentum of market penetration efforts and collectively grow the market to its potential. This will be very important in emerging markets such as India." //

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Alzheimer's

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neither correlates particularly well with actual symptoms.

"The plaques don't correlate well at all," Ashe said. The pharma industry continues to learn that the hard way, with nothing to show, at least so far, for decades of strategies aimed at amyloid beta.

Tau pathology, which occurs later in the disease, correlates somewhat better. But in previous work, Ashe and her team had shown that tangles could be disentangled from cognitive deficits.

In work published in 2005, Ashe and her team showed that in a transgenic tau-driven model of AD, suppressing tau expression improved memory, even though tangles continued to accumulate. That work, Ashe said, demonstrated that "the tangles are not the cause of the disease."

For amyloid beta, the realization that plaques are not the cause of disease has shifted attention to targeting soluble oligomers. In the Oct. 10, 2016, issue of *Nature Medicine*, Ashe and her team suggest that for tau, the key to disease lies in its cleavage by caspase-2.

Cleavage at a certain amino acid, they showed in a mouse model of tau-driven AD, led to tau's translocation into synapses, where it affected receptors and impaired synaptic transmission. Memories are physically stored as changes in synaptic strength, and mice developed memory deficits. Those deficits could be reversed by inhibiting caspase-2.

In their studies, Ashe and her team found that the cut form of tau and the full-length version co-operate in an as-yet-unknown way to produce neural damage and memory deficits. Mice expressing a version of tau that could not be cut by caspase-2 developed neither neurodegeneration nor memory deficits.

Figuring out the exact nature of the interaction, Ashe said, "is going to take more work. . . . We need to understand whether the cleaved form is acting from inside the cell, or whether it might be getting released from the cell and acting to stimulate in another way."

What's already clear, though, is that cleaved tau is not working through tangles. The specific form studied by Ashe and her team, which is cut at amino acid 314 and called deltatatau314, does not form tangles.

Ashe and her team plan to investigate "how delta-tau causes full-length tau to mislocalize to dendritic spines," she said. She also plans to work with a medicinal chemist to develop a caspase-2 inhibitor that crosses the blood-brain barrier.

Ashe said that caspase-2 is "potentially a really nice target." In knockout studies, mice lacking caspase-2 had a normal life expectancy of roughly 900 days, and physiological abnormalities did not become apparent until the animals were about 450 days old.

Clinical treatment with a caspase-2 inhibitor would not completely abolish caspase-2 activity. "In our studies, we did not need to lower the activity very much," she said. And "drug companies like proteases – they are relatively conventional targets."

Protease inhibitors are mainstays in antiviral treatments, and are being explored in many other indications as well.

Caspase-2 has also been implicated in Huntington's disease and in neurodegeneration in amyloid precursor protein (APP)-driven mouse models of AD, but the enzyme does not cut either mutant huntingtin or APP. In their paper, Ashe and her colleagues wrote that "an intriguing question is whether the cleavage of tau by caspase-2 mediates APP- and huntingtin-induced synaptic deficits."

Another advantage of going after caspase-2, she said, is that it targets a process that occurs late in AD.

Some form of amyloid beta, "probably not the plaques themselves," triggers abnormalities in tau, but tau pathology ultimately becomes unlinked from amyloid beta.

"We're not making any assumptions about what's triggering the problem," she said. "What we're trying to do is block tau from going into the dendritic spines, where it causes synaptic dysfunction." //

Supernus

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endpoint of change from baseline to the sixth week in the ADHD Rating Scale-IV. The 4-mg dose arm demonstrated a statistically significant and clinically relevant difference compared to placebo, though the 2-mg dose arm was not statistically significantly different compared to placebo. Dasotraline was generally well-tolerated. The most common treatment-emergent adverse events (TEAE, reported in 5 percent or more of patients and greater than placebo) included: insomnia, decreased appetite and weight decreased. The overall discontinuation rate due to TEAEs in dasotraline-treated individuals was 9.3 percent, Sunovion said.

