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PEDIATRIC EPILEPSY DATA UP NEXT

Phase III ganaxolone study trips up Marinus; additional trials ongoing

By Jennifer Boggs, Managing Editor

The team at Marinus Pharmaceuticals Inc. will be digging into results from the missed phase III study in drug-resistant focal onset seizures, hoping to determine why ganaxolone failed to mirror the reduction in seizure rate observed in earlier trials.

"We don't have an answer to that yet," Jaakko Lappalainen, Marinus' vice president of clinical development, responded to analyst's question during a Monday morning call. He added that nothing in the conduct of the trial or the study population appears to have undermined the results, "but we'll be focusing laser-like" on the data over the

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Alpine makes smooth run to $48M series A for immunotherapy platform

By Marie Powers, News Editor

A year after its founding, Alpine Immune Sciences Inc. (AIS) sped to a $48 million series A round that was led by Orbimed Advisors and joined by Frazier Healthcare Partners and Alpine Bioventures. In January 2015, Alpine Bio founded and provided the seed funding for Seattle-based AIS, which is

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REGULATORY

SCOTUS upends Fed's take on infringement, damages in *Halo v. Pulse*

By Mark McCarty, Regulatory Editor

The Supreme Court has yet again repudiated the Federal Circuit in a patent law decision, this time in a case testing the lower court's perspectives on infringement and enhanced damages.

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VACCINES

Paxvax wins FDA approval for U.S. cholera vaccine

By Michael Fitzhugh, Staff Writer

Paxvax Inc. has gained FDA approval for Vaxchora, the only cholera vaccine to be approved in the U.S. The approval comes with a valuable tropical disease priority review voucher that CEO Nima Farzan

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FUND

HEAVILY OVERSUBSCRIBED

Gilde Healthcare closes fourth fund at $282M

By Cormac Sheridan, Staff Writer

DUBLIN – Fourteen exits in the last three years enabled Gilde Healthcare to close out rapidly its fourth fund, Gilde Healthcare IV, at €250 million (US$282 million). That mark represented its hard cap or upper limit – it had sought €200 million initially.

The fund, which, like its predecessor, will be split across therapeutics, med tech and diagnostics, and digital health, was heavily oversubscribed. "Actually it's the first time I had to disappoint quite a number of limited partners," managing partner Pieter van der Meer told *BioWorld Today*.

Some 90 percent of its investors came in again, including Royal Philips NV, of Amsterdam, the Netherlands. Johnson & Johnson Innovation also participated, as a new investor. "Our coverage of Europe was important to them," van der Meer

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CHINA

MORE OVERSEAS

CFDA zeroes in on quality, but conducted fewer GMP inspections in China

By Cornelia Zou and Bonnie Wang, Staff Writers

HONG KONG – Aiming to address a perceived disparity in the quality of manufacturing of drugs for the China

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REGULATORY FRONT

U.S. lawmakers and doctors are sending the **Centers for Medicare & Medicaid Services** (CMS) a strong message that the final rule on its proposed Medicare Part B Drug Payment Model must address stakeholder concerns. Otherwise, **Congress** will try to stop the pilot program, which would change the reimbursement formula for Part B drugs for almost all doctors who administer them. Opponents of the program claim it would shut down some practices and drive patients into more expensive or less safe settings for therapies such as chemotherapy. Noting that 242 House members expressed their opposition to the plan during the comment period, Reps. Tom Price (R-Ga.), John Shimkus (R-Ill.) and Charles Boustany Jr. (R-La.) said they are prepared to advance H.R. 5122 to stop the proposal if CMS refuses to work with stakeholders. Meanwhile, the **American Medical Association** recently passed a resolution saying that unless CMS withdraws or significantly modifies the program, it will work with Congress to block the pilot through legislation or the restriction of CMS funding. (See *BioWorld Today*, May 18, 2016.)

The **U.S. Department of Health and Human Services** signed a memorandum of understanding Monday with **Cuba's Ministry of Public Health**. The agreement establishes coordination on a number of public health issues, including global health security, communicable and noncommunicable diseases, R&D and information technology.

The **CFDA** and the **Bill & Melinda Gates Foundation** signed a memorandum of understanding to work together to improve China's drug supervision capability and drug technical standards. Efforts will be made, under the agreement, to implement international expert introduction projects for drug evaluation and inspection and to create a drug supervision think tank to support China's reform of its drug evaluation and approval system, the CFDA said.

The **FDA** released a draft guidance Monday with recommendations for designing a nonclinical development program for a new drug or biologic intended to treat osteoporosis. In addition to the required pharmacology and toxicology studies, the FDA said long-term nonclinical studies are needed to evaluate the drug's effects on bone quality in adequate animal models. The studies should have bone-specific pharmacologic and toxicologic endpoints. Comments on the draft are due by Aug. 13.

