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BUYING R-TECH UENO FOR $278M

Sucampo Pharmaceutical's big move sets stage for more growth, diversification: CEO

By Jennifer Boggs, Managing Editor

Sucampo Pharmaceuticals Inc. is buying Japanese firm R-Tech Ueno Ltd. through an all-cash tender offer valued at ¥33 billion (US$278 million), a deal CEO Peter Greenleaf said marks both the culmination of the company's transformation over the past year and the trajectory of its future growth via business development efforts.

The deal, set to close in the fourth quarter pending a successful tender offer, is expected to boost the company's revenue, give the Bethesda, Md.-based firm supply

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Immatics, MD Anderson alliance results in U.S. firm focused on T-cell immunotherapies

By Nuala Moran, Staff Writer

LONDON – The rush into T-cell immunotherapy continues, with Germany's Immatics Biotechnologies GmbH teaming up with MD Anderson Cancer Center in the formation of a $60 million U.S. subsidiary.

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THE BIOWORLD BIOME

Amyotrophic lateral sclerosis mutation affects trade routes

By Anette Breindl, Senior Science Editor

Three separate studies have identified the nuclear pore as a key area affected by the C9ORF972 mutation that is the major cause of inherited amyotrophic lateral sclerosis (ALS), as well as a

See ALS, page 5

FINANCINGS

Bispecifics: Merus attracts $80.5M series C for its immunotherapy pipeline

By Michael Fitzhugh, Staff Writer

Merus BV, a Dutch developer of bispecific antibodies for cancer immunotherapy, claimed the first tranche of a €72.8 million (US$80.5 million) series financing led by Sofinnova Ventures and

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REGULATORY

MI3 alert bemoans negative impact of MDUFA, PDUFA

By Mari Serebrov, Regulatory Editor

On the eve of the next round of user fee negotiations, MDUFA and PDUFA received scathing grades for their unintended consequences and negative impact on drug and device innovation.

Overall, the five-year agreements scored a -3, on a scale of -10 to +10, according to a Medical Innovation Impact Index (MI3) alert issued by the Initiative for Patient-Centered Innovation at Fairleigh Dickinson University.

While the prescription drug and medical device user fee agreements have provided additional resources for the FDA and aimed for shorter review times over the years, the alert pointed out that they've created a "disjointed, cumbersome and exploding body of law" that's actually hampering reviews and discouraging innovation.

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NEWCO NEWS

WATCH YOUR TONGUE

Thetis using 'salty' chemistry to transform diabetes care

By Marie Powers, News Editor

In his 35 years at Pfizer Inc., including tenure as the New York-based pharma's director of R&D operations, Frank Sciavolino was immersed in the science

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REGULATORY FRONT

The **Patent and Trademark Office** has accepted inter partes review (IPR) petitions filed by **Mylan NV**, of Hertfordshire, UK, challenging two patents on Copaxone 40 mg/mL. Licensed to Teva Pharmaceuticals Industries Ltd., of Jerusalem, the method patents relate to treating multiple sclerosis through the administration of at least three 40-mg subcutaneous injections of glatiramer acetate over seven days with at least one day between each injection. The PTO has yet to accept another Mylan petition seeking an IPR on a related patent, the company said.

The **National Institute of Allergy and Infectious Diseases** launched a study that will expose healthy adults to respiratory syncytial virus (RSV) to shed more light on how RSV infections develop and the immune system responds. The pilot study will enroll up to 60 healthy men and nonpregnant women, ages 18 to 50. Study participants, who will receive a drop of liquid containing RSV in each nostril, will be hospitalized in isolation at the NIH Clinical Center in Bethesda, Md., for one to two weeks and monitored daily. Staff will conduct blood draws and sample nasal secretions to study the development of infection. RSV is the most common cause of lower respiratory tract infections, including pneumonia and bronchiolitis.

SB Medical Inc., of Toronto, and **TC Medical Group**, of St. Michael, Barbados, were fined $45 million and required to forfeit $30 million for orchestrating a conspiracy to smuggle misbranded prescription drugs into the U.S., the **FDA** reported. The sentencing followed guilty pleas entered in federal district court in May. According to court documents, the companies smuggled non-FDA approved orthopedic injections, rheumatology infusions, cosmetic devices, eye products and cancer drugs that were sourced from countries such as France, India, Italy and Turkey. The companies sent multiple small shipments to addresses in various states with falsified Customs forms. The drop shippers who received the packages in the U.S. removed any indications that the shipments were from abroad and then re-shipped them to doctors and clinics with a U.S. return address. The drop shippers stored the drugs and devices in the basements of their homes, often violating storage requirements, the FDA said.

The **FDA** finalized its 2014 draft guidance on conducting shedding studies for virus or bacteria-based gene therapy and oncolytic products during preclinical and clinical development. The final guidance provides more clarity and addresses questions raised during the comment period and at a Nov. 6 meeting of the Cellular, Tissue and Gene Therapies Advisory Committee, the FDA said in a notice slated for publication in Thursday's *Federal Register*.

STOCK MOVERS 8/26/2015

Company	Stock in $	Change in %
Nasdaq Biotechnology	+$173.65	+5.09%
Galmed Pharmaceuticals	+$1.39	+18.91%
Immune Design Corp.	+$1.55	+11.16%
Marinus Pharmaceuticals	+$1.20	+9.35%
Skyepharma	+$27.75	+10.38%
Verastem Inc.	-$1.72	-26.02%

Biotechs showing significant stock changes Wednesday

IN THE CLINIC

Emisphere Technologies Inc., of Roseland, N.J., said that **Novo Nordisk A/S**, of Bagsvaerd, Denmark, will initiate a global phase IIIa development program with oral semaglutide (NN9924), a once-daily oral formulation of the long-acting glucagon-like peptide-1 analog semaglutide, for the treatment of type 2 diabetes that relies on Emisphere's Eligen technology, which facilitates the absorption of small and large molecules without altering their chemical form, biological integrity or pharmacological properties.