Shares of Supernus (NASDAQ:SUPN) closed Tuesday at \$23, down \$1.69. //

IN THE CLINIC

Agilis Biotherapeutics LLC, of Cambridge, Mass., said Taiwan regulators authorized a phase IIb study of gene therapy AGIL-AADC, an adeno-associated virus vector containing the human gene for the AADC enzyme, in patients with aromatic L-amino acid decarboxylase (AADC) deficiency. Eighteen patients have been treated to date in prospective studies using a single administration, and the latest phase IIb trial will enroll a third cohort of patients in two parts: one evaluating the AGIL-AADC therapy dose used in prior studies and a second exploring single administration of an increased dose.

Daiichi

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of an undisclosed immuno-oncology target as part of the U.S. firm's efforts to create a pipeline of immunotherapy drugs that target key regulators of the immune response to cancer.

"While this collaboration will help strengthen our immuno-oncology capabilities, it also aligns with our overall mission of discovering and delivering science that can change the standard of care for patients with cancer," said Antoine Yver, global head of oncology research and development at Daiichi Sankyo.

If preclinical development of the immuno-oncology target is successful, Daiichi Sankyo will have the exclusive option for the research, development, manufacturing and commercialization of the drug globally. The company declined to give any information on a time frame for getting the drug into clinical development.

In a separate announcement, however, Daiichi Sankyo said DS-8201a, a novel HER2-targeting antibody-drug conjugate that has shown potential for treating breast cancer, gastric cancer and gastroesophageal junction adenocarcinoma, was well-tolerated with no dose-limiting toxicities. The company will now send the drug into the second part of its phase I trial.

"These preliminary results are compelling and warrant further clinical evaluation of DS-8201a in several different patient populations expressing HER2," said Yver.

"While the results of this study provide important preliminary proof of concept for the novel mechanism of the action of DS-8201a, additional research will be needed to further confirm these findings," added Jose Baselga, physician-in-chief and chief medical officer at Memorial Sloan Kettering Cancer Center, New York.

Brennan pointed out that DS8201a is one of multiple drugs the company has in its pipeline for treating cancer.

"Compounds in phase III development include quizartinib, an oral FLT3-ITD inhibitor for newly diagnosed and relapsed/refractory FLT3-ITD-positive acute myeloid leukemia; pexidartinib, an oral CSF-1R inhibitor for tenosynovial giant cell tumor, also known as pigmented villonodular synovitis and giant cell tumor of the tendon sheath, which is also being investigated in combination with anti-PD1 immunotherapy, pembrolizumab, in a range of solid tumors; and tivantinib, an oral MET inhibitor for second-line treatment in patients with MET-high hepatocellular carcinoma, in partnership with Arquele Inc.," she said.

Daiichi Sankyo, like many Japanese companies, faces the troubling issue of a shrinking market at home as the nation rapidly turns grayer. While there is more need for medicine, there is also less money to fund research and development as social security costs rise.

"One of the hardest things is health care," said Nancy Morrow-Howell, director of the Harvey A. Friedman Center for Aging at

Washington University in St. Louis. "Health care has become such a problem because we have to live a long time with chronic conditions. Health care costs so much because we're living longer with chronic conditions."

Japan will be at the front line of such conditions.

"Based on the results of the medium-fertility projection, Japan is expected to enter a long period of population decline. The population is expected to decrease to around 116.62 million by 2030, fall below 100 million to 99.13 million in 2048, and drop to 86.74 million by 2060," the National Institute of Population and Social Security Research wrote in a report.

Koji Ogawara, at Daiichi Sankyo's Japan office, said his company, like most in Japan, would not comment on the government's drug pricing policies. However, he acknowledged that the nation's shrinking population has led the company to look for new strategies for the future.

"One of our visions is to have enriched regional value products aligned with regional markets, including in developing nations," he said.

"We are expanding our business in developing nations [and regions] such as China, Brazil and Southeast Asia, etc., by providing olmesartan, [an] anti-hypertension [treatment] and edoxaban, an oral anticoagulant, etc., which are medicines for lifestyle diseases," Ogawara added.

