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FLUSHED WITH ESMYA SUCCESS

Fibroid optics: Street eyes next phase III as Allergan, Gedeon chalk up first win

By Randy Osborne, Staff Writer

With positive phase III data in hand and another study under way, Allergan plc with partner Gedeon Richter plc could be on their way to the first non-invasive, long-term option for women with uterine fibroids in the U.S., as the therapeutic space gains momentum.

Fibroids and endometriosis are "both sizable markets" with a strong need for lasting therapies, Cowen and Co. pointed out in a research report earlier this year, and ulipristal acetate "could have a role" in the former in the U.S., though it's only

[See Allergan, page 3](#)

Perusing 'rich menu' of indications, Aptinyx lands \$65M series A

By Michael Fitzhugh, Staff Writer

Aptinyx Inc., an Evanston, Ill.-based spinout of Allergan plc-acquired Naurex Inc., has completed a \$65 million series A financing that will carry the company's lead candidate through initial clinical proof of concept in a yet-to-be chosen CNS indication, while also funding discovery in its specialty, small-molecule

[See Aptinyx, page 4](#)

FINANCINGS

AC Immune's series E adds \$44M as European biotech's private equity reaches \$725M to date

By Cormac Sheridan, Staff Writer

DUBLIN – AC Immune SA closed a CHF42.7 million (US\$43.5 million) series E round, taking to CHF126.7 million the

[See AC Immune, page 5](#)

THE BIOWORLD BIOME

PURPLE PUDDLES

Cheap, quick platform technology leads to cheap, quick Zika diagnostic

By Anette Breindl, Senior Science Editor

An experimental Zika diagnostic can rapidly and inexpensively detect Zika virus and determine its specific strain, opening up the possibility of much improved

[See Zika, page 6](#)

REGULATORY

U.K.'s early access scheme working but challenges remain

By Nuala Moran, Staff Writer

LONDON – Two years after it was instituted, the U.K.'s Early Access to Medicines Scheme (EAMS) has succeeded in getting drugs to patients in advance of a formal marketing approval, but the aim that therapies arrive a year beforehand has not been met, and the fact the scheme is not funded makes it hard for small biotechs to participate.

"The aim was to give patients with life-threatening or seriously debilitating conditions access to medicines without a marketing authorization, where there is clear unmet need. It has succeeded in doing this," said Daniel O'Connor, expert medical assessor, licensing division, U.K. Medicines and Healthcare products Agency (MHRA).

To date, the MHRA has given scientific opinions on eight products under the

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CHINA

China: Immunotherapy getting bad rap, recent case study exemplifies

By Shannon Ellis, Staff Writer

SHANGHAI – Several weeks ago a 21-year-old man named Wei Zexi, diagnosed with terminal synovial sarcoma, a rare form of cancer of the soft tissue, died. In the weeks since

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REGULATORY FRONT

Four years after the U.S. Congress passed the Jumpstart Our Business Startups (JOBS) Act, the **SEC** is amending its rules to reflect the new, higher thresholds for registration, termination of registration and suspension of reporting required by that law and the Fixing America's Surface Transportation Act. Also in keeping with JOBS, the amendments revise the definition of "held of record" in Rule 12g5-1 under the Securities Exchange Act to exclude certain securities held by people who received them through employee compensation plans. The amendments, slated for publication in Tuesday's *Federal Register*, will go into effect June 9.

Record-keeping issues with a contract manufacturer are delaying the European launch of **Merck & Co. Inc.**'s hepatitis C drug, Zepatier (elbasvir and grazoprevir). The Kenilworth, N.J., company expects **EMA** approval by midyear. But the "European launch will be delayed until the fourth quarter or perhaps until the end of the first quarter of 2017, depending on how quickly these matters can be resolved," Roger Perlmutter, executive vice president and president of Merck Research Laboratories, said in a first quarter earnings call last week. The problem surfaced in the course of the European review for Zepatier, with the EMA concluding that the contract manufacturer needed to improve its quality management systems. Merck said it doesn't believe the problems affect the safety, efficacy or quality of the drug and they shouldn't affect the supply to the U.S., Perlmutter said. The FDA approved Zepatier in January. (See *BioWorld Today*, Feb. 1, 2016.)

Concerned that the **FDA** is not revising, finalizing and withdrawing draft guidances in a timely way, Republican members of the **Senate Health, Education, Labor and Pensions (HELP) Committee** are asking for a progress report from the agency. In a letter to Commissioner Robert Califf, the senators noted that several doctors and industry have said that, since the FDA is sending untitled and other letters based on draft guidance, they have no choice but to "follow draft

guidance as if final, even if the most up-to-date science would suggest an alternative path." Last year, in response to an earlier inquiry from the HELP Committee about its delay in issuing final guidance, the agency said it takes between 425 to 797 days to finalize a guidance. And as of the FDA's March 2015 response, 172 draft guidances had been pending since before December 2013. The senators requested an update on the number of pending drafts and the time it's taking the agency to finalize them.

The **U.S. Federal Trade Commission** approved a modified final order giving London-based **Hikma Pharmaceuticals plc** 20 more days to complete divestitures required for its \$2 billion acquisition of Roxane Laboratories Inc. and Boehringer Ingelheim Roxane Inc. from **Boehringer Ingelheim GmbH**, of Ingelheim, Germany. Under the order, Hikma must divest the rights and assets for two generic drugs, prednisone tablets and lithium carbonate capsules, to **Renaissance Pharma Inc.**, of Newtown, Pa., and relinquish the U.S. rights to market flecainide acetate tablets to its drug development partner, Mumbai, India-based **Unimark Remedies Ltd.** Hikma also must divest its equity interest in Unimark.

EARNINGS

Horizon Pharma plc, of Dublin, reported first quarter net sales of \$204.7 million. In its orphan drug franchise, sales of urea cycle disorders drug Ravicti (glycerol phenylbutyrate) totaled \$37.1 million, while Actimmune (interferon gamma-1b) reached sales of \$25.5 million. The rheumatology franchise was led by gout drug Krystexxa (pegloticase), which recorded \$16.2 million in sales for the quarter. Sales of Pennsaid 2 percent (diclofenac sodium topical solution) led the primary care franchise, with first quarter sales of \$55 million. On a non-GAAP basis, Horizon reported net income of \$55.4 million, or 35 cents per share, beating consensus estimates of 30 cents per share. As of March 31, the firm had cash and equivalents of \$385.9 million. Shares of Horizon (NASDAQ:HZNP) gained \$1.86, or 13.9 percent, to close at \$15.27 on Monday.

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BUSINESS OFFICE

Donald R. Johnston (Senior Director, Current Awareness), Sarah Cross (Marketing Director), Penney Holland (Web Production Manager)

CONTACT US

Jennifer Boggs, (770) 810-3120 // Anette Breindl, (770) 810-3134 // Sarah Cross, (770) 810-3138 // Michael Fitzhugh, (770) 810-3064 // Penney Holland, (770) 810-3047 // Donald R. Johnston, (770) 810-3118 // Nuala Moran, 44-7778-868-579 // Randy Osborne, (770) 810-3139 // Marie Powers, (770) 810-3136 // Mari Serebrov, (770) 810-3141 // Cormac Sheridan, 353-87-6864323 // Peter Winter, (770) 810-3142 // Lynn Yoffee, (770) 810-3123



Allergan

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available in Canada and Europe at the moment.