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Sucampo

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chain control over flagship product Amitiza (lubiprostone) – the constipation drug currently is manufactured by R-Tech Ueno – and diversify its pipeline into other areas, including the hot, emerging immuno-oncology space.

"We previously stated that a key goal is to execute on a business development strategy and transactions that were ... immediately accretive and diversify our pipeline," Greenleaf told investors on an early Wednesday conference call. The latest move is "our first major step toward these objectives."

But Sucampo had been working quietly since Greenleaf took the helm early last year to lay the groundwork for building out a global, development and commercial biopharma firm. Much of that focused on bolstering the Amitiza business, expanding its commercial partnership with Takeda Pharmaceutical Co. Ltd. beyond the U.S., inking a Chinese partnership with Harbin Gloria Pharmaceuticals Co. Ltd. and working to broaden Amitiza's use by filing for approval in Canada and picking up a positive recommendation for the drug by the UK's National Institute for Health and Care Excellence.

Amitiza, approved for chronic idiopathic constipation, opioid-induced constipation and irritable bowel syndrome with constipation, so far, has continued to see sales grow, despite competition from Ironwood Pharmaceuticals Inc.'s Linzess (linaclotide) and, most recently, the addition of Movantik (naloxegol, Nektar Therapeutics Inc. and Astrazeneca plc). Management had predicted that the new entrants would help grow the constipation market for all players, and sales so far – Takeda reported U.S. sales increased 15 percent year over year to $88.2 million for the second quarter – have borne that out. (See *BioWorld Today*, Sept. 17, 2014.)

Sucampo is forecasting Amitiza to continue growing, with mid- and long-term revenue growth in the high single digits to mid teens, estimates that appear more likely following last year's resolution of a generic challenge to Amitiza, which preserves patent protection until 2021.

"Much of what we did in 2014 might be viewed as sort of small moves," Greenleaf told *BioWorld Today*, adding that the firm also changed out "probably 80 percent" of the management team, specifically bringing in experts in both small molecules and biologics and rounding out those scientific additions with experienced clinical, regulatory and commercialization leaders.

"So the early, smaller moves might not be seen as transformational truly, but they were the building blocks," he added.

The R-Tech Ueno agreement, however, is expected to have a "substantial positive impact on future financial results," Greenleaf told investors. Sucampo anticipates almost doubling its net income in 2016 vs. 2015, reaching $55 million to $60 million and is guiding for a 2016 earnings per share of $1.20 to $1.30.

In addition to saving on manufacturing payments to R-Tech Ueno, Sucampo also will pick up manufacturing revenue R-Tech Ueno earns from Amitiza partners Takeda, Gloria and Mylan NV, which sells the drug in Japan. For the three months ending June 30, R-Tech Ueno reported ¥1.5 billion in revenue from Amitiza.

The Japanese firm also receives revenue from Rescula (unoprostone isopropyl), approved for the management of open-angle glaucoma and ocular hypertension. That drug, however, has gone generic, so sales are relatively limited, with R-Tech Ueno reporting about ¥182 million for the three months ending June 30.

Upon closing of the deal, Sucampo expects annual cost savings of $5 million, starting in 2016.

PRIORITIZING THE PIPELINE

Sucampo's offer for R-Tech Ueno consists of about $54 million in cash and 2.5 million Sucampo shares, representing roughly 5.5 percent of shares outstanding. Specific terms call for Sucampo's Japanese subsidiary to offer ¥1,900 per share in cash for 56 of the outstanding shares in the tender offer. Taking into account the market volatility of the past week, that price marks a 16 percent premium to the Japanese firm's three-month volume-weighted average price.

Shares of R-Tech Ueno (TOKYO:4573) closed Wednesday at ¥1,278, up ¥108 or 9.23 percent.

Sucampo expects to acquire 56 percent of the outstanding shares via the tender offer. The remaining 44 percent will be acquired for ¥1,400 per share from R-Tech Ueno's founders and a related entity, the company said.

R-Tech Ueno was founded in Tokyo in 1989 by Ryuji Ueno and Sachiko Kuno, who went on in 1996 to establish a U.S. firm that later became Sucampo. The now-husband-and-wife team is largely focused on philanthropy, though the couple retains a significant stake in Sucampo.

Plans for integrating R-Tech Ueno into Sucampo are still in the works, Greenleaf said. For one, the company will move from having 13 to 15 employees in Japan to more than 90 employees.

There's also the expanded pipeline to consider. Sucampo already has made an early commitment for two R-Tech Ueno programs aimed at vascular adhesion protein 1, or VAP1, a target with potential in multiple indications, including orphan diseases, autoimmune and inflammatory disorders and cancer. The most advanced, RTU-1096, could have applications in nonalcoholic steatohepatitis, chronic obstructive pulmonary disorder and even immuno-oncology, and plans are under way to move into a phase I multiple ascending-dose study.

An earlier-stage intravenous VAP1 inhibitor, which has indicated potential in acute cerebral infarction, is ready to move into investigational new drug application-enabling studies.