Amgen Inc., of Thousand Oaks, Calif, reported Monday that the **FDA**'s Arthritis Advisory Committee will review its biosimilar application for ABP 501 July 12. The candidate, which references Humira (adalimumab, Abbvie Inc.), is Amgen's first biosimilar application to be accepted by the FDA. It has a PDUFA date of Sept. 25.

OTHER NEWS TO NOTE

Addex Therapeutics SA, of Geneva, said it completed the first part of a project funded by the Swiss Commission for Technology and Innovation (CTI) to characterize the firm's mGlu4 and mGlu7 receptor allosteric modulators in models of neurodegenerative and psychiatric diseases. ADX88178, an mGluR4 positive allosteric modulator, when administered chronically in a preclinical model of Parkinson's disease, was able to induce a reduction in the motor impairments observed in the model, but without significantly affecting the progression of the observed neurodegeneration. The effect of ADX71743, an mGluR7 negative allosteric modulator, and ADX88178 were tested on electrophysiological slice recordings at the thalamus-to-amygdala synapses, with experiments demonstrating an ability to impact the excitatory neurotransmission in the amygdala. The team recently was awarded a second grant by CTI to support continued characterization of those compounds in fear conditioning and reward models using combined electrophysiological and optogenetic methods.

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Marinus

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next few days.

In the meantime, the Radnor, Pa.-based firm said it will discontinue the program in adult focal onset seizures; however, it in no way plans to halt midstage studies testing the CNS-selective GABAA modulator in pediatric orphan indications – PCDH19 pediatric epilepsy and fragile X syndrome – and remains on track with a soon-to-launch phase I study of an intravenous formulation of ganaxolone in status epilepticus.

"We're committed to continuing the development of ganaxolone," said CEO Christopher M. Cashman. "It works, it's active and it's safe." He added that Marinus intentionally broadened its portfolio "to prepare for and overcome setbacks that are inherent in the CNS area," and the phase III miss allows "us to sharpen our focus" on other opportunities.

Not surprisingly, those assurances did little to assuage Wall Street. Shares of Marinus (NASDAQ:MRNS) hit a 52-week low at $1.50 Monday morning. The stock fell $3.72, or 69.7 percent, to end the day at $1.62, by far its lowest closing since going public nearly two years ago at $8 per share.

Hopes had been relatively high following phase II data of ganaxolone as an adjunctive treatment in 147 adults with focal onset seizures. Results presented during the American Epilepsy Society meeting in December from a post-hoc analysis showed that nearly twice the number of ganaxolone-treated patients achieved a 40 percent or greater improvement in weekly seizure frequency compared to those in the placebo group (30.5 percent vs. 16.7 percent); the rates for patients achieving a 30 percent or greater improvement was 43.9 percent for the ganaxolone arm vs. 25 percent for the placebo arm.

The phase III trial was similarly designed, though Chief Medical Officer Albena Patroneva acknowledged that being a global study – the phase II trial had been conducted solely at U.S. sites – may have resulted "a little more variability," though not enough to throw off the results. Both Patroneva and Lappalainen pointed out that the placebo responses in the phase III study were well within reason; it was the activity of ganaxolone that fell short.

The primary endpoint, defined as the percent change in 28-day seizure frequency from baseline, came in with a "p" value of 0.1537. The median reduction of focal onset seizures in the ganaxolone group was 21.8 percent vs. 10.25 percent in the placebo group during the titration and the 12-week treatment period. The study randomized 359 patients at 61 sites in the U.S., Germany, Poland, Australia, Bulgaria and Russia. The mean age was 41, the mean years since epilepsy diagnosis was 24.5 years and 76 percent of patients were receiving two or more concomitant antiepileptic drugs.

While the safety profile was generally consistent with earlier studies – overall the number of serious adverse events was similar for the ganaxolone and placebo groups at 5 percent and 5.1 percent, respectively – a total of 44 patients (25 percent) in the ganaxolone arm discontinued the study. That was higher than the rate of 10 percent to 15 percent expected – possibly a result of the slightly higher dose, with patients receiving 1,800 mg/day vs. 1,500 mg/day in the phase II trial – though Lappalainen said that was unlikely a contributing factor for the trial's failure.

The discontinuation rate in the placebo arm was 14 percent, or 26 patients.

Lappalainen also dismissed a powering issue as an unlikely reason for the miss, as well as the fact that Marinus opted to change from a liquid formulation in the phase II study to a pill in the phase III study. "We did collect pharmacokinetic [data]," he said. But there is "no indication to believe that would have been an issue."

The refractory population remains a difficult one to treat. It comprises patients who are not able to control seizures despite taking as many as three or more antiepileptic drugs. Marinus has estimated that roughly 30 percent to 35 percent of patients fall into that category. And, as Chief Medical Officer Patroneva noted, "with every new antiepileptic, the population becomes even more resistant."