Allergan, of Dublin, and Budapest, Hungary-based Gedeon offered positive data from Venus I, one of two pivotal phase III trials evaluating the efficacy and safety of the selective progesterone receptor modulator, branded Esmya elsewhere. The study included 157 patients, with 101 randomized to Esmya 5 mg and 10 mg and 56 to placebo. All co-primary and secondary endpoints with both treatment arms hit statistically significant results over placebo ($p < 0.0001$).

Evercore ISI analyst Umer Raffat found a potential differentiator in Esmya data showing hot flush reported by only 5 percent of patients, as compared to a whopping 65 percent of patients taking gonadotropin-releasing hormone (GnRH) analogues such as Lupron (leuprolide, Abbott). Prior results, he noted in an alert to investors, "suggest much more sustained effect on reduction of fibroid volume. We will look for this data in detailed medical conference presentations." GnRH agonists also are known to induce a low-estrogen, menopausal-like state and to promote bone loss, though, so they are not recommended for use for more than six months.

The co-primary efficacy endpoints in the Venus I study were percentage of patients with absence of uterine bleeding and time to absence of such bleeding. Significantly more patients in the 10-mg group (58.3 percent; $p < 0.0001$) and the 5-mg group (47.2 percent; $p < 0.0001$) achieved absence of bleeding compared to placebo (1.8 percent).

Secondary efficacy endpoints were the percentage of patients with absence of uterine bleeding from day 11 to end of treatment and the change from baseline in the Uterine Fibroid Symptom and Health-Related Quality of Life (UFS-QOL) questionnaire revised activities subscale at the end of treatment. Significantly more patients in the 10-mg group (58.3 percent; $p < 0.0001$) and the 5-mg group (43.4 percent; $p < 0.0001$) achieved absence of bleeding from day 11 to the end of treatment compared to placebo (zero). The improvement from baseline in the UFS-QOL revised activities subscale was significantly greater in the 10-mg group (59; $p < 0.0001$) and the 5-mg group (52.1; $p < 0.0001$) compared to placebo (21.2).

Target populations for fibroid drugs include women undergoing hysterectomies, which number 600,000 annually in the U.S., with between 170,000 to 300,000 having the procedure done because of uterine fibrosis, as well as those with symptoms of fibroids who are not bound for surgery. Fibroids are usually diagnosed and treated in patients ages 35 to 54, but can show up in those younger than 35. In the U.S. about 42 million fall into that age range, and clinical literature suggests that 20 percent to 40 percent of all women bear fibroids – which means a significant population of treatment-

eligible patients in the U.S. alone, though about 5.5 million seek treatment each year.

ELAGOLIX 'WELL POSITIONED'

Evercore's Raffat pointed out that the approvals gained by Esmya so far are limited to pre-operative treatment. "On the other hand, the FDA is allowing Allergan to enroll patients with [fibroid] signs and symptoms, but not necessarily preparing for surgery," a pathway that "greatly expands the target population, he noted. "Having said that, keep in mind Esmya is not a chronic therapy. The FDA is allowing Esmya to be dosed for one cycle, then break, and then another cycle. Based on the second phase III trial, perhaps the FDA may limit the maximum number of cycles to two," in his view. Allergan estimates peak sales as high as \$1 billion, and the drug could launch in the U.S. sometime in 2018, with patent protection solid through 2029.

San Diego-based Neurocrine Biosciences Inc. with partner Abbvie Inc., of North Chicago, has the GnRH antagonist elagolix in late-stage development for endometriosis and fibroids. Neurocrine reported in its first quarter earnings last week that it collected a \$15 million milestone payment from Abbvie related to the launch of phase III work with elagolix against fibroids – the company's sole revenue source for the quarter. Abbvie is on track to present phase III results with elagolix in endometriosis at the American Society for Reproductive Medicine meeting in October in Salt Lake City, and data from the fibroids program are likely to follow next year. Elagolix "looks to be well positioned to capture share in both these segments," in Cowen's opinion.

Also in the game: Repros Therapeutics Inc., of The Woodlands, Texas. Last month, the firm reported that vaginal administration of its Proellex, a selective blocker of the progesterone receptor, at doses of 6 mg and 12 mg achieved significant reduction in excessive menstrual bleeding, the key symptom of uterine fibroids. Normal menstrual blood loss in a menstrual cycle is approximately 35 mL, and women experiencing blood loss of > 80 mL are considered to suffer from menorrhagia or excessive menstrual bleeding. In the small phase IIb study, 13, 15 and 14 women with confirmed uterine fibroids were enrolled in the 6-mg, 12-mg and placebo arms, respectively.

At baseline, the mean amount of blood lost for one menstrual cycle was 255 mL, 274 mL and 238 mL for each arm, respectively. The blood loss ranged from a low of 94 mL to a high of 654 mL. The most severe menstrual bleeding at baseline was observed in the 12-mg group. When a high-enough concentration of Proellex is achieved in circulation, amenorrhea (cessation of menses) is achieved, the findings show. Just over half, 52 percent, of Proellex-treated subjects became amenorrheic with no evidence of a dose effect, Repros said. //

Aptinyx

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modulators of the N-methyl-D-aspartate (NMDA) receptor. Following a phase I study to test the safety of its lead candidate, slated to start around midyear, the company expects to select a first indication for the molecule during the fourth quarter, Norbert Riedel, Aptinyx's president and CEO, told *BioWorld Today*. Neuropathic pain, Parkinson's disease, traumatic brain injury and post-traumatic stress disorder are all in the running, he said. A trial enrolling patients from the chosen indication is likely to start during the first half of 2017.

"The challenge is that we have a rich menu to choose from. We want to be really thoughtful," he said.

New Leaf Venture Partners led the tranching financing. It also included investments by Frazier Healthcare Partners, Longitude Capital and Osage University Partners, as well as existing investors such as Adams Street Partners, LVP Life Science Ventures, Pathocapital, Goudy Park Capital, Beecken Petty O'Keefe & Co. and Northwestern University. (See *BioWorld Today*, Sept. 16, 2015.)

A trio of new directors is joining the company's board in tandem with the funding: Former senior vice president and development head for Pfizer Inc.'s neuroscience program, New Leaf managing partner Liam Ratcliffe, brings particularly relevant experience to the table. But the company is also likely to benefit from the significant track records of Frazier managing general partner James Topper and Longitude Capital founder and managing director Patrick Enright.

BUILDING ON MODULATION

Aptinyx's platform was developed based on research from the laboratory of Joseph Moskal, a professor of biomedical engineering at Northwestern University, director of the university's Falk Center for Molecular Therapeutics, founder of Naurex and now chief scientific officer of Aptinyx.