Beyond those programs, Sucampo will need to prioritize. The combined company will boast a total of 10 assets. "While we

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Immatics

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Immatics U.S. Inc. will bring together MD Anderson's cell therapy expertise with Immatics' Xpresident cancer peptide discovery technology, to develop both autologous and allogeneic treatments. The formation of the subsidiary is funded by $40 million from its parent company and a $19.7 million grant from the Cancer Prevention and Research Institute of Texas.

To date, Tuebingen, Germany-based Immatics has applied its Xpresident technology to the discovery of tumor-specific peptides as the basis of cancer vaccines. The lead product, IMA901 is in a pivotal phase III study in renal cell carcinoma, with results due at the end of September.

The move into T-cell therapy marks a second diversification with Immatics also announcing this week that it is moving into antibody therapeutics via a collaboration with Morphosys AG.

In both cases, Immatics is building on its ability to explore the intracellular proteome, said Harpreet Singh, co-founder of Immatics and CEO of the Houston-based U.S. subsidiary. "We have got the globally largest database of intracellular cancer antigens and believe we own this space, which is the result of 15 years research," he told *BioWorld Today*.

While the agreement with Munich, Germany-based Morphosys involves de novo discovery and is unlikely to result in any preclinical candidates for two to three years, Immatics U.S. will start its first T-cell therapy clinical trial in 2016.

It is planning a three-pronged approach, starting with the identification and extraction of a patient's own T-cells that can recognize cancer peptides discovered by Immatics, their ex-vivo expansion and re-administration.

The second approach will involve genetically engineering a patient's own T-cells to express T-cell receptors specific to Immatics' targets. Thirdly, Immatics will engineer off-the-shelf T-cells as the basis of allogeneic therapies. The company claims it is alone in pursuing all three options.

Singh said Immatics has had discussions with the FDA and is working on the details of the clinical development plan in collaboration with two MD Anderson scientists, Patrick Hwu, head of cancer medicine, and Cassian Yee, professor of medical melanoma oncology.

With the one exception of Adaptimmune Ltd., which has delivered positive phase II data in synovial sarcoma, T-cell immunotherapy has been focussed on targeting CD-19 in the treatment of hematological cancers, using chimeric T-cell receptors.

Cambridge, UK-based Adaptimmune's sarcoma data is important in providing the first signal that T-cell immunotherapy can work in solid tumors, and Singh said Immatics wants to use its target repertoire to build on this.

"The whole space of T-cell immunotherapy is very exciting, and it has delivered by showing sustained clinical responses in acute leukemia. But there is a problem [in treating solid tumors] in terms of the availability of targets," said Singh. (See *BioWorld Today*, Oct. 17, 2014.)

Rather than an organ-specific cancer, the first clinical trial at MD Anderson will involve treating a range of solid tumors that express targets identified by Immatics.

"We have spent the past year doing very broad target discovery, covering a large number of cancers. As a result we have 21 high-priority targets, with more to come," Singh said.

Immatics will gain access to various technologies developed or in-licensed by MD Anderson, including technology for the expansion of T cells and a T-cell platform for allogeneic cell therapies. "We are not here to re-invent adoptive cellular therapies [ACT]: what we bring are the targets. We will rely on proven ACT technologies," said Singh.

MD Anderson is a minority shareholder in Immatics U.S. Inc. and will contribute its expertise and conduct clinical trials. However, Immatics will have overall responsibility for managing the programs.

Singh said the $60 million committed to date will finance development over four years. The terms of the grant specify that the money be used to advance the first two programs into clinical development.

Meanwhile, the antibody collaboration with Morphosys will marry the Xpresident tumor peptide discovery technology with Morphosys' Ylanthia antibody fab library, which comprises more than 100 billion fully human antibodies.

Simon Moroney, CEO of Morphosys, said finding novel targets against which to screen this library is not easy. "Immatics' technology opens up a completely new way of discovering targets that are intracellular but are presented by MHC [major histocompatibility complex] receptors," He told *BioWorld Today*.

The companies will both develop antibodies aimed at proprietary targets discovered by Immatics and pay each other milestones as their respective programs progress in development. //

OTHER NEWS TO NOTE

Advaxis Inc., of Princeton, N.J., said it inked an agreement with **Knight Therapeutics Inc.**, of Montreal, to commercialize Advaxis' portfolio in Canada, including axalimogene filolisbac (ADXS-HPV) for human papilloma virus-associated cancers, ADXS-PSA for prostate cancer and ADXS-HER2 for HER2 expressing solid tumors. Under the terms, Knight will purchase 359,454 Advaxis shares at $13.91 each, about a 7 percent premium to the stock's closing price on Aug. 25. Also, Canadian investment advisor, Sectoral Asset Management, will purchase about 1.44 million shares of Advaxis stock at the same price. The combined gross proceeds to Advaxis are approximately $25 million. Knight will be responsible for all commercial activities related to Advaxis' current and future products in Canada, and Advaxis is eligible to receive double-digit royalty as well as sales milestones.

ALS

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smaller number of frontotemporal and other dementias.

About 40 percent of inherited ALS cases are due to a repeat expansion in an intron of the C9ORF972 gene, and there are several different theories for why the expansion is toxic. The expansion consists of the DNA sequence GGGGCC, and it has been an open question whether this RNA is toxic because it interacts with RNA-binding proteins and keeps them from performing their natural functions, because it is translated into amino acid dimers that are toxic, a combination of the two, or other reasons altogether.

In their experiments, the authors used different methods to look at proteins that interacted with the mutation in flies and yeast. They identified transportation between the nucleus and the cytoplasm as a function of several of those interaction proteins.