Daiichi Sankyo shares (TYO:4568), which ended last week at ¥2,454.5 (US\$23.82), closed Tuesday at ¥2,493. //

OTHER NEWS TO NOTE

Allergan plc, of Dublin, said the FDA accepted for filing the NDA for Avycaz, seeking the addition of new phase III trial data evaluating Avycaz in patients with complicated urinary tract infections (cUTI), including pyelonephritis, due to designated susceptible pathogens to the current product label. The FDA granted priority review status to that application based on the previous qualified infectious disease product designation for Avycaz and is expected to take action on the filing in the first quarter of 2017. Avycaz is an antibiotic developed to treat certain serious gram-negative bacterial infections. It consists of ceftazidime, a third-generation cephalosporin, and avibactam, a non-beta lactam beta-lactamase inhibitor. It was first approved in the U.S. in February 2015 for the treatment of adult patients with complicated intra-abdominal infections (cIAI), in combination with metronidazole, and cUTI, including pyelonephritis, caused by designated susceptible bacteria, including certain *Enterobacteriaceae* and *Pseudomonas aeruginosa*. In June 2016, the FDA approved the addition of data from a phase III cIAI trial to the label that evaluated the safety and efficacy of Avycaz, in combination with metronidazole, for the treatment of cIAI, including data from a subset of patients with infections caused by ceftazidime-nonsusceptible pathogens and a subset of patients with pathogens producing certain extended-spectrum beta-lactamases.

OTHER NEWS TO NOTE

Aum Lifetech Inc., of Philadelphia, said it has, with collaborators at the Beckman Research Institute at the City of Hope in California and McGill University in Canada, developed a new approach to combat HIV. Encouraging data showing the inhibition of HIV replication using the firm's FANA antisense technology were presented at the annual Oligonucleotide Therapeutics Society meeting in Montreal. The ability of FANA antisense oligonucleotides to be self-delivered in cellular and in vivo models without the use of any conjugates, carriers or formulations make them very attractive for development of nucleic acid therapeutics, or more precisely RNA silencing therapeutics, for a wide spectrum of genetic diseases, the company said. In that study, Aum succeeded in effectively targeting HIV RNA and saw promising preliminary results.

Cellerant Therapeutics Inc., of San Carlos, Calif., reported preclinical data showing potent killing of leukemic blast and

stem cells by CSC030-ADC, the company's antibody-drug conjugate candidate being developed for acute myeloid leukemia (AML). CSC030-ADC targets CSC030, or the C-type-like lectin 1, a cell surface antigen widely expressed in nearly all AML cell subtypes, including leukemic stem cells, but not on normal hematopoietic stem and progenitor cells. Data were presented at the World ADC meeting in San Diego.

Celsion Corp., of Lawrenceville, N.J., disclosed a collaboration with the Children's Research Institute to conduct a clinical study of Thermodox, Celsion's heat-activated liposomal encapsulation of doxorubicin, in combination with magnetic resonance-guided high intensity focused ultrasound to treat relapsed or refractory solid tumors in children and young adults. The investigator-sponsored phase I study is being partially funded by the NIH and is expected to commence in the fourth quarter.

Cleveland Biolabs inc., of Buffalo, N.Y., said the Department of Defense modified its Joint Warfighter Medical Research Program contract award with CBLI valued at up to \$9.2 million, which supports further development of entolimod as a medical radiation countermeasure. The modification changes the original statement by eliminating certain tasks no longer deemed critical for the preparation of a BLA of entolimod as a radiation countermeasure and establishes new tasks to address questions raised by the FDA, including an aim to conduct a pharmacokinetic/pharmacodynamic biocomparability study in a nonhuman primate model, along with other drug manufacturing-related activities. The aggregate amount of consideration payable to CBLI will be unaffected.

Critical Outcome Technologies Inc., of London, Ontario, declared its next clinical candidate, COTI-219, described as an oral, small-molecule compound targeting the mutant forms of KRAS. COTI-219 was discovered using the company's drug discovery technology platform, Chemsas.