The company's molecules are designed to enhance synaptic plasticity, strengthening the network for neural cell communication, a pathway that underlies multiple nervous system conditions. They can either promiscuously or selectively bind certain NMDA receptor subunits implicated in target diseases, thus modulating the receptor instead of simply turning it off, something that Riedel said Aptinyx's competitors would prefer to do, but so far lack the ability to achieve.

"What I love is that we own this chemistry," said Riedel. "It's completely proprietary to Aptinyx, and we have great IP around it."

Allergan, of course, likes the company's chemistry too. It acquired Naurex's early stage pipeline, including rapastinel (GLYX-13) and NRX-1074, in an all-cash transaction of \$571.7 million, plus future contingent payments up to \$1.15 billion. Part of the proceeds of that deal went on to establish Aptinyx's

initial operating budget, giving it more breathing room than most companies at its stage enjoy. (See *BioWorld Today*, Dec. 4, 2014, and July 28, 2015.)

But the deal also included a channel by which Allergan can still access the expertise behind those molecules. That piece took the shape of a discovery and preclinical development agreement with Aptinyx for the right to in-license any covered compounds discovered and profiled for certain target indications during a collaboration term of up to five years. Riedel said that work is progressing well.

NMDA PROGRESS

Meanwhile, plenty of other companies are continuing to explore the NMDA receptor space, including Sage Therapeutics Inc., Vistagen Therapeutics Inc. and Axsome Therapeutics Inc., among others.

Sage's first candidate selected for development from its NMDA receptor program is SAGE-718, an oxysterol-based NMDA positive allosteric modulator. The company said in March that it had begun nonclinical studies of the molecule, with an initial development focus on two rare conditions, Smith-Lemli-Opitz syndrome and anti-NMDA receptor encephalitis.

Sage also sees a role for NMDA beyond the therapeutic space, it said in a recent SEC filing. The company said it believes that measuring levels of anti-NMDA antibodies or decreased levels of cerebrosterol, a naturally occurring oxysterol, may represent biomarkers to identify for future studies broader patient populations characterized by cognitive dysfunction and neuropsychiatric symptoms resulting from NMDA receptor dysfunction or hypofunction, such as certain subpopulations of people with depression, Alzheimer's disease, attention deficit hyperactivity disorder, schizophrenia, Huntington's disease and neuropathic pain.

Vistagen, of South San Francisco, is also making progress in the space. It recently reported an ongoing phase IIa study of its orally available prodrug, AV-101, in subjects with treatment-resistant major depressive disorder (MDD) is being carried ahead and funded by the National Institutes of Mental Health. The company is preparing to launch a pivotal phase IIb study of AV-101 for the adjunctive treatment of MDD in patients with an inadequate response to standard antidepressants during the fourth quarter of 2016. The company recently said it also believes AV-101 could have broad therapeutic utility for indications including chronic neuropathic pain, epilepsy, Huntington's disease and Parkinson's disease.

Axsome, meanwhile, said last month that it had received pre-investigational new drug application guidance from the FDA on its proposed clinical developmental plan for AXS-05, a combination of bupropion and the NMDA receptor antagonist dextromethorphan, that it's developing for the treatment of agitation in patients with Alzheimer's disease. Based on the feedback, Axsome plans to file an IND by the end of 2016 for a phase II/III trial. //

AC Immune

[Continued from page 1](#)

total investment it has raised since its inception in 2003 and taking the year's running total for private equity financing of European biopharma to \$725 million.

That number is well ahead of the \$388 million raised at the same point last year – and it is also more widely distributed. A number of large-scale transactions in the early months of 2015 – including those of Nabriva Therapeutics AG (\$120 million), Crispr Therapeutics AG (\$89 million) and Kymab Ltd. (\$50 million) – flattered what would otherwise have been a lackluster performance. This time round, more companies are raising significant sums of cash to enable to them to progress their pipelines. Early stage funding appears to be readily available for companies that offer investors a compelling story. Four of the top 10 European deals logged so far this year involved series A rounds, and B rounds accounted for another four. (See chart, below.)

In geographical terms, the U.K. is the most dynamic market, accounting for nine of the 31 publicly disclosed transactions logged to date, while France accounted for another five. Switzerland came next with four deals, while Sweden and Germany each accounted for three. Only one of the Swedish deals, Solna-based Aprea AB's \$50.7 million B round, was on a significant scale, however.

In cash terms, the U.K. is even more dominant – companies based there collectively raised \$277.8 million – about 38 percent – of the total, while accounting for 29 percent of the transactions. Even though the U.K., like the rest of Europe, had several small-scale transactions below \$5 million, it also landed four of the top 10. (Dalcour Pharma UK Ltd.'s \$100 million B round, which it closed in April, has been excluded from this analysis as the company's main operations are based in Canada. Dublin-based Iterum Therapeutics Ltd. is a borderline

case – its principals and R&D are U.S.-based but the company was incorporated in Ireland at its inception in 2014, hence its inclusion.)

Whether the sector can continue that positive run remains an open question for now.

The IPO markets remain weak, but several private equity firms have cash to invest, having recently closed new funds. The most recent is London-based MVM Life Science Partners, which closed a new \$233 million health care fund last week, which is focused on drug development as well as devices and medical technology. Last month, Forbion Capital Partners, of Naarden, the Netherlands, closed its third life sciences fund at \$208 million, and its early stage affiliate, Biogeneration Ventures, is seeking another \$57 million. London-based Medicxi Ventures, a spin-off from the life sciences arm of Index Ventures, closed a \$250 million fund in February. Paris-based Sofinnova Partners closed a €300 million (US\$342 million) fund in late 2015. (See *BioWorld Today*, Feb. 2, 2016.)

AC Immune, of Lausanne, Switzerland, declined to comment on its latest round, but its ability to raise cash on this scale demonstrates its investors' continued faith in its focus on Alzheimer's disease and, latterly, on conditions with some overlap in disease biology, including Down syndrome.

The company's destiny is strongly linked with the progress of Roche AG unit Genentech, which has licensed its anti-amyloid-beta antibody [crenezumab](#) and is currently testing the drug in a high-profile phase II prevention trial in high-risk individuals in Colombia, and in a phase III trial in patients with prodromal to mild Alzheimer's.

An anti-Abeta vaccine, ACI-24, is in a phase I/IIa trial in patients with mild to moderate disease. It is also undergoing a phase I trial in patients with Down syndrome. ACI-35, a vaccine that targets phosphorylated tau proteins, is undergoing a phase Ib trial in Alzheimer's with partner Johnson & Johnson. //

Top 10 private equity deals in European biopharma

Company	Location	Stage	Amount
Mission Therapeutics Ltd.	UK	C	\$86.3M
Cardioentis AG	Switzerland	B	\$60M
Autolus Ltd.	U.K.	B	\$56.6M
Aprea AB	Sweden	B	\$50.7M
AC Immune SA	Switzerland	E	\$43.5M
Inivata Ltd.	U.K.	A	\$42.2M
Iterum Therapeutics Ltd.	Ireland	A	\$40M
Medday Pharmaceuticals SAS	France	B	\$38.8M
Orchard Therapeutics Ltd.	UK	A	\$30.5M
Etherna Immunotherapies NV	Belgium	A	\$26.6M

Source: BioWorld

Zika

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monitoring of the virus as it spreads through the Americas.