The findings were reported in three papers in the Aug. 26, 2014, online issues of *Nature* and *Nature Neuroscience*. //

Sucampo

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have begun to examine the potential during the due diligence process, our goal will be to take a much closer look during the three months" it will likely take to close the transaction, Greenleaf said.

"We'll accelerate the high priority programs and invest only where we believe we can have the greatest impact," he added. For those not deemed strategic fits, "we'll look for additional value by monetizing" through partnerships or out-licensing.

POSITIONING FOR GROWTH

Sucampo plans to finance the R-Tech Ueno deal through a $250 million term loan, leaving the firm with plenty of cash on its balance sheet – $127.7 million as of June 30 – in addition to the cost savings and additional revenue. If all goes as planned, the company will have the capacity for further deals in the near future.

"We also recognize we need to continue to do pipeline work, to bring in more external assets," Greenleaf said. "We'll digest this [transaction] and figure out what our next investment play" will be.

Also to be determined along the way will be the company's commercial strategy. In response to an analyst's question on the call, Greenleaf said Sucampo likely would take on commercial responsibilities in areas where it made sense to do so in terms of cost-to-return ratio. With the right customer base and in the right geography, the company could make "those types of investments to build a commercial organization."

"We don't see ourselves as just an R&D partnership house here," he added.

But Sucampo has no plans to build the kind of infrastructure, either globally or in the U.S., needed to reach the larger markets. "Obviously, that would be areas such as primary care and potentially even some cardiovascular areas where you need to touch a large, large number of physicians."

But where there's "a solid return on investment, we'll take a swing at that on our own in the right geography." Either way, "we'll be asset-selective," he said.

Shares of Sucampo (NASDAQ:SCMP) closed Wednesday at $24.55, up 61 cents. //

FINANCINGS

Advanced Inhalation Therapies Ltd., of Tel Aviv, Israel, has filed its F-1 with the SEC for a $36 million IPO. The company reported in its filing that it is developing a single 160 ppm nitric oxide (NO) formulation and delivery system to treat various respiratory infections for which current treatments have limited effectiveness. The system is designed to deliver a high dosage of NO to the lungs, with the potential to eliminate microbial infections including bacteria, fungi and viruses. The platform is focused on lower respiratory tract Infections, including the first two targets – children with bronchiolitis mainly caused by respiratory syncytial virus and lung infections in patients with cystic fibrosis (CF). The firm completed a phase IIa study in infants with bronchiolitis and an investigational new drug application submission to the FDA is planned for the first half of 2016 with a U.S.-based phase IIb trial to follow shortly after. A similar pathway and timeline is being followed in CF-related lung infections with a U.S. phase IIb trial planned with CF patients who are older than 10 for 2016. The company plans to apply to list its ordinary shares on the Nasdaq Capital Market under the symbol AITP.

Intrexon Corp., of Germantown, Md., said it closed its public offering of common stock, including the exercise in full by the underwriters of their option to purchase an additional 731,707 shares of common stock at $41 per share. The exercise brought the total number of shares of common stock sold to 5.6 million shares with total gross proceeds of approximately $230 million.

OTHER NEWS TO NOTE

Alvogen Inc., of Pine Brook, N.J., entered an agreement with **Pfizer Inc.**, of New York, to pick up a portfolio of four products: three injectables and one inhaled solution. Two are on-market products, Clindamycin injection and Acetylcysteine inhalation solution. Acetylcysteine will continue to be marketed by **Fresenius AG**, of Bad Homburg, Germany, with Alvogen receiving profit-sharing payments. In addition, Alvogen will gain two pending abbreviated new drug applications, Voriconazole injection and Melphalan injection. Both are expected to launch as early as 2016. Pfizer is required to divest those products as a condition of the Lake Forest, Ill.-based **Hospira Inc.** acquisition.

Merus

Continued from page 1

Novo A/S, with additional backing from RA Capital Healthcare Fund, Rock Springs Capital, Tekla Capital Management, an unnamed U.S. investor and earlier supporters. The new funds will help it advance its sole clinical candidate, a potential treatment for HER2-expressing solid tumors, and move an experimental treatment for acute myeloid leukemia (AML) into the clinic.

Sofinnova's Anand Mehra and Novo's Jack Nielsen joined Merus' board as part of the round, a sign that an IPO the company has contemplated could still be in its future.

The company's existing investors, including Novartis Venture Fund, Johnson & Johnson Innovation Inc., Pfizer Venture Investments, Bay City Capital, LSP Life Sciences Partners and Aglaia Oncology Fund, also participated in the financing.

"The proceeds from this financing provide us with funding to advance our key clinical and preclinical programs and to broaden our pipeline," said Ton Logtenberg, Merus' CEO in a statement.

Merus' first bispecific antibody, MCLA-128, targets HER2 and HER3. Dosing began in February for an open-label European phase I/II trial in solid tumors.

The study was slated to enroll 52 patients with advanced epithelial tumors at the outset, with a primary endpoint of safety. Secondary endpoints include, among others, the immunogenicity of MCLA-128 as well as anti-tumor response and clinical benefit. At the trial's start, Logtenberg said it had been "selected among thousands of candidates tested in functional assays and shows tumor cell killing activities that cannot be achieved with combinations of conventional HER2 and HER3 monoclonal antibodies."

Preclinical data presented at the 106th AACR meeting in Philadelphia in April showed that MCLA-128 inhibited cell cycle progression and heregulin-induced HER3 and Akt phosphorylation more potently when compared with a combination of Roche AG's Herceptin (trastuzumab) and Perjeta (pertuzumab).