TRIALS ONGOING

While investors are clearly viewing the disappointing data from the focal onset seizures trial as a negative readthrough to the ongoing trials, Marinus execs took pains during Monday's call to highlight the differences in study populations. In the pediatric orphan indications, for instance, the patients might present with seizures, but the "underlying mechanism is way more relevant to our mechanism of action," Patroneva explained. "These kids come with GABA deficiency, which translates not only into seizures but also behavioral problems."

Ganaxolone is a synthetic analogue of allopregnanolone, a CNS-produced neurosteroid that modulates GABA, or gamma-aminobutyric acid, but it's formulated in a way to avoid hormonal side effects. It's designed to bind to sites on the GABAA receptor, both synaptic and extrasynaptic sites.

An ongoing phase II study is testing ganaxolone as either an oral liquid suspension or capsule in patients with protocadherin 19 gene, or PCDH19, female epilepsy is expected to yield data next month. The study has enrolled 11 patients, with a primary endpoint of the percent change in seizure frequency per 28 days relative to baseline.

Another phase II study is testing the drug in patients with fragile X syndrome, a genetic condition resulting from a mutation in the fmr1 gene that leads to a number of developmental programs.

Patroneva said Marinus also remains confident for the clinical program in status epilepticus, which she views as a different population than patients with focal onset seizures. She described a "robust preclinical program, where we subjected

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Alpine

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developing protein-based immunotherapies using its variant immunoglobulin domain, or vIgD, platform technology, to interact simultaneously with multiple targets in the immune synapse using a single molecule.

Alpine Bio was launched in 2013 by Mitch Gold, managing partner and former CEO of Dendreon Corp., and David Miller, principal and former investment analyst, to invest in biopharma start-ups – particularly in the fields of cancer and rare diseases. Jay Venkatesan, executive vice president and general manager of Oncothyreon Inc., joined Alpine Bio last year. (See *BioWorld Today*, Sept. 3, 2013.)

"We saw the whole field going toward this combination approach – next-generation checkpoint inhibitors combined with co-stimulatory signals – and thought there was a better way to do this through a single molecule," Gold told *BioWorld Today*.

AIS "started to play around with a couple of ideas," he added and, with early data on the science in hand, reached out to Kite Pharma Inc. with the goal of leveraging an outgrowth of its vIgD technology that AIS calls TIP, or transmembrane immunomodulatory protein. While vIgDs are standalone drugs, TIPs are engineered to become part of engineered cellular therapies to potentially increase specificity, persistence and efficacy. Early data from the TIP program suggested the approach might be particularly effective in hematologic cancers.

Those conversations led to a potential $535 million licensing agreement that gave Kite, of Santa Monica, Calif., exclusive access to two undisclosed TIP targets designed to improve the engineering of its next-generation chimeric antigen receptor (CAR) and T-cell receptor candidates. (See *BioWorld Today*, Oct. 28, 2015.)

That deal in hand, Gold's agenda at the 2016 J.P. Morgan Healthcare Conference in San Francisco was to pick the brains of a few key investors about the direction of the immuno-oncology (I-O) field and to determine whether people could grasp the science at AIS.

Orbimed's Thompson "got it right away," and signed on, Gold said. Several additional conversations led to a quick close for the round.

In conjunction with the series A, Gold stepped in as executive chairman and acting CEO of AIS. Venkatesan was named president of AIS and a board member. Jamie Topper, managing general partner of Frazier's life sciences team, and Peter Thompson, private equity partner with Orbimed, also joined the AIS board.

The amount of the round was designed to allow AIS to reach a data readout for first-in-human studies, providing a significant milestone for the company from a valuation standpoint. Gold declined to say how long that might take, but the company has not yet disclosed its own pipeline.

He acknowledged the trend toward larger initial rounds designed to bring companies to potential exits but noted that amounts are dictated by the technology and opportunity.

"We're not just moving a single product forward," he said. "This is a true platform. We have hundreds of targets that we can pursue that are relevant to both immuno-oncology and autoimmune disease. Our development plans warranted a budget of this size."

Gold praised Kite as "a phenomenal" first partner for AIS and said the programs in the partnership "are progressing very nicely." AIS plans to use insights gleaned from the collaboration to structure future deals in the engineered T-cell space.

But "certainly, the core thesis and belief that drives this company is to advance our own products," Gold emphasized. "We have no intention of getting into the CAR-T space, but we have the full intention of moving our own products forward in immuno-oncology and, potentially, partnering out certain programs on the autoimmune side."

Although the company's expanded board hasn't had time to meet and sanction a timeline, "our goal is to get our first product in the clinic sometime in 2018," he added.

Citing a story by Reuters in which Richard Pazdur, director of the Office of Hematology and Oncology Products in the FDA's Center for Drug Evaluation and Research, took the industry to task for gravitating to the same I-O approach, Gold raised a similar question, asking, "Do we really need a fifth or sixth or seventh generation PD-1 [inhibitor] out there?"