More broadly, James Collins told *BioWorld Today*, what his team has created is “a rapid, inexpensive platform” that can be used to create “diagnostics that are themselves cheap and quick.”

Collins is a founding core member of Harvard University’s Wyss Institute for biologically inspired engineering, professor of biological engineering at the Massachusetts Institute and the corresponding author of the paper reporting the new test, which appeared in the May 6, 2016, online issue of *Cell*.

Along with the celebrations of Mother’s Day, last weekend marked a more disturbing anniversary. Brazil’s first confirmed case of Zika virus infection was diagnosed on May 7, 2015.

Mostly harmless to adults, the virus has been linked to microcephaly as well as other fetal malformations if pregnant women become infected.

To date, the overwhelming majority of microcephaly cases have occurred in Brazil. In February of this year, the World Health Organization (WHO) declared the Brazilian microcephaly cluster a “Public Health Emergency of International Concern,” meaning that the situation is “serious, sudden, unusual or unexpected; carries implications for public health beyond the affected State’s national border; and may require immediate international action,” according to the WHO definition.

Zika virus has also been linked to increased incidence of Guillain-Barre syndrome, an autoimmune condition that is not usually fatal, but can require intensive care that can easily overwhelm the health care capacities of resource-poor nations.

As with any emerging disease, diagnostics are a key part of both epidemiological surveillance and individual treatment decisions, and the WHO has declared that “quality-assured, safe and effective diagnostics are therefore a top priority in our medical response” to the epidemic. Antibody-based diagnostics can easily mistake dengue and Zika infections, and though two tests, the Zika Mac ELISA and the Trioplex Real-Time PCR Assay, have received emergency use authorization by the FDA, there are no fully approved diagnostic tests, and the existing tests need a high level of supporting infrastructure.

The test described in *Cell* combines two advances developed previously by Collins and his team with CRISPR gene-editing technology.

The first were what the team has named “toehold switches,” RNA sensors that can be programmed to activate a gene when it encounters the sequence it is programmed to detect.

The second was a paper-based synthetic gene network capable of being used outside of the environs of a research lab. The basic concept, Collins explained, is to “take the internal machinery of a cell, put it on paper, freeze-dry it, and at some later point rehydrate it,” at which point it can be used to detect the RNA sequence its toehold switch is programmed for.

Collins and his colleagues first used the same concept to

develop a diagnostic for Ebola virus.

In the work now published in *Cell*, the team tested the ability of nearly 50 different Zika genome fragments to activate their respective toehold switches, leading to the expression of a reporter gene that turned the paper purple. The team also developed what they called “a low-cost and tractable method for viral RNA extraction,” briefly boiling their samples to get at the viral RNA and then amplifying that RNA.

The system was able to detect Zika virus from the blood of an infected monkey, showing that the test was sensitive enough to detect the viral levels present during an infection.

Unlike antibody-based diagnostics, and despite the fact that the two viruses are about half identical in their sequences, the test was able to distinguish Zika from dengue virus, which overlaps with Zika geographically.

By adding the gene-editing technology CRISPR, the team was also able to develop a test that could distinguish the American strain of Zika virus, which may be more strongly associated with the risk of both fetal microcephaly and Guillain-Barre syndrome, from the African strain.

The Wyss Institute has “a keen interest” to translate the findings, either with a for-profit or a nonprofit entity as partner, and has a number of possible interested parties.

And though Zika virus may currently be the most urgent application, it is far from the only one. The platform could be used broadly to develop tests for other viral infections such as influenza, Ebola and HIV, as well as bacterial infections, including Lyme disease and leprosy, and even cancer. //

EARNINGS

Incyte Corp., of Wilmington, Del., reported first quarter net product revenues from JAK inhibitor Jakafi (ruxolitinib) totaling \$183 million, up 59 percent over the same quarter in 2015. Product royalties from sales of the drug outside the U.S., where it is branded Jakavi and sold by Basel, Switzerland-based **Novartis AG**, totaled \$22 million. Total revenues for the quarter reached \$263.5 million. Incyte recorded net income of \$24 million, or 13 cents per share, missing expectations of 20 cents per share, though analysts noted that one-time payments, including a \$35 million payout to partner **Eli Lilly and Co.**, of Indianapolis, had not been modeled in consensus estimates. As of March 31, Incyte had cash, equivalents and marketable securities totaling \$811 million. Shares of Incyte (NASDAQ:INCY) closed Monday at \$72.86, up \$2.17.

FINANCINGS

Merus Labs BV, of Utrecht, the Netherlands, set a price range for its proposed Nasdaq IPO, planning to offer 4.3 million shares at \$14 to \$16, which would bring in \$64.5 million in gross proceeds at the midpoint price. According to the company’s SEC filing, current investors have stated an intention to purchase \$33 million of shares. Proceeds will be used to develop the firm’s bispecific antibody platform against cancer. Merus is seeking a listing under the ticker MRUS.

EAMS

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EAMS scheme. As a result, prescribers are given confidence in the safety and efficacy and patients are getting access. There are “no major plans to change the scheme,” but O’Connor said that based on comments and an independent review of EAMS, there will be some changes to guidance to provide more clarity on EAMS criteria and to try to extend the timeline by encouraging companies to make earlier applications.

O’Connor was speaking at a conference in London last week on “Accelerated Development and Access to Innovative Medicines for Patients.” The event, which was jointly organized by the MHRA and the U.K. Bioindustry Association (BIA), included a review of EAMS from the perspective of different stakeholders that have been involved in its implementation.

In addition to the MHRA reviewing drugs that are yet to be licensed, EAMS involves accelerated appraisal by the health technology assessment body NICE (National Institute of Health and Care Excellence) and a faster route to commissioning in the National Health Service (NHS). Once NICE has issued positive guidance recommending the use of an EAMS product, the NHS must make it available within 30 days. (For drugs appraised in the standard process, the NHS has up to 90 days to implement NICE guidance).

To become a candidate for EAMS, a product must first be categorized as a promising innovative medicine, a status that is similar to FDA’s breakthrough therapy designation.

Although stressing improved patient access, EAMS also has commercial intent, having originated in a life sciences Ministerial Industry Strategy Group. The BIA and the Association of the British Pharmaceutical Industry lobbied hard for the scheme, with an eye on the broader picture of reducing the time lag between regulatory approval, NICE’s technology appraisal process and subsequent commissioning.

The first drug to go through EAMS was Merck & Co. Inc.’s first-in-class PD-1 inhibitor, Keytruda (pembrolizumab). It took longer than expected to get MHRA’s positive opinion, which was secured only 130 days in advance of formal EU marketing authorization.

However, that was a meaningful outcome, with more than 500 patients receiving treatment for metastatic or unresectable melanoma between the MHRA nod and EU approval, Joanna Maitland Smith, executive director of scientific affairs at Merck U.K. (Merck Sharp & Dohme), told the conference.