The company's second active bispecific program, MCLA-117, is in development for the treatment of AML and is expected to enter the clinic in the first quarter of 2016. By binding to CD3 expressed by T cells and C-type lectin domain family 12, member A expressed by AML cells and cancer initiating cells, is thought to trigger the immune system to kill AML tumor cells and their precursors.

Bispecifics are single human monoclonal antibodies that have two different binding specificities encoded by the variable regions. Merus' transgenic mice, called Memo, are used to produce human antibodies, which form the base of its bispecifics. Though Merus, among others, has tangoed with Regeneron Pharmaceuticals Inc. over aspects of the technology – U.S. Patent No. 8,502,018, "Methods of modifying eukaryotic cells" in particular – on Aug. 10, the company reported prevailing against its foe in the U.S. District Court for the Southern District of New York, where Judge Katherine B. Forrest decided that Regeneron had, according to Merus, "engaged in inequitable conduct in connection with obtaining" the patent.

Earlier financings for Merus, which is based in Utrecht, the Netherlands, have included a €31 million (US$42 million) extension to its series B round, bringing the round's total round to an impressive €47.6 million (US$53.9 million). And in May, together with Selexis SA, Merus landed a €2.1 million (US$2.4 million) Eurostars grant to develop bispecific antibody combination products for the treatment of colorectal cancer. (See *BioWorld Today*, Oct. 9, 2013.)

Back in April, the company generated significant buzz about when the Dutch financial newspaper, *Het Financiële Dagblad*, reported that Merus was plotting an IPO on Nasdaq later this year. Whether those plans are still in the works or indefinitely delayed given the volatility of current market conditions was unclear. //

OTHER NEWS TO NOTE

Audentes Therapeutics Inc., of San Francisco, said the FDA and the EMA both granted orphan drug designation for AT001, which is being developed for X-linked myotubular myopathy, a rare, inherited disorder that affects skeletal muscles from birth. AT001 is based on adeno-associated virus gene therapy technology designed to restore the ability of skeletal muscle to produce myotubularin.

Daiichi Sankyo Co. Ltd., of Tokyo, reported that the UK's National Institute for Health and Care Excellence determined that the company's direct factor Xa inhibitor Lixiana (edoxaban) is a cost-effective use of National Health Service resources for the treatment and prevention of recurrent deep vein thrombosis and pulmonary embolism in adults. In a separate determination, the institute also determined that Lixiana is clinically and cost effective compared with warfarin and can be recommended as an alternative to warfarin for preventing stroke and systemic embolism for people with non-valvular atrial fibrillation who have one or more additional risk factors for stroke, an indication for which the drug recently received European marketing authorization.

Eli Lilly and Co., of Indianapolis, said the U.S. District Court for the Southern District of Indiana ruled in the company's favor regarding infringement of the vitamin regimen patent for Alimta (pemetrexed for injection). In the case of *Eli Lilly and Co. v. Teva Parenteral Medicines Inc., et al.*, the court ruled that the vitamin regimen patent would be infringed by the generic challengers' proposed products. The patent provides intellectual property protection for Alimta until May 2022. In March 2014, the court previously upheld the validity of the vitamin regimen patent. The Alimta compound patent remains in force through early 2017.

Innovation

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When the user fee programs come up for reauthorization every five years, industry and the FDA negotiate fee amounts and agency performance goals that have to be approved by Congress. But rather than simply green-lighting the agreements, Congress piles on new responsibilities and programs in what becomes a bulky bill.

The new programs are then layered on top of all the ones added in previous user fee agreements, without giving the existing programs the time needed to mature and settle into practice, according to the MI3, a real-world analysis and scoring system based on interviews with legal and medical experts who regularly interact with government agencies. The result is great uncertainty and inconsistency – among drug- and device-makers and at the FDA itself – that may unintentionally discourage innovation and make it difficult for the agency to meet the review targets set out in the agreements.

For instance, because of the "more rational safety and effectiveness standards" and the faster review times added to PDUFA for niche therapies targeting unmet medical needs, "drug developers are preferentially focusing their efforts on these small populations and neglecting other diseases that affect huge populations of patients," the alert said. This mass move into "orphan drugs" artificially skews approval times and makes it look like "the FDA is actually functioning as it should, when it is not performing its mandate to promote health appropriately," the MI3 added.

REALITY OF REVIEW TIMES

The user fee agreements have improved drug and device approval times, but they leave a lot of wiggle room, especially since the FDA reckons its performance based on "review days" instead of actual calendar days. Under that system, the agency can stop and start the clock at its discretion. Thus, the agency gives itself top grades for meeting its statutory approval dates, while the actual review times are much longer than they appear.

The MI3 shows that PDUFA I, which took effect in 1992, cut the mean approval time of a new molecular entity from 29 months in the late 1980s to 18.6 months. Five years later, the mean approval time for standard drug applications was reduced to 13.4 months under PDUFA II. And with the added resources provided by the user fees, the FDA was able to eliminate a pre-PDUFA backlog of applications.

Although the FDA has continued to pat itself on the back for meeting review times under subsequent PDUFAs, the alert said the numbers show a different reality. Under PDUFA V, the current agreement, the goal is six months for priority reviews and 10 months for standard reviews. In 2013, the median approval time for drugs was slightly more than 10 months, meaning that the FDA missed its PDUFA goal for more than half the applications, the MI3 reported.