The next generation of I-O drugs, instead, should examine new approaches that exploit the function of the immune system, he maintained.

"The immune system has natural ligands that have evolved over hundreds of thousands of years that closely keep in check the immune balance," Gold said. AIS is re-engineering that power to engage multiple targets simultaneously.

"Clearly, the next generation of products will be more efficacious because they're hitting multiple pathways simultaneously," he said. "And if you have one molecule that offers a multiplicity of effects, you should also be able to get a cost advantage downstream. That, to me, is what biotech has always been about: using innovation to create more efficacious and, potentially, more cost-effective drugs." //

OTHER NEWS TO NOTE

Arix Bioscience Ltd., of London, said it provided development capital to **Optikira LLC**, of Cleveland, an early stage firm developing drugs to prevent blindness. Formed by Biomotiv LLC in 2015, Optikira uses technologies stemming from intellectual property licensed from the University of California, San Francisco, to develop small-molecule therapeutics that prevent cell death in pathologies caused by misfolded or unfolded proteins. Initial work will focus on retinitis pigmentosa.

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Infringement

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The high court, minus Antonin Scalia, turned around an 8-0 decision trashing the Federal Circuit's two-part test for willful infringement, leaving the determination of whether to award enhanced damages to the discretion of district courts.

The Supreme Court handed down its decision in *Halo v. Pulse* on Monday, a case the court had conjoined with *Stryker v. Zimmer.* Both cases tackled the question of how damages are calculated in the event of willful infringement of a patent, a premise that was reset nine years ago via *re Seagate*, which constructed a two-part test consisting first of a need to demonstrate that the alleged infringer acted despite an objectively high likelihood that its commercial activities indeed infringed an existing patent. The second standard described in *Seagate* required a demonstration that the purported infringer knew or should have known that its activities constituted infringement.

Stryker emerged from the Court of Appeals for the Federal Circuit in December 2014, at which point Zimmer Inc., of Warsaw, Ind., was required to pay Kalamazoo, Mich.-based Stryker Corp. $70 million for infringement of patents for the latter's pulsed lavage systems. The award was a far lesser sum than the nearly $230 million Stryker had sought. Zimmer also was unable to recoup any legal costs incurred in the lawsuit. The Supreme Court took oral arguments in the *Halo/Stryker* case in February, and at least some observers believed at the time that the tenor of the questions posed by the justices suggested that the court was not on board with the Federal Circuit's two-part test as spelled out in *Seagate*.

Justice Antonin Scalia died 10 days before the Feb. 23 hearing, which means the final tally in *Halo* represents the entirety of the justices who were on hand for oral arguments. However, the Supreme Court has handed down unanimous or near-unanimous decisions in a large number of recent patent cases, suggesting that Scalia's presence would have had no impact on the outcome in *Halo*.

The Supreme Court justices stated in their decision that the statute "contains no explicit limit or condition on when enhanced damages are appropriate," and cited *Martin v. Franklin Capital* as a case in which the high court had declared that the word "may" carries a connotation of discretion. The justices further asserted that *Octane Fitness v. Icon Health* had established that enhanced damages "are not to be meted out in a typical infringement case," but instead ought to be deployed "as a sanction for egregious infringement behavior."

The court said *Seagate* provided a test that correctly reflects the gist of *Octane*, but the justices characterized the Federal Circuit's language in *Seagate* as both "unduly rigid" and inappropriately restrictive of "the statutory grant of discretion to district courts." The eight justices stated that the objective recklessness mandate in *Seagate* "excludes from punishment many of the most culpable offenders" of patent law, citing the example of the "wanton and malicious pirate" whose objective is commercial gain with no regard for the law.

The Supreme Court argued further that the "clear and convincing" standard for recklessness found in *Seagate* is also inconsistent with the statute, returning to *Octane* as instructive. The opinion, penned by Chief Justice John Roberts, stated that *Octane* undercuts the "clear and convincing" standard because the statute offers "no basis for imposing a heightened standard," arguing further that despite that Congress imposed "a higher standard of proof elsewhere in the Patent Act," the standard of a preponderance of evidence has always governed litigation over infringement.

Roberts wrote that the determination of whether attorney's fees should be repaid should likewise be governed by a district court's discretion as directed by the statute, rather than by a "multipart standard of review in favor of abuse of discretion review."

Konstantin Linnik, a partner in the intellectual property practice at Nutter, McClennen & Fish in Boston, told *BioWorld Today* that in addition to giving district courts more discretion regarding damages, the outcome in *Halo* "also reiterates the Supreme Court's approach to patent law as being consistent with other areas of the law." Linnik said the justices see patent law as something that requires no special rules, which might seem to fly against the presence of a specialized patent court in the form of the Federal Circuit.