Curis Inc., of Lexington, Mass., said it expanded its product pipeline with the addition of CA-327, an oral, small-molecule immune checkpoint antagonist targeting programmed death ligand-1 (PD-L1) and T-cell immunoglobulin and mucin domain containing protein-3 (TIM-3). The company licensed the PD-1/TIM-3 antagonist program, and designated CA-327 as the development candidate, by exercising its option under the collaboration, license and option agreement established with **Aurigene Inc.**, of Boston, in January last year. The in-license of CA-327 comes three months after the collaboration's first oral immuno-oncology program entered the clinic and less than a month after a \$24.5 million investment in Curis by Aurigene. CA-327 is the third program in their collaboration. The first two programs comprise an orally available small-molecule antagonist of PD-L1 and V-domain Ig suppressor of T-cell activation, or VISTA, in the immuno-oncology field, and an orally available, small-molecule inhibitor of interleukin-1 receptor-associated kinase 4 in the precision oncology field. In September, the agreement was amended allowing Aurigene to invest up to 10.2 million shares of Curis' common stock in lieu of \$24.5 million of milestone and other payments. (See *BioWorld Today*, Jan. 22, 2015.)

Wondering what you missed in *BioWorld Insight*?

BIOPHARMA COMPANIES ABLE TO GENERATE \$12.6B IN 3Q

Financings in the biopharma sector were decidedly better in the third quarter compared to their dismal showing during the second quarter. The total generated from public and private transactions were \$12.7 billion over double the amount that was raised in the second quarter. In the period, investor confidence returned fueling a broad market rally after its tumble following Brexit and this helped the biotech sector. The strong showing has helped bring the year-to-date financings to \$25 billion – *BioWorld Insight* breaks down the numbers in its 3Q analysis.

BIOTECH IPOs SLOW IN 3Q DESPITE IMPROVEMENT IN GENERAL MARKETS

Biotech IPOs were sluggish in the third quarter, with only seven companies successfully completing their offerings on U.S. exchanges raising a collective \$396 million in the process according to BioWorld analysis. This was 42 percent below the 12 biotech IPOs, raising \$1.35 billion in the third quarter last year and 36 percent off the 11 companies completing their offerings in the second quarter this year, raising \$564 million. Although it looks as though investors are not supporting new biotech issues as once they did, there was, however, a notable improvement in the IPO market in general with tech companies, in particular, finding considerable support once again.

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IN THE CLINIC

Auris Medical Holding AG, of Zug, Switzerland, said, based on insights from the recently completed TACTT2 trial testing Keyzilen (AM-101) in acute inner ear tinnitus, it is submitting a protocol amendment to regulatory agencies in Europe for TACTT3, the ongoing second phase III trial. In the amended protocol, the change in Tinnitus Functional Index score will be elevated from a key secondary endpoint to an alternate primary efficacy endpoint. Certain patient subgroups will be included in confirmatory statistical testing, and the trial size will be increased to enhance statistical sensitivity to the effects of treatment. Top-line results from the expanded TACTT3 trial are now expected in early 2018. Auris said the outcomes from TACTT2 and the regulatory path forward will be reviewed with the FDA in early December. Auris reported in August that Keyzilen failed to hit its endpoints in the TACTT2 study. (See *BioWorld Today*, Aug. 19, 2016.)

China Biologic Products Inc., of Beijing, said Shandong Taibang Biological Products Co. Ltd., its majority-owned subsidiary, recently obtained CFDA approval to begin clinical trials of its human antithrombin III (ATIII) product, which is intended to treat hereditary and acquired ATIII deficiency in connection with surgical or obstetrical procedures, and to treat thromboembolism. Studies are slated to start in 2017.

Excicure Inc., of Skokie, Ill., reported results from its phase I trial testing AST-005 a spherical nucleic acid, or SNA, designed to reduce the expression of tumor necrosis factor messenger RNA (TNF mRNA), demonstrating the drug met the safety and tolerability requirements in patients with mild to moderate psoriasis. Pharmacodynamics assessments performed from the treated plaque area revealed that treatment with the highest dosing strength of AST-005 gel resulted in a statistically significant decrease in TNF mRNA expression in the psoriatic skin.

Kempharm Inc., of Coralville, Iowa, said the FDA accepted its IND for KP415, an extended-release d-threo-methylphenidate prodrug for the treatment of attention deficit hyperactivity disorder. The company expects to start and complete proof-of-concept studies prior to the end of this year, with additional clinical trials starting in the first half of 2017.