There was a significant workload involved in securing the EAMS designation, with Maitland Smith noting she has a file of more than 3,000 emails relating to the process. It was hard dealing with the work at a time when corporate resources were focused on preparing the regulatory file and it required considerable coordination to ensure consistency between the marketing authorization application and the file being prepared for MHRA.

Her colleagues in the U.S. head office questioned whether EAMS offered any advantages, but Maitland Smith said she was able to persuade them that having a positive scientific opinion from MHRA would add credibility, and the involvement of NICE and NHS commissioners would reduce access timelines following EU marketing approval.

NOT ENOUGH TIME?

As well as being the first EAMS drug, Keytruda also is the product to have held the designation for longest. Others have hovered around two months, and in one case it was 21 days. But in another, the gap between EAMS designation and marketing approval was only 10 days – too short for the designation to be acted on.

Even so, more patients are getting access to unlicensed drugs than companies estimated in their EAMS submissions, said Malcolm Qualie, pharmacy lead at NHS Specialized Services, who has been involved in implementing EAMS. However, the short EAMS periods have created difficulties for clinicians. “They don’t want to start talking to the patients and then EAMS ends,” Qualie said.

Nick Crabb, project director, scientific affairs at NICE, noted the EAMS periods generally have been too short for real-world evidence generation, which is one of the objectives of the scheme. “There’s not enough time from a NICE perspective,” he said. The MHRA is prepared to consider products in phase II development. “So if companies engaged earlier, more patients would benefit and we would get more real-world evidence.” Crabb said.

Steve Bates, chief executive of the BIA, is delighted to see the “delicate flower” of EAMS is growing, but is not convinced it can survive hard frosts. “Why it works is not just the process, but the attitude and commitment across the system,” he explained.

It remains an issue that EAMS is not funded and companies must supply drugs free of charge. Other countries have similar access schemes that are funded. “If our early access scheme is not globally competitive, this is not good,” said Bates. “This is about industrial strategy.” //

FINANCINGS

Sophiris Bio Inc., of San Diego, said it is raising about \$5 million at a price of \$1.40 per share in an at-the-market offering. For each share of common stock, investors also will get a warrant to purchase one-half of a share. Net proceeds will be used for general corporate purposes and to service outstanding debt owed under a secured promissory note. Roth Capital Partners served as sole placement agent. Sophiris is advancing topsalsyn (PRX302) as its lead program for urological disease. Shares of Sophiris (NASDAQ:SPHS) closed Monday at \$1.34, down 23 cents, or 14.7 percent.

China

[Continued from page 1](#)

his death, public debate and outrage have hit upon various elements of his story, illustrating a volatile mix of distrust in online transparency, lax oversight of regulations governing cell treatments and commonplace greed. It is also giving immunotherapy, a promising form of cancer treatment, a bad reputation in China.

Wei's cancer was treated with DC-CIK immunotherapy at a military hospital in Beijing, a hospital he selected after it came up as a top result on the Chinese search engine, Baidu. The young man was reported to have paid ¥200,000 (US\$36,000) for the treatment.

The first wave of recrimination has been hotly centered on Baidu, China's premier online search engine. Before Wei died, he posted several touching videos sharing his plight. He also shared his dismay that the treatment he received had been ineffective and that Baidu's top search result was in fact a paid advertisement for a private clinic. What has enraged the public is that Baidu's search results are for sale, with the highest bidder getting top billing.

Wei sought treatment at the Second Hospital of Beijing Armed Police Corps, ostensibly a top-notch state hospital, but the hospital outsourced the key department to a for-profit group called the Biological Treatment Center. The owners of the center are said to hail from Putian, Fujian – local news reports stated 80 percent of China's private hospitals are owned by people from Putian.

Baidu will be investigated for its sponsored search results by several government agencies, including China's internet watchdog and the National Health and Family Planning Commission (NHFPC). The company has agreed to assist with the investigation.

But the controversy has taken its toll on Baidu's Nasdaq-listed stock, dropping \$20 from a high of \$195 on April 15 to \$175 as of May 6. Many in China are blaming part of the problem on lack of access to more independent search engines such as Google, which is blocked by the great firewall of China.

FOR-PROFITS UNDER MILITARY HOSPITALS UMBRELLA

The second wave of public concern has been targeting the practice of public and military hospitals outsourcing services to private clinics. In many cases, patients are unaware that the trusted state-backed hospital they are visiting is not managing their care.

The practice of outsourcing is banned for public hospitals and the NHFPC reiterated that in a recent notice. But the health ministry has no authority over the country's network of military hospitals. Although that looks set to change, as the military has come under greater scrutiny as a part of President Xi Jinping's anti-corruption campaign.

In March, China's Central Military Commission issued a circular that plans were under way to terminate all commercial

activities undertaken by the military. It is expected that the military hospital system – originally designed to care for military personnel – will no longer be able to treat civilians as a revenue-generating activity.

DUBIOUS DC-CIK TREATMENT

The latest focus of attention has been on the experimental cellular immunotherapy itself. Wei received dendritic cell cytokine-induced killer cells (DC-CIK).

DC-CIK is an untargeted treatment in which a low-dose T-cell cocktail is made from the patient's extracted blood before being reinserted to boost the immune system to fight cancer. CIK cells are immune effector cells featuring mixed T- and natural killer cells. They are generated by incubating mononuclear cells with interferon-gamma, anti-CD3 antibody, recombinant human interleukin (IL-) 1 and recombinant human IL-2.

Dendritic cells act as messengers to deliver key information about invading pathogens and can help to activate killer cells. Their main function is to process antigen material and present it on the cell surface to the T cells of the immune system.

The DC-CIK is reported to have been developed by professors at Stanford University but fell out of favor in the U.S. to treat cancer when clinical trials failed to prove sufficient efficacy although the treatment is considered safe. That did not stop DC-CIK from becoming a cancer treatment in China, in violation of regulations that state it should not be used for clinical treatment and reserved for scientific research only.

There are currently 30 DC-CIK clinical trials listed on clinicaltrials.gov. Three trials list no location, while the remaining 27 studies originate in China.

POOR IMPLEMENTATION OF REGULATIONS

On May 6, *China Daily*, an English, state-run newspaper reported, "China's top health authority reiterated on Thursday that the clinical use of immunotherapy for cancer treatment . . . (is) banned." The article also was featured on the NHFPC English website. The English statement makes the mistake of conflating immunotherapy with cell treatments.

In fact, no cellular treatment has ever been approved as a mainstream clinical therapy in China. In 2009, cellular treatments were classified as third-class medical technologies, a category reserved for risky, experimental treatments permitted for research purposes if approved by a hospital ethics committee, treatment is provided free of charge and patients are fully informed of the study. Advertising of stem cell treatments is also barred, though a quick internet search shows that has not stopped.

In 2015, the ministry issued administrative measures on clinical research and applications that involve human stem cells, giving a role to the CFDA as well as NHFPC to oversee clinical trial development and further protect patients. (See *BioWorld Today*, Sept. 2, 2015.)