Over the past 10 years or so, the Supreme Court "has been taking up a lot of these [patent] cases at a highly unusual rate," Linnik said, adding that most of the time, the Supreme Court has overturned the Federal Circuit in a manner that would seem to reflect "more of a generalist court perspective."

"The only thing that explains all these [overturned] cases is a more general approach to patent law, which is quite different from what the Federal Circuit has been developing for several decades," Linnik said. He added that he is not skeptical of the value of the Federal Circuit, but "some people have expressed the view that the Federal Circuit has done the job it needs to do and now it's overdoing it."

Nonetheless, Linnik said the Federal Circuit still has a role to play in at least reconciling conflicts in the decisions rendered by the circuit and district courts. "Any pending cases will have to be decided under the new standards, effective as of today," Linnik explained, but he said completed lawsuits may perhaps not need to be revisited. On the other hand, both the Stryker and Halo cases are now up for grabs again as a result of the outcome.

"The fact that it would appear to be easier to obtain enhanced damages under this standard" suggests that patent holders will be more willing to assert their patents," Linnik said, musing that the Halo decision would take some of the wind out of at least one piece of legislation making the rounds on Capitol Hill.

One bill affected by the outcome in Halo is S. 632, the Strong Patents Act of 2015, which in section 108 would have amended the statute so as to allow courts to impose treble damages assuming "a preponderance of the evidence" demonstrates willfulness. //

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Paxvax

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told *BioWorld Today* the company is likely to sell.

Priority review vouchers, which can be used by either the original sponsor or another sponsor to secure a priority review for a different FDA application, have sold for as much as $350 million. (See *BioWorld Today*, Aug. 20, 2015.)

The live, weakened vaccine, taken as a single oral liquid dose, is expected to become commercially available during the third quarter. It will be priced in line with other travel vaccines, which typically cost between $100 and $300. Vaxchora is the company's second licensed product after Vivotif, an FDA-approved oral typhoid vaccine it bought from Crucell Switzerland AG in mid-2014. (See *BioWorld Today*, July 29, 2014.)

FDA approval for Vaxchora covers the prevention of cholera caused by serogroup O1 — the most common cause of cholera — in adults ages 18 through 64 traveling to cholera-affected areas. Although the company declined to disclose market size estimates, Farzan said that Paxvax has seen data suggesting that about 8 million travelers from the U.S. visit the cholera endemic areas each year. An average of five to 10 cases of the infection are reported annually in the U.S., according to the Centers for Disease Control and Prevention.

Farzan called FDA approval an important first step for the company. "Any global health organizations and countries where cholera is endemic require approval from a Western regulatory agency prior to working with developers to make a vaccine available in countries where a disease is endemic," he said.

Because people regularly exposed to a disease often require a stronger formulation than those populations, like people living in the U.S., who have not been exposed, the company is working on a new formulation of the vaccine, he said.

The company has also completed a phase II randomized, double-blind study investigating the efficacy of Vaxchora vs. Shantha Biotechnics Ltd.'s Shanchol in Malian adults. The study was conducted in collaboration with the University of Maryland and the Centre pour le Développement des Vaccins in Bamako, Mali. Farzan said that Paxvax anticipates the results of the study to be published soon.

Cholera, a disease caused by *Vibrio cholerae* bacteria, can be acquired by ingesting contaminated water or food and causes a watery diarrhea that can range from mild to extremely severe. Vaxchora consists of CVD 103-HgR, a live, orally attenuated *Vibrio cholerae* strain. It is derived from the Inaba strain, 569B, by eliminating the gene that codes for the enzymatically active subunit A of cholera toxin, according to Thomson Reuters Cortellis Clinical Trials Intelligence. Accordingly, the strain only produces the non-toxic B subunit of the toxin, which is immunogenic and able to elicit immune responses against the bacterium as well as the toxin itself.

The vaccine's efficacy was demonstrated in a randomized, placebo-controlled human challenge study of 197 U.S. volunteers from 18 through 45. Of the 197 volunteers, 68 Vaxchora recipients and 66 placebo recipients were challenged by oral ingestion of *Vibrio cholerae*. Efficacy was 90 percent among those challenged 10 days after vaccination and 80 percent among those challenged three months after vaccination.

Two placebo-controlled studies to assess the immune system's response to the vaccine were also conducted in the U.S. and Australia in adults 18 through 64. In the 18 through 45 group, 93 percent of Vaxchora recipients produced antibodies indicative of protection against cholera. In the 46 through 64 group, 90 percent produced antibodies indicative of protection against cholera.

Redwood City, Calif.-based Paxvax was founded in 2007 by Kenneth Kelley. While the company initially focused on developing an oral vaccine against Avian influenza (H5N1), it later pivoted to focus on travel and biodefense vaccines, in-licensing Vaxchora.