If the FDA were truly meeting its PDUFA review dates, there would not be such a demand for priority review vouchers, the MI3 said, noting the rising value of the vouchers, with the most recent one selling for $350 million. (See *BioWorld Today*, Aug. 20, 2015.)

Device review times also have improved, but not to the extent specified under MDUFA. From 2010-2014, review times were 13 percent better for 510(k) devices and 31 percent better for pre-market approval (PMA) devices than a decade earlier, according to the FDA.

Yet the average review time for a PMA for the first half of this year was 17.1 months and a humanitarian device exemption (HDE) took 16.7 months, the MI3 pointed out. But the 2015 MDUFA goals called for the agency to complete 80 percent of the standard PMA reviews within six months and HDEs within 2.5 months.

The current MDUFA review time for a 510(k) is three months, but the average 510(k) review last year took twice as long. A device company submitting a 510(k) in 2014 had a 22 percent chance of getting it cleared within the three-month target and a 61 percent chance of having it cleared within six months, according to the MI3.

THE NEXT ROUND

Rather than simply pointing out the problems, the MI3 made several recommendations for the next round of MDUFA/PDUFA legislation. No. 1 on the list is that Congress refrain from adding any new programs. Other recommendations include:

- adding an explicit, unchanging definition of "safety and effectiveness," and immediately correcting existing rules and guidance to comport with that definition;
- requiring mandatory review performance from the FDA based on actual business days rather than "review days," with penalties for not meeting its performance criteria (such as a 1 percent fee reduction for every day of delay);
- ending most expedited review programs ("If the FDA met its review times and honored the definition and principles of safety and effectiveness and least-burdensome approach [for devices], there would be no calls for performance incentives by industry," the alert noted);
- having the FDA ombudsman report to the agency commissioner instead of the center directors;
- requiring the FDA to make quarterly reports to Congress, which would then hold annual agency performance oversight meetings;
- requiring FDA advisory committees to vote on the approvability of new products and make recommendations on labeling based on the existing body of data in appropriate patient populations;
- mandating that advisory committees be comprised of experts who treat the disease under consideration, allowing conflict-of-interest rules to be waived so the committees can include members who have conducted clinical studies or consulted for more than one drugmaker. //

Thetis

Continued from page 1

side of the business and didn't necessarily see himself in the role of a CEO. Despite his role as the co-founder and head of Thetis Pharmaceuticals LLC, Sciavolino opted for the title of chief scientific officer. Although the company has no formal CEO, it's not devoid of leadership, however; co-founder Gary Mathias serves as chief financial officer (CFO) and the 2011 start-up boasts a roster of experienced board members and advisors from across biopharma and academia.

The management structure is a reflection of the strong science bent at privately held Thetis, which is applying expertise in amino-lipid chemistry to the discovery and development of drugs to treat cardiometabolic and other diseases. The company uses amino acid-based scaffolds that are ionically linked to one or more biologically active agents to create new molecular entities (NME). The ionic compounds essentially perform in the same manner as simple table salt, breaking into their component entities in gastric fluids and precluding systemic exposure to the bioactive agent.

Chief among the company's candidates is TP-113, a docosahexaenoic acid (DHA)-metformin candidate targeting in a single molecule a previously unrecognized pathway that affects both peripheral and hepatic glucose metabolism in type 2 diabetes. Another promising asset is TP-452, a cholesterol-lowering agent that could represent the next generation beyond the emerging protein convertase subtilisin/kexin type 9 (PCSK9) inhibitor class.

The Southport, Conn.-based biotech uses its High Efficiency Amino Lipid Enabled Release, or HEALER, platform to transform approved drugs or previously studied agents into NMEs with improved pharmacokinetic, pharmacodynamic or physico-chemical properties to enhance efficacy, tolerability and patient convenience. The approach, itself, is hardly new; many biopharmas are revisiting known agents to pursue development in previously untried or unsuccessful indications without the cost of conventional small-molecule drug research and development. But Thetis is going boldly into major indications as well as rare diseases.

Diabetes drug development is a wide-open field, given the "demise" of the thiazolidinediones class and the "fading" of sulfonylurea medicines, according to Sciavolino. Although dipeptidyl peptidase 4, or DPP-4, and sodium-glucose co-transporter 2, or SGLT2, inhibitors remain important contributors to manage diabetes – in addition to metformin – "the whole area is entirely focused on glucose control," he said.

Insulin resistance and lipid levels, though they also contribute to the pathology of the disease, often are overlooked by drug developers, Sciavolino maintained, so Thetis is aiming to keep – even enhance – glycemic control while incorporating reduction in the other key disease drivers.

"We think TP-113 is an entry that can address that pathology," he told *BioWorld Today*.

COMPANY AIMS TO OPEN THREE INDS IN 2016

DHA, in the form delivered by Thetis, is a free fatty acid (FFA) that is quickly taken up by muscle and liver cells following oral dosing and is converted into protectin DX, or PDX, Sciavolino explained. PDX was shown by other researchers to reduce insulin resistance in muscle cells. In July, Thetis presented preclinical data at the International Chair on Cardiometabolic Risk Congress on Chronic Societal Cardiometabolic Diseases in Quebec City confirming that the oral candidate has the potential to reduce insulin resistance, decrease hepatic glucose output and reduce plasma triglycerides.

TP-452, which Sciavolino highlighted during a well-attended presentation in June at the BIO International Convention in Philadelphia, is an ionic derivative of docosapentaenoic acid (DPA) that shows potential as adjunct therapy to statins for oral treatment of LDL-C. Preclinical and clinical data suggest that DPA down-regulates both 3-hydroxy-3-methyl-glutaryl-CoA (HMGCoA) reductase and PCSK9, providing DPA with the prospect to reduce cholesterol biosynthesis and to increase LDL receptor levels.