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China

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But as the Wei case illustrates, implementation of China's rules remain a challenge.

China's uncertain commercial path for cellular treatments, however, has not stopped Juno Therapeutics Inc. in creating a joint venture with Wuxi Aptec to bring the groundbreaking chimeric antigen receptor and T-cell receptor technologies here. And some experts are hopeful that the current controversy will pressure the government to formalize a new set of guidelines that will provide a regulatory path for commercial approval and the necessary expertise within the CFDA to do so. (See *BioWorld Today*, April 11, 2016.) //

OTHER NEWS TO NOTE

Abbvie Inc., of North Chicago, and partner Janssen Pharmaceutica NV, a unit of New Brunswick, N.J.-based **Johnson & Johnson**, said the FDA updated prescribing information for Bruton's tyrosine kinase inhibitor Imbruvica (ibrutinib) to include data from two phase III trials supporting the expanded use in patients with chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL). The label now includes overall survival results in previously untreated CLL/SLL patients from the RESONATE-2 (PCYC-1115) trial. In addition, the label was updated to include safety and efficacy data from the phase III HELIOS (CLL3001) trial testing Imbruvica in combination with bendamustine and Rituxan (rituximab, Biogen Inc. and Roche AG) vs. placebo plus bendamustine/Rituxan in relapsed/refractory patients with CLL/SLL. The FDA also approved a new indication, under a November supplemental new drug application, to include the treatment of patients with SLL, with or without the deletion of chromosome 17p.

Chiesi Farmaceutici SpA, of Parma, Italy, said it agreed to acquire worldwide rights from **The Medicines Co.**, of Parsippany, N.J., to Kengreal (cangrelor) and Clevidipine (clevidipine) as well as rights to Argotroban for injection. All three are cardiovascular products approved in the U.S. for use in the hospital setting. The deal is valued at up to \$792 million, consisting of \$260 million in cash payable at closing, up to \$480 million in sales-based payments, the assumption by Chiesi of up to \$50 million in milestone payment obligations and about \$2 million for product inventory.

Cynata Therapeutics Ltd., of Melbourne, Australia, inked a worldwide license option agreement allowing **Apceth GmbH & Co. KG**, of Munich, Germany, to use its Cymerus technology in combination with genetic modification technologies designed to open up therapeutic fields to mesenchymal stem cells, or MSCs, particularly in the treatment of cancer. Under the terms, Cynata gets an immediate, undisclosed up-front cash payment and is eligible for success-based milestones reaching more than A\$40 million (US\$29.3 million), plus royalties on product sales. Apceth is evaluating Cynata's technology in its in-house cell

culture and genetic modification systems as part of an initial collaboration, expected to conclude toward the end of this year.

Dimension Therapeutics Inc., of Cambridge, Mass., reported preclinical results from its hemophilia A program, partnered with Leverkusen, Germany-based **Bayer AG**, demonstrating that the selection and combination of specific product components – including the capsid, enhancer and promoter – further optimized product performance, including long-term expression of factor VIII, the protein missing or deficient in hemophilia A that DTX201 is designed to provide. The studies, which involved mice and cynomolgus macaques, were presented at the American Society of Gene and Cell Therapy meeting in Washington. Bayer and Dimension are advancing the AAV gene therapy product in investigational new drug application-enabling studies under the firms' 2014 collaboration. (See *BioWorld Today*, June 24, 2014.)

Epizyme Inc., of Cambridge, Mass., said it inked a collaborative deal with the Lymphoma Study Association (LYSA) to research the process of combining tazemetostat with R-CHOP for those with diffuse large B-cell lymphoma (DLBCL). LYSA is a French organization dedicated to clinical and translational research for lymphoma, and is certified by the French National Cancer Institute. Under terms of the deal, the phase Ib/II trial will be jointly conducted with the Lymphoma Academic Research Organisation, part of LYSA. The trial will involve elderly, high-risk patients with newly diagnosed DLBCL and is expected to begin enrollment midyear. Financial terms were not disclosed.

Gtx Inc., of Memphis, Tenn., reported preclinical data from its selective androgen receptor degrader (SARD) program, demonstrating that the SARDs selectively bind to the ligand binding domain and interact with the N-terminal domain of the androgen receptor (AR) and inhibit and degrade the AR at very low concentrations. Those data suggest the SARDs might be dual-interacting AR antagonists and degraders. Results were presented at the American Urological Association meeting in San Diego.

Immune Design Corp., of Seattle, and **Gritstone Oncology Inc.**, of South San Francisco, said they inked a clinical collaboration to develop personalized immunotherapies combining both firms' technologies. The deal will involve the application of Immune Design's Zvex discovery platform with Gritstone's genomics and proteomics platform for identification of patient-specific tumor antigens to develop neoantigen-based immunotherapies. The companies will be jointly responsible for development activities, with an initial likely focus in non-small-cell lung cancer. The first clinical trial is expected to start in 2017. Financial terms were not disclosed.

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OTHER NEWS TO NOTE

Incyte Corp., of Wilmington, Del., and **Ariad Pharmaceuticals Inc.**, of Cambridge, Mass., said they agreed that Incyte would acquire Ariad's European operations and will also enter a license agreement for rights to develop and commercialize Ariad's leukemia drug, Iclusig (ponatinib), in Europe and other select countries. The deal, which will add Ariad's established pan-European team of 125 employees to Incyte staff, will help Incyte set up operations in Europe, while allowing Ariad to focus on promoting Iclusig in the U.S. market and strengthening its financial position. Under the terms, Incyte will acquire all shares of the parent company of Ariad's European subsidiaries in exchange for \$140 million in cash. Terms of the Iclusig license agreement will give Incyte exclusive rights in the European Union and 22 other countries, including Switzerland, Norway, Turkey, Israel and Russia, in exchange for tiered royalties of between 32 percent and 50 percent on net sales of Iclusig in the territory and up to \$135 million in potential development and regulatory milestones for Iclusig in new oncology indications in the territory. Ariad may also become eligible to receive additional milestones for non-oncology indications, if approved, in the territory. Incyte has agreed to fund a portion of the ongoing clinical development of Iclusig in Ariad's OPTIC and OPTIC-2L trials through cost-sharing payments of up to \$7 million in each of 2016 and 2017. Terms of the licensing deal also include an option for an acquirer of Ariad to buy back Iclusig rights. The transaction is expected to be earnings accretive for Incyte in 2018. Shares of Incyte (NASDAQ:INCY) closed Monday at \$72.86, up \$2.17, while shares of Ariad (NASDAQ:ARIA) gained 20 cents to close at \$7.18.

MGB Biopharma Ltd., of Glasgow, Scotland, said it conducted a pre-investigational new drug (pre-IND) meeting with the FDA regarding its regulatory strategy for MGB-BP-3 in the U.S. The company presented data from phase I and preclinical data in *Clostridium difficile* infections and anticipates receiving a qualified infections disease product status for MGB-BP-3. MGB said it is gearing up for a phase II study.