Private equity investor Cerberus Capital Management L.P. acquired a majority economic interest in Paxvax with a $105 million investment in the company announced in December. Ignition Growth Capital and other existing investors remained as minority shareholders in the company. //

OTHER NEWS TO NOTE

Biotie Therapies Corp., of Turku, Finland, said it has delisted its American depositary shares from Nasdaq, effective June 13, and will delist its shares from Nasdaq Helsinki as soon as permitted. Biotie agreed earlier this year to an acquisition by **Acorda Therapeutics Inc.**, of Ardsley, N.Y., for $363 million in cash. (See *BioWorld Today*, Jan. 20, 2016.)

Contravir Pharmaceuticals Inc., of Edison, N.J., said it completed its merger with **Ciclofilin Pharmaceuticals Inc.**, of San Diego, acquiring all of its outstanding equity interests. Ciclofilin's lead asset is CPI-431-32, which is in development for hepatitis B virus. Future milestone payments will be allocated among the holders of Ciclofilin common stock and will consist of up to an aggregate $17 million cash and up to 10 percent of Contravir's issued and outstanding common stock.

DBV Technologies SA, of Bagneux, France, said preclinical data published in the *Journal of Allergy and Clinical Immunology* suggests that, independent of the route of sensitization, treatment with epicutaneous immunotherapy, or EPIT, provides protection against food-induced anaphylaxis during therapy and after treatment discontinuation in animal models. Findings show that when mice were challenged after four weeks without treatment, EPIT-treated mice were still significantly protected while mice treated with oral immunotherapy (OIT) regained clinical reactivity, independent of the initial route of sensitization. Treg generation with OIT was impaired in allergic mice, which led to the lack of sustained protection after OIT was discontinued. In mice treated with EPIT, the skin-gut immune communication generated gut-homing, antigen-specific LAP+Foxp3-Tregs that directly suppressed systemic anaphylaxis and provided sustained protection after treatment discontinuation.

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Gilde

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said. Other named participants include the Danish Growth Fund and the European Investment Fund.

Based in Utrecht, the Netherlands, with an office in Cambridge, Mass., the fund is transatlantic as well as cross-sectoral. Upward of one-third of its cash will go into U.S. deals. But Europe is its main focus, particularly its home market, the U.K., Germany and Denmark.

Spain has recently emerged as a source of deal flow as well. Fund III invested in two ventures, Palma de Mallora-based drug developer Laboratoris Sanifit SL and Barcelona-based Stat Diagnóstica & Innovation SL, which develops integrated molecular and immunoassay diagnostics systems. Gilde led the latter firm's €25 million C round in April.

"Spain is a surprise in the last one or two years. We've been looking at opportunities in that country for nearly a decade," van der Meer said. Companies based there are now reaching a level of maturity that has started to attract international investors.

Fund IV will seek similar opportunities to those pursued by Fund III. Gilde is mainly focused on companies that "have reached a certain level of validation," van der Meer said. For the different categories it invests in, that can mean different things. For a drug developer, for example, it could mean some patient data, but preclinical programs are not off the menu. For med-tech firms, Gilde expects regulatory approval, and it steps in to fund commercialization. In digital health, it seeks companies that have products on the market with some cash coming in – it invests in scale-up. But the overriding consideration is time to exit.

Successful exits from Fund III include Munich-based Definiens AG, which London-based Astrazeneca plc acquired for €150 million plus undisclosed milestones. Gilde was involved in helping to shift the company's strategy from digital pathology services to higher-value biomarker discovery, which the Medimmune arm of Astrazeneca is now employing for immuno-oncology research. "Initially we thought it would be a medtech or a diagnostics company," van der Meer said.

Medtronic Inc., of Minneapolis, picked up Sapiens Steering Brain Stimulation BV, of Eindhoven, the Netherlands, for $200 million cash. And Oxford, U.K.-based Circassia Pharmaceuticals plc picked up specialty pharma firm Prosonix Ltd. (also of Oxford) for £70 million up front (US$99.1 million), with possibly £30 million more to come. Most of Gilde's exits took the form of trade sales, but another Dutch firm, Leiden-based cystic fibrosis drug developer Proqr Therapeutics NV, raised $98 million in a Nasdaq IPO in Sep. 2014.

It is still sitting on a potentially lucrative exit involving Pfizer Inc. and portfolio firm AM Pharma BV, of Bunnik, the Netherlands, which is developing a human recombinant firm of alkalkine phosphatase for acute renal injury. New York-based Pfizer has already put down $87.5 million to acquire an option on the firm, pending readout from a phase II trial this year. If successful, the total value of the deal could reach $600 million. (See *BioWorld Today*, May 12, 2015.)

Within the therapeutics domain, Gilde is focused both on innovative drug development and on specialty pharma, an approach that can help to balance risk. Immuno-oncology, gene editing, including RNA editing, and infectious disease are all important themes. Digital health, as well as being a domain in its own right, also holds out the promise to pharma and medtech that it can help to build more value into their products.