"We have an agent which is mechanistically different from the agents that are currently available," Sciavolino said. "The statins are inhibitors of HMGCoA reductase. The PCSK9s are antibodies that inhibit PCSK9. What we're looking at is a dual mechanism of action which down-regulates both."

The company's pipeline also includes TP-252, an eicosapentaenoic acid (EPA)-free fatty acid derivative that Thetis is advancing in familial adenomatous polyposis, and TP-8452, a fixed-dose combination of TP-452 and atorvastatin to reduce LDL-cholesterol in statin-resistant patients. The assets have composition-of-matter patent protection with global coverage. In fact, last week, the company received a notice of allowance from the U.S. Patent and Trademark Office for its patent application covering pharmaceutical compositions of mineral amino-acid derivatives of DPA, EPA and DHA.

Although the entire pipeline remains at the discovery or preclinical stage, Thetis plans to move TP-113 into an investigational new drug (IND) application next year – one of three INDs the company aims to open in 2016. Following a phase I pharmacokinetics study, "we will move very quickly into determining the level of insulin resistance in diabetic patients," Sciavolino said. Provided those studies bear out the company's thesis, "we will pursue development in the U.S. through phase IIa, and international markets will be handled through a pharma partner," he added. "It's not our intention to move this to commercialization on our own."

The need to address the "significant deficits" of insulin resistance and lipid levels in patients with diabetes is urgent, Sciavolino maintained, as alternative treatments for diabetes such as beta cell transplant or stem cell therapies represent "long-term, very exploratory propositions." Sciavolino predicted the need for decades of additional development before such treatments offer "practical value" to individuals with diabetes.

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And although advances in insulin pumps have improved day-to-day diabetes management, "we see '113 as being an entry into the oral anti-diabetes market in the range of about six years – maybe even less." Since the company is using agents with established safety records, Sciavolino expects to pursue regulatory filings using the 505(b)(2) pathway.

Thetis has raised $7.5 million since its inception, including a $5.5 million series A in 2013 that was led by Connecticut Innovations with participation from Stonehenge Partners and angel investors. The firm has a clear runway through the end of next year "with committed dollars," according to co-founder Gary Mathias, the company's chief financial officer, "and our investor group will continue to support the company."

Because the company's pipeline is built around its HEALER platform, Thetis also has maneuverability, Mathias pointed out.

"The goal of our fundraising efforts is to raise sufficient amounts of capital to allow us to take several of our development candidates into early clinical development and show proof of concept," he told *BioWorld Today*.

With the company's amino-lipid chemistry recognized by the FDA as nontoxic, Thetis has the luxury of evaluating the commercial landscape and regulatory pathway for individual bioactive agents, "and that's what drives the candidates we select," Mathias added. //

OTHER NEWS TO NOTE

Enumeral Biomedical Holdings Inc., of Cambridge, Mass., formed a collaboration with the University of Massachusetts Medical School, which includes UMass Memorial Health Care Inc. Under the terms, UMass Medical School will furnish Enumeral with tissue and blood samples from melanoma patients who are treated with Yervoy (Ipilimumab, Bristol-Myers Squibb Co.), and Enumeral will cover the cost of tissue collection. Enumeral will have access to the samples for research-only use in in-vitro studies. No financial details were disclosed.

Nantkwest Inc., of Los Angeles, along with teams at the University of Michigan and Thomas Jefferson University, disclosed a $1 million challenge award from the Prostate Cancer Foundation to study the company's natural killer (NK) cell-based therapy in advanced prostate cancer. The immunotherapeutic approach is designed to harness activated NKs, optimize them by loading chimeric antigen receptors (CARs) and then target the prostate-specific membrane antigen (PSMA). The efficacy of Nantkwest's PSMA-CAR NK cell therapy will be tested in preclinical models of androgen-sensitive and hormone therapy-resistant prostate cancer. A phase I trial in prostate cancer patients will be initiated and the capacity of PSMA-CAR NK cell therapy to activate other components of the immune system will be assessed.

Novo Nordisk A/S, of Bagsvaerd, Denmark, said it plans to invest $2 billion over the next five years in new production facilities in Clayton, N.C., and Måløv, Denmark, to help the firm meet worldwide demand for its diabetes medicines. The facilities in Clayton will produce active pharmaceutical ingredients for both oral semaglutide and a range of Novo's current and future GLP-1 and insulin products, while a new production facility in Denmark will be used for tableting and packaging oral semaglutide and future oral products. The facilities are expected to be operational during 2020.

Ovascience Inc., of Cambridge, Mass., said it published an analysis of real-world patient experience comparing the Augment fertility treatment to standard in vitro fertilization (IVF), showing that, in the same woman with the same IVF cycle, Augment-treated eggs had statistically significant higher rates of embryo selection and transfer based on standard embryo quality measures, which resulted in statistically significant higher rates of pregnancy, compared to standard IVF. Data were published in the *Journal of Fertilization: In Vitro– IVF-Worldwide Reproductive Medicine, Genetic & Stem Cell Biology*.