Opko Health Inc., of Miami, and Vifor Fresenius Medical Care Renal Pharma, a common company of **Galenica Ltd.**, of Bern, Switzerland, and **Fresenius Medical Care**, of Bad Homburg, Germany, entered a collaboration and license agreement for the development and commercialization of Rayaldee, an oral vitamin D prohormone, in Europe, Canada, Mexico, Australia, South Korea and certain other international markets for the treatment of secondary hyperparathyroidism (SHPT) in patients with chronic kidney disease and vitamin D insufficiency. Under the terms, the parties will also collaborate to develop and commercialize Rayaldee for the treatment of SHPT in dialysis patients, and Opko granted Vifor Fresenius an option to acquire rights to the U.S. market for treatment of dialysis patients. Opko will get a \$50 million up-front payment, plus up to an additional \$52 million in regulatory and launch milestones and \$180 million in sales-based milestones, in addition to tiered, double-digit royalties. Should Vifor Fresenius exercise its option for rights to the U.S. dialysis market, it will pay Opko additional commercial-

based milestones, as well as double-digit royalties. Rayaldee is under review in the U.S., with a PDUFA date of Oct. 22.

Pernix Therapeutics Holdings Inc., of Morristown, N.J., said the U.S. Patent and Trademark Office's appeal board denied a petition for inter partes review, which was filed by Graybar Pharmaceuticals LLC – now Gray Square Pharmaceuticals LLC. The petition was filed against Pernix in November and asked for review of certain portions of U.S. Patent No. 7,332,183 that is set to expire in 2026. That patent covers Treximet for acute migraine without aura.

Pluristem Therapeutics Inc., of Haifa, Israel, said it was awarded NIS12.7 million (US\$3.3 million) from the Israel Innovation Authority (previously the Office of the Chief Scientist) of the Israeli Ministry of Economy & Industry to support clinical trials and R&D activities for calendar year 2016. Pluristem is developing placenta-based cell therapy for off-the-shelf products targeting inflammation, ischemia, hematological disorders and radiation damage.

Puretech Health plc, of Boston, said it launched Vor Biopharma, an immune-oncology company that will focus on development of targeted cell therapies. Vor is researching chimeric antigen receptor T-cell therapy, and licensed its core technology from its scientific co-founder, Siddhartha Mukherjee, assistant professor of medicine at Columbia University.

Sorrento Therapeutics Inc., of San Diego, said it engaged Guggenheim Securities and PJT Partners to review a number of strategic alternatives to maximize shareholder value. No further details were disclosed. Sorrento shareholder Wildcat Capital Management LLC sent a letter to Sorrento's board last week urging it to "remedy the ongoing destruction of significant shareholder value." Wildcat holds an ownership stake of about 6.5 percent in Sorrento.

Takeda Pharmaceutical Co. Ltd., of Osaka, Japan, said it entered a partnership with the Bill & Melinda Gates Foundation to support polio eradication in developing countries, with funding from the \$38 million grant being used by Takeda to develop, license and supply at least 50 million doses per year of Sabin-strain inactivated poliovirus vaccine to more than 70 countries.

Theravance Biopharma Inc., of Dublin, said the FDA approved the supplemental new drug application for Vibativ (telavancin) to expand the product's label to include data describing the treatment of patients with concurrent *Staphylococcus aureus* bacteremia in both of the antibiotic's currently approved indications in the U.S. Vibativ is approved for the treatment of adult patients with hospital-acquired and ventilator-associated bacterial pneumonia caused by susceptible isolates of *S. aureus* when alternative treatments are not suitable, and for adults with complicated skin and skin structure infections caused by susceptible isolates of gram-positive bacteria, including *S. aureus*, both methicillin-susceptible and methicillin-resistant strains. Theravance priced a \$94.1 million public offering earlier this month. (See *BioWorld Today*, May 2, 2016.)

OTHER NEWS TO NOTE

Uniqure NV, of Amsterdam, the Netherlands, reported preclinical data at the American Society of Gene and Cell Therapy meeting in Washington, including results from nonhuman primates (NHPs) highlighting the potential of alternative administration routes by recombinant AAV-based vectors to improve delivery into the liver to achieve higher transduction efficiency and expression levels, which are crucial for the treatment of diseases associated with a deficiency of enzymatic activity in the liver such as hemophilia A and B. A separate study, using different AAV serotypes (AAV5 and AAV1) for repeated liver-targeted gene delivery in NHP's, demonstrated that combining different AAV serotypes in a potential therapeutic regimen is a successful strategy for re-administration. Studies in central nervous system diseases, designed to evaluate the transduction efficiency and vector distribution pattern following MRI-guided delivery of a gene therapy into specific regions of the brain, showed that a dose-dependent distribution profile could be modified to mediate expression patterns as a potential therapeutic strategy to treat a broad range of neurodegenerative diseases. Uniqure also presented in vivo re-administration data, using a two-step AAV injection, showing a significant dose-dependent reduction in anti-AAV5 antibodies following AAV decoy injection.

VBI Vaccines Inc., of Cambridge, Mass., and **Scivac Therapeutics Inc.**, of Rehovot, Israel, completed their merger, with VBI surviving as a wholly owned subsidiary of Scivac, which is changing its name to VBI Vaccines. The combined firm will trade on Nasdaq under the ticker VBIV and will advance a hepatitis B vaccine and a pipeline of technologies aimed at expanding vaccine protection in underserved markets. (See *BioWorld Today*, April 15, 2016.)

Wave Life Sciences Ltd., of Cambridge, Mass., said it is advancing its program in Duchenne muscular dystrophy (DMD) based on preclinical data demonstrating an approximate 25-fold improvement in exon-skipping efficiency compared to drisapersen and eteplirsen, exon-skipping DMD candidates from Novato, Calif.,-based **Biomarin Pharmaceutical Inc.** and Cambridge, Mass.-based **Sarepta Therapeutics Inc.**, respectively. Wave also said its muscle-targeting technology demonstrated substantial improvement in distribution to critical tissues in animal models, including skeletal muscle, diaphragm and heart. Investigational new drug application-enabling studies are set to start later this year.

IN THE CLINIC

Acucela Inc., of Seattle, started a phase II trial to assess the benefits of emixustat hydrochloride for the treatment of proliferative diabetic retinopathy (PDR). The randomized, placebo-controlled study will last for three months, during which 20 patients will be dosed once daily with oral emixustat. Pre-specified study endpoints include changes in cytokine

expression levels associated with PDR severity and changes in ocular neovascularization. The drug is a once-daily, orally administered small molecule that inhibits RPE65, an enzyme crucial to the visual cycle, the chemical pathway in the retina central to the initiation of visual perception, Acucela said.

Allergy Therapeutics plc, of Worthing, U.K., disclosed positive top-line results from the Pqbirch204 phase II study for birch-induced seasonal allergic rhinitis. The study met its primary endpoint, turned up a statistically significant dose-response relationship and proved safe and well tolerated, with adherence greater than 90 percent, the company said.