"We see an important convergence occurring where both pharma and medtech are looking for ways to involve the patient with their products," van der Meer said. "A lot is driven in the end by the necessity to reduce cost while improving quality."

Gilde is close to completing the final investment from Fund III and will move seamlessly to Fund IV. It aims to close one or two transactions from the new fund this year, van der Mer said.

The new fund takes the total raised by Dutch VC firms this year to about $770 million.

Earlier this month, Life Science Partners' new fund LSP5 also reached the hard cap of $280 million, well in excess of its $170 million target. It will focus on drug development, med tech and diagnostics. In April, Naarden-based Forbion Partners, which is focused exclusively on drug discovery and development, closed Forbion Capital Fund III at €183 million. //

OTHER NEWS TO NOTE

Eleven Biotherapeutics Inc., of Cambridge, Mass., said it entered an exclusive license deal with **Roche Holdings AG**, of Basel, Switzerland, relating to Eleven's interleukin-6 (IL-6) technology, granting Roche worldwide rights to develop and commercialize EBI-031, a humanized monoclonal antibody for potential treatment of ocular diseases, and for all other IL-6 antagonist antibody technology owned by Eleven. Under the terms, Eleven will get an up-front payment of $7.5 million, with potential future milestone payments of up to $262.5 million, with the first milestone payment of $22.5 million upon an investigational new drug application (IND) becoming effective on or before Sept. 15. Eleven also could be entitled to royalties for next sales of future products containing EBI-031 or any other potential future products containing other IL-6 compounds. In separate news, Eleven said it filed an IND with the FDA to start a phase I trial of EBI-031. The drug, which has potential for diseases such as diabetic macular edema and uveitis, became the top prospect for Eleven following disappointing data for late-stage candidate EBI-005 (isunakinra), an IL-1-targeting drug, in severe allergic conjunctivitis and dry eye disease. Shares of Eleven (NASDAQ:EBIO) gained 52 cents, or 27.8 percent, to close Monday at $2.39. (See *BioWorld Today*, May 19, 2015, and Jan. 20, 2016.)

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CFDA

Continued from page 1

market, the CFDA is ramping up its focus on offshore drug manufacturers. The regulator last year stepped up the number of overseas good manufacturing practice (GMP) inspections it carried out, while domestically, it put more of the onus on companies to police themselves.

The 2015 report on drug inspections released this month shows that the number of GMP inspections at pharmaceutical companies in Mainland China has fallen significantly over the past year while the number of overseas inspections has increased by one-fifth.

The CFDA released the latest report via its Center for Food and Drug Inspection (CFDI). In total, 698 inspections were carried out, including pharmaceutical GMP certification inspections, pre-approval inspections, GMP follow-up visits, good agricultural practice certification inspections for traditional Chinese medicine, unannounced inspections and overseas inspection.

Most noticeably, the number of enterprises that received GMP inspections was halved in the last year, 221 in 2015 compared to 482 in 2014. Only nine, or 4.1 percent, of these companies failed last year but 7.7 percent had to address some deficiencies compared with 4.4 percent the year before. The ratio of companies receiving warning letters rose marginally from 30.3 percent to 30.8 percent.

"The increase of self-inspection is the reason behind the decrease of CFDA's GMP inspections," a health care equity analyst in Shanghai told *BioWorld Today*. "The regulators are asking more and more companies to do self-inspections first, and withdraw pending applications online if they find problems ahead of the CFDA inspection. The quality of self-inspections is up, so the overall inspection number is down."

Nine companies failed the CFDA GMP inspections in Shanxi, Liaoning, Jilin, Henan, Hunan, Guangxi and Shaanxi provinces.

On the biologics side, manufacturers of nine vaccine products, three blood products and 30 other biological drugs applied for GMP certification in 2015.

Among all the inspections the CDFI conducted last year, deficiencies were mainly found in laboratory and quality control systems, production systems and material systems.

As the number of domestic inspections dropped, the number of inspections of manufacturing facilities overseas increased 20 percent in 2015 from 28 to 34. And the regulator said more such increases are likely.

China started doing overseas inspection in April 2011. The CFDI has appointed 68 teams of inspectors to work on 73 drugs so far. All products for clinical trial applications, production applications, re-registration and supplementary application were considered, including 46 chemical drugs, 18 biological drugs (vaccines and blood products) and nine herbal medicines.

According to the report, in the first three years of overseas inspections, inspectors found that foreign companies often "didn't value China's pharmaceutical laws and regulations, didn't produce as per China's requirements, and had different treatments on products exported to China and to other countries."

So Chinese regulators expanded the scope of their overseas inspections.

Analysts see this as a way of the government to protect domestic drugmakers, giving them more time and space for their growth.

"The CFDA is leaning toward import substitution. All of the documents released by the National Health and Family Planning Commission and the CFDA [on drug inspection] have this inclination, so there are more and more overseas inspections," said the equity analyst who's been looking at the pharma market in China for three years.