Merrimack Pharmaceuticals Inc., of Cambridge, Mass., reported final results from the pivotal phase III NAPOLI-1 study on the use of Onivyde (irinotecan liposome injection) in combination with fluorouracil (5-FU) and leucovorin in patients with metastatic pancreatic ductal adenocarcinoma at the European Society for Medical Oncology meeting in Copenhagen. In the extended analysis of NAPOLI-1, the previously described overall survival advantage was maintained for Onivyde in combination with 5-FU and leucovorin vs. 5-FU and leucovorin alone: 6.2 months vs. 4.2 months ($p=0.039$). Findings also showed that one in four patients treated with the Onivyde combination regimen survived one year or more.

That was represented by a 26 percent probability of survival at one year for patients receiving Onivyde in combination with 5-FU and leucovorin vs. 16 percent for patients who received 5-FU and leucovorin alone. Disease control was achieved in twice as many patients treated with the Onivyde regimen (52 percent) compared to 5-FU and leucovorin alone (24 percent). Onivyde gained FDA approval last year, though the second-line pancreatic cancer drug has recorded slower than expected sales, resulting in a work force reduction at Merrimack earlier this month. (See *BioWorld Today*, Oct. 23, 2015, and Oct. 4, 2016.)

OWC Pharmaceutical Research Corp., of Petach Tikva, Israel, said it started the final phase for testing the efficacy of its topical cream cannabinoid-based compound for treating psoriasis and related skin conditions.

Transgene SA, of Strasbourg, France, said it entered a collaboration with **Merck KGaA**, of Darmstadt, Germany, and **Pfizer Inc.**, of New York, under which Transgene will sponsor a phase I/II study evaluating the potential of the therapeutic vaccine candidate TG4001 in combination with avelumab, an investigational fully human anti-PD-L1 IgG1 monoclonal antibody, for the treatment of human papillomavirus-positive head and neck squamous cell carcinoma, after failure of standard therapy. The trial is expected to begin in France, with the first patient expected to be recruited in the first half of 2017.

OTHER NEWS TO NOTE

Gamida Cell Ltd., of Jerusalem, said the FDA granted breakthrough therapy designation to the company's lead product candidate, Nicord, in development as a graft modality for bone marrow transplantation in patients with high-risk hematological malignancies such as leukemia and lymphoma. A phase III registration study of Nicord is planned to begin before the end of the year.

Genentech Inc., of South San Francisco, a member of the Roche Group, said the FDA accepted a supplemental biologics license application (sBLA) and granted priority review for Lucentis (ranibizumab injection) for the treatment of myopic choroidal neovascularization (mCNV), a complication of severe near-sightedness that can lead to blindness. The sBLA is based on results from the phase III RADIANCE study that demonstrated treatment with Lucentis provided superior visual acuity gains in people with mCNV compared to verteporfin photodynamic therapy, the only treatment currently approved by the FDA for mCNV.

Heat Biologics Inc., of Durham, N.C., said it advanced a biomarker discovery collaboration with **Adaptive Biotechnologies Inc.**, of Seattle, which will use its immune profiling assay, immunoseq, to enable an in-depth characterization of the immune response to Heat's Impact and Compact-based immunotherapies, including HS-410, its phase II product candidate for non-muscle invasive bladder cancer.

OTHER NEWS TO NOTE

Immunovaccine Inc., of Halifax, Nova Scotia, said top-line preclinical data presented at the World Vaccine Congress Europe in Barcelona, Spain, showed in mice studies that malarial targets identified by the University of Edinburgh's Centre for Immunity, Infection and Evolution and formulated using Depovax generated strong, sustained, antibody responses that could prevent, after a single injection, a process in severe malaria known as "rosetting" that can result in hypoxia, organ damage, and, in some cases, death. In addition, researchers were able to combine antigens into a single vaccine administration that was able to protect red blood cells from rosetting across a wide range of malarial strains.