Aurinia Pharmaceuticals Inc., of Victoria, British Columbia, said the Japanese Pharmaceuticals and Medical Devices Agency has supported of its initiation of a study of the immunosuppressant calcineurin inhibitor peptide voclosporin in healthy Japanese volunteers. With positive results from the pending phase IIb AURA-LV study in lupus nephritis and supportive safety, tolerability, pharmacokinetic and pharmacodynamic data from that study, the company said it hopes to be able to incorporate Japanese patients into future global voclosporin studies, eliminating the need to conduct a stand-alone Japanese trial.

Avexis Inc., of Chicago, presented an interim analysis from the ongoing phase I trial of AVXS-101 in spinal muscular atrophy type 1 at the American Society of Gene & Cell Therapy meeting in Washington, showing that the gene therapy candidate continues to demonstrate a favorable safety profile in patients, with no new treatment-related safety or tolerability concerns identified. All patients in both the low-dose and proposed therapeutic-dose cohorts remain without an event, defined as death or until a patient requires at least 16 hours per day of ventilation support for breathing for 14 consecutive days in the absence of an acute reversible illness, or perioperatively. The mean motor function score continues to increase, with two patients having achieved motor function in a range considered to be normal. Shares of Avexis (NASDAQ:AVXS) gained \$6.10, or 24.1 percent, to close Monday at \$31.43.

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IN THE CLINIC

Boehringer Ingelheim Canada Ltd., of Burlington, Ontario, a unit of Boehringer Ingelheim GmbH, reported that LUX-Lung 7, a randomized, head-to-head, phase IIb trial comparing the first- and second-generation targeted therapies for the treatment of EGFR mutation-positive non-small-cell lung cancer (NSCLC), showed that the company's own therapy, afatinib, significantly improved progression-free survival, time to treatment failure and objective response rates vs. London-based **Astrazeneca plc's** gefitinib. Both afatinib and gefitinib demonstrated similar improvements in patient-reported outcome measures with no significant differences in health-related quality of life, **Boehringer** said. The study included 319 patients with stage IIIb/IV EGFR mutation-positive NSCLC, who received no prior treatment and were randomized 1-to-1 to daily afatinib 40 mg or gefitinib 250 mg. Patients were stratified by mutation type (Del19 or L858R) and the presence of brain metastases. Results of the study were published in *The Lancet Oncology*. Elsewhere, **Boehringer** announced the enrollment of the first patient in a global phase III trial evaluating the efficacy and safety of nintedanib in combination with pemetrexed/cisplatin, followed by continuing nintedanib monotherapy, as a first-line treatment for patients with unresectable malignant pleural mesothelioma. The study, called Lume-Meso, will randomize 397 patients in a double-blind, global comparison of nintedanib in combination with pemetrexed/cisplatin or matching placebo in combination with pemetrexed/cisplatin. For patients whose disease has not progressed after a maximum of six cycles of chemotherapy, nintedanib or matching placebo will continue to be administered orally as a monotherapy on a daily basis, until disease progression or unmanageable side effects. The primary endpoint is progression-free survival, and overall survival is the key secondary endpoint. Other secondary endpoints include objective tumor response and disease control. The estimated primary completion date for the study is August 2018.

Chimerix Inc., of Durham, N.C., reported top-line results from an interim analysis of its Advise trial of brincidofovir (BCV) for serious adenovirus (AdV) infection. Data from week 24 of the study showed a strong antiviral effect, which was correlated with overall survival. BCV rapidly reduced AdV levels in the blood (viral load to a level below the limit of detection) in a majority of those highly immunocompromised patients. Rapid reductions in AdV viral load were correlated with improved survival at day 90 and at week 24 following diagnosis in pediatric patients. All enrolled subjects in the Advise trial received 12 weeks of open-label oral brincidofovir, and are followed for 24 weeks after completing treatment. Two-thirds of the subjects in cohort B (disseminated AdV disease) were pediatric allogeneic hematopoietic cell transplant recipients. Pediatric subjects had a 32 percent all-cause mortality at day 90, and 42 percent all-cause mortality at week 24. In adults, all-cause mortality at day 90 was 57 percent and at week 24 was 71 percent. Final data will include follow-up through week 36 (24 weeks after the last dose of BCV), and will be available in the second half of 2016. The company attempted

to collect historic controls from the same medical centers as patients from Advise; however, they did not reflect the high-risk patients enrolled in Advise and thus did not provide a valid comparison for outcomes. In view of that, the company said it is planning a prospective, comparative trial of brincidofovir in Adv, that will allow stratification of patients based on risk factors for outcomes.

Foamix Pharmaceuticals Ltd., of Rehovot, Israel, said the first patient was dosed in its phase III program to evaluate the efficacy and safety of its topical minocycline foam 4 percent, FMX101. The program consists of two multicenter studies that are each planned to enroll about 450 patients with moderate to severe acne, first into a 12-week, double-blind, vehicle-controlled phase to be followed by nine months of open-label treatment with the active foam. Patients will be treated once daily for 12 weeks in the initial double-blind portions of the studies. The company expects to report top-line results from the blinded phase of the trials in the first half of 2017.

Neuroderm Ltd., of Rehovot, Israel, started patient enrollment in a long-term safety study (Trial 012) of the company's continuously administered subcutaneous levodopa/carbidopa (LD/CD) formulation used in both ND0612H and ND0612L. The one-year, open-label study will investigate the long-term safety of low- and high-dose regimens of ND0612. The study is expected to enroll about 100 patients, including patients who have previously completed the company's phase II and III studies as well as new patients. ND0612H and ND0612L are designed to significantly reduce motor complications in Parkinson's disease patients through continuous, subcutaneous delivery of LD/CD solution. At least 50 patients will be treated with the highest dose regimen. ND0612, continuously administered through a belt pump, is designed to maintain steady LD/CD levels to improve motor fluctuations that cannot be adequately controlled with oral therapy and, in the case of advanced patients, provide an alternative to treatments requiring surgical intervention.

Nordic Nanovector ASA, of Oslo, Norway, said its investigational new drug application for a new phase I study of Betalutin in a second non-Hodgkin lymphoma indication is now open with the FDA. The company plans to investigate Betalutin in relapsed diffuse large B-cell lymphoma patients who are ineligible for stem cell transplant. Betalutin comprises a tumor-seeking anti-CD37 antibody conjugated to a low-intensity radionuclide (lutetium-177).

X4 Pharmaceuticals Inc., of Cambridge, Mass., said it dosed the first patient in a phase I/II study of X4P-001, X4's lead CXCR4 inhibitor, in patients with advanced clear cell renal cell carcinoma (ccRCC). The phase I portion will test the safety and tolerability of escalating doses of X4P-001 combined with Inlyta (axitinib, Pfizer Inc.), a kinase inhibitor approved to treat advanced RCC after failure of one prior systemic therapy. The study is designed to establish a maximum tolerated dose (MTD), or a recommended dose if the MTD is not achieved, for the drug combination. Preliminary results from that portion of the study are expected in early 2017.

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