Peregrine Pharmaceuticals Inc., of Tustin, Calif., reported preclinical results highlighting the ability of bavituximab, the company's phosphatidylserine (PS)-signaling pathway inhibitor, to promote antitumor T cell-mediated activity in several tumor types. Data presented at the Immunotherapy and Vaccine Summit meeting in Boston, demonstrated that combining the enhanced T-cell antitumor activity of bavituximab-like antibodies with checkpoint inhibitors, such as anti-PD-1 antibodies, results in significantly improved tumor control in multiple models of cancer. Among the findings were data showing that bavituximab-like antibodies significantly increase the prevalence of tumor infiltrating CD8-positive T cells and immune-activating cytokines, while decreasing macrophages and myeloid cells that allow the tumor to evade immune detection. Bavituximab also increased the number of activated CD8-positive cells in the tumor, which stimulates PD-1 expression, thereby up-regulating the target for checkpoint inhibitors such as anti-PD-1 and anti-PD-L1, the company reported.

Sarepta Therapeutics Inc., of Cambridge, Mass., said the FDA filed the new drug application (NDA) for eteplirsen for the treatment of Duchenne muscular dystrophy (DMD) amenable to exon 51 skipping. The agency granted the application priority review status, with a PDUFA date of Feb. 26, 2016. About 13 percent of people with DMD are estimated to have a mutation addressable by eteplirsen/exon 51 skipping. Sarepta submitted the rolling NDA earlier this year and is only two months behind **Biomarin Pharmaceutical Inc.**, of San Rafael, Calif., which submitted an application for drisapersen, its exon 51-skipping drug for DMD. Drisapersen has a PDUFA date of Dec. 27, 2015. (See *BioWorld Today*, May 21, 2015.)

OTHER NEWS TO NOTE

Viamet Pharmaceuticals Inc., of Research Triangle Park, N.C., and the Mycoses Study Group Education & Research Consortium (MSGERC) said they established a collaboration to advance a therapy for cryptococcal meningitis and other life-threatening fungal infections. The partnership will combine the antifungal drug discovery and development expertise of Viamet with the strategic clinical development expertise of the MSGERC and will initially focus on VT-1129, the company's antifungal agent expected to enter the clinic later this year for cryptococcal meningitis.

IN THE CLINIC

Oncoceutics Inc., of Hummelstown, Pa., reported that the first patients have been enrolled in the expansion phase of its first-in-human trial with ONC-201 at the Rutgers Cancer Institute of New Jersey. Previously, Oncoceutics reported the completion of the dose escalation portion of the trial, called "Oral ONC-201 in Treating Patients With Advanced Solid Tumors." During the expansion phase, ONC-201 will be administered at an oral dose of 625 mg every three weeks. The study is intended to confirm the safety and pharmacokinetic profiles of ONC-201 in patients with advanced solid tumors and will also assess surrogate and clinical efficacy endpoints and biomarkers. The primary endpoint is the dose limiting toxicity rate during cycle 1 of treatment with oral ONC-201.

Oncolytics Biotech Inc., of Calgary, Alberta, completed enrollment of 166 patients in a randomized phase II study of the reovirus variant Reolysin in patients with previously treated advanced or metastatic non-small-cell lung cancer. The trial is being sponsored and conducted at Queen's University in Kingston, Ontario. Patients with squamous cell histology were randomized to receive either Reolysin given in combination with docetaxel (test arm) or docetaxel alone (control arm), while patients with non-squamous cell histology were randomized to receive either Reolysin given in combination with pemetrexed (Alimta, Eli Lilly and Co., the test arm) or pemetrexed alone (control arm). The primary objective of the trial is to evaluate the effect of Reolysin in combination with standard salvage chemotherapy on the progression free survival of patients with advanced or metastatic non-small cell lung cancer.

Syndax Pharmaceuticals Inc., of Waltham, Mass., entered a collaboration with Basel, Switzerland-based **Roche AG**'s unit Genentech to evaluate the safety, tolerability and preliminary efficacy of Syndax's entinostat, an oral small molecule that targets immune regulatory cells (myeloid-derived suppressor cells and regulatory T cells), in combination with Genentech's atezolizumab (MPDL3280A), a fully humanized monoclonal antibody targeting protein programmed cell death ligand 1, in patients with triple-negative breast cancer.

Needham, Mass.-based **Verastem Inc.'**s stock (NASDAQ:VSTM) fell 25.7 percent to $4.91 a share in after-hours trading after the company revealed two deaths in a phase II trial of its lead candidate, VS-6063 (defactinib), in patients with KRAS mutant non-small-cell lung cancer. The data are to be presented at the 16th World Conference on Lung Cancer next month. Though the full abstract is under embargo, the company stated: "Two subjects reported as having grade 5 respiratory failure were on multiple concomitant medications and presented with multiple co-morbidities. Both were thoroughly evaluated and reported to the regulatory authorities in 2013 and 2014 when they occurred." The company defended the safety of VS-6063, adding that, "The totality of safety and efficacy data seen to date with VS-6063 across multiple clinical trials, multiple tumor types and stages of treatment is promising. In addition, in the company's registration-directed COMMAND trial in mesothelioma, an independent data safety monitoring board has met and reviewed study data, including adverse events, three times and recommended no changes to study protocol. There have been over 300 patients treated to date with VS-6063, including patients on drug for more than one year."

XTL Biopharmaceuticals Ltd., of Raanana, Israel, said previously reported results of a phase IIb study on the safety and efficacy of its lead drug candidate, hCDR1 (edratide) for the treatment of lupus were published in the *Lupus Science & Medicine Journal*. A 0.5-mg dose administered weekly subcutaneously was found to be the most effective dose and the drug showed no safety signals in the 26-week study. Data support the need for additional longer-term studies that incorporate recent advances in the understanding and treatment of lupus.

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