Kymab Ltd., of Cambridge, U.K., and **Epimab Biotherapeutics Inc.**, of Shanghai, signed a crosslicensing and development agreement to develop bispecific therapeutic antibodies against multiple targets. They will focus their efforts on immuno-oncology and will combine antibodies sourced from Kymab's Kymouse platform with Epimab's Fabs-In-Tandem Immunoglobulin, or FIT-Ig, platform to generate multiple bispecific antibodies. Kymab will have the development and commercialization rights to those bispecifics in all geographical regions outside of China, and, under the terms of the agreement, Epimab will have the rights to the China market. Each company is eligible to receive milestone payments and royalties for development programs pursued by the other.

Meiragtx Ltd., of New York, said it expanded its gene therapy program to treat amyotrophic lateral sclerosis (ALS). With collaborators, the firm is working on a therapy to target TDP-43 toxicity in ALS patients. The cellular protein TDP-43 is misregulated in the vast majority of all ALS patients and is emerging as a possible Achilles' heel in the treatment of the neurodegenerative disease, the company said.

Neurocrine Biosciences Inc., of San Diego, said the FDA accepted for priority review its new drug application for Ingrezza (valbenazine, previously NBI-98854) to treat tardive dyskinesia and set a PDUFA date of April 11, 2017. (See *BioWorld Today*, Oct. 9, 2015.)

Paratek Pharmaceuticals Inc., of Boston, signed a Cooperative Research and Development Agreement with the U.S. Army Medical Research Institute of Infectious Diseases to study omadacycline against pathogenic agents that cause infectious diseases that affect public health and biodefense. The studies are designed to confirm humanized dosing regimens of omadacycline for efficacy against pathogens such as *Yersinia pestis* (plague) and *Bacillus anthracis* (anthrax). The trial is being funded through the Defense Threat Reduction Agency/ Joint Science and Technology Office and the Joint Program Executive Office for Chemical and Biological Defense/Joint

Project Manager Medical Countermeasure Systems/Biodefense Therapeutics. Terms call for Paratek to provide omadacycline and technical expertise to support preclinical pharmacokinetic and efficacy studies of the broad-spectrum antibiotic, which could generate data to support additional development for biodefense purposes. Omadacycline is in phase III development by the company to treat acute bacterial skin and skin structure infections. (See *BioWorld Today*, June 20, 2016.)

Protein Sciences Corp., of Meriden, Conn., said the FDA approved its quadrivalent formulation of Flublok influenza vaccine, which is designed to protect against four strains of influenza, three of the same strains found in trivalent Flublok plus an additional B strain.

Renova Therapeutics Inc., of San Diego, said it obtained an exclusive, worldwide license to a urocortin 3 gene patent from the nonprofit Research Development Foundation (RDF), which Renova plans to research for development of paracrine gene therapy treatments in cardiovascular diseases such as heart failure. The patent expands the intellectual property estate of the company, which has previously obtained a license agreement for RDF's patent portfolio of stresscopin and urocortin genes and peptides. Renova's paracrine gene therapy is based on a systemic approach designed to introduce genes capable of directing the body's cells to work more normally.

Second Genome Inc., of South San Francisco, is conducting microbiome profiling and analysis for the King's College London's Enquiring About Tolerance (EAT) study in eczema and food allergies in young children. The randomized, controlled study of food allergy prevention will investigate both skin and gut microbiota of more than 300 infants at multiple points over the course of the first year of life, seeking to discover whether early introduction of allergenic foods into an infant's diet can prevent the development of food allergies. EAT also will examine whether other allergic conditions, such as asthma, eczema and hay fever, can be prevented by the same approach. The work will be conducted by Second Genome Solutions, an internal team that provides microbiome research support to external partners.

VBI Vaccines Inc., of Cambridge, Mass., said it completed a pre-IND meeting with the FDA to discuss the development plan for VBI-1901, its glioblastoma multiforme immunotherapy candidate, and the firm now anticipates filing the IND in the first half of next year. The FDA will consider a fast track designation for VBI-1901 at the time of submission, the company said.

Xbiotech Inc., of Austin, Texas, said the U.S. District Court for the Western District of Texas granted the company's motion to dismiss in the 2015 securities class action lawsuit brought against the firm and certain of its directors. The judge dismissed the lawsuit with prejudice, barring the plaintiff from refileing the claim.