In January, the CFDI released the list of foreign manufacturers to be inspected in 2016. The regulators aim to go to 49 companies, including one added in April, mainly in Europe, the U.S., Japan and Vietnam to do on-site drug manufacturing inspections. Subsidiaries of pharma majors such as Novartis Europharm Ltd., Glaxosmithkline Australia Pty. Ltd. and Glaxosmithkline Biologicals SA are on the list which may grow longer again later this year. The CFDA said in a May notice that the number will grow substantially this year.

Most of local companies are very serious about the inspections as the GMP certificate and pre-approval inspections are crucial to both their production capability and profitability. But the eagerness to pass sometimes backfires.

"The number one rule of going through inspection is honesty," said Tian Shaolei, deputy section chief from the CFDI during the recent DIA annual meeting in Beijing. "Sometimes companies go out of their way to pass their inspections. I inspected a company once and took notes in my notebook along the way, in the afternoon they handed me all the materials on the issues I wrote down in my notebook, which I left closed on the table while I was out for lunch."

"It can be understood that companies want to do well in front of the CFDA inspectors, but there's no need to over-do it, just study the standards and be honest," Shaolei noted. //

OTHER NEWS TO NOTE

Enbiotix Inc., of Cambridge, Mass., said it inked a deal with the Mayo Clinic to continue development of the firm's candidate, EPP-001, an engineered bacteriophage product to deliver biofilm-dispersing enzymes to treat *Staphylococcus aureus* infections in prosthetic joints. In addition, Enbiotix received a funding award from Mayo Clinic Ventures, which is helping to facilitate the project. Additional terms of the financing and collaboration agreement were undisclosed.

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Marinus

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animals to what is the equivalent of refractory status epilepticus and we did see ganaxolone working very powerfully in this preclinical model."

She added that "we do believe the extrasynaptic activity of ganaxolone is very relevant to what these patients are experiencing," particularly when treatment with benzodiazepines no longer work. "You need a mechanism that is delivering something additional to what [benzodiazepine] delivers."

Marinus plans an update on the status epilepticus program "shortly," CEO Cashman said, adding. "All systems are go on that program."

Marinus' plan is to initially develop ganaxolone as an intravenous formulation in that indication, with an oral follow-on to come next. "We'll be taking the data we're learning from [the phase III study] and integrating it into that status epilepticus program," he said.

Other firms working in that space include Sage Therapeutics Inc., another member of the 2014 IPO class, which is in phase III testing with SAGE-547, an allosteric modulator of both synaptic and extrasynaptic GABAA receptors, in super-refractory status epilepticus, for which it has both orphan status and fast track designation.

Marinus, which ended the first quarter with cash, equivalents and investments totaling $51.4 million, has enough runway to get "close to the end of 2017," Cashman said. //

OTHER NEWS TO NOTE

Faron Pharmaceuticals Ltd., of Turku, Finland, said it entered a licensing deal with **Pharmbio Korea Co. Ltd.**, of Seoul, South Korea, for the development and commercialization of Traumakine in Korea. Under the terms, Pharmbio will obtain an exclusive Korean license in exchange for an initial signing fee of €750,000 (US$844,738), and is entitled to receive additional, undisclosed development-based milestones plus one-third of Traumakine profits, representing a double-digit royalty on net sales, depending on end-user pricing. Pharmbio also will cover development costs in Korea. Traumakine, a recombinant version of human interferon-beta-1a, is in development for the treatment of acute respiratory distress syndrome. It's being tested in the pivotal pan-European phase III INTEREST trial.

Galena Biopharma Inc., of San Ramon, Calif., said the FDA grated two orphan drug designations to its cancer immunotherapy peptides, GALE-301 and GALE-301/GALE-302, derived from folate-binding protein for the treatment (including prevention and recurrence) of ovarian cancer. In clinical trials, GALE-301, and GALE-301/GALE-302 are combined with the immune adjuvant, granulocyte macrophage-colony stimulating factor for the treatment of ovarian cancer in the adjuvant setting.

Glycomimetics Inc., of Rockville, Md., said it received fast track designation from the FDA for its E-selectin antagonist GMI-1271 for the treatment of adults with relapsed or refractory acute myeloid leukemia (AML) and elderly patients, age 60 and older, with AML. The company recently dosed the first patient with relapsed or refractory disease in the phase II portion of the ongoing phase I/II study.

Lannett Co., of Philadelphia, received FDA approval for its abbreviated new drug application for Neomycin Sulfate Tablets USP, 500 mg, the therapeutic equivalent to the reference listed drug, Neomycin Sulfate Tablets USP, 500 mg, of Teva Pharmaceuticals USA, Inc.

Medivation Inc., of San Francisco, said it filed with the SEC a definitive consent revocation statement and, in conjunction, mailed a letter to stockholders urging them to reject the bid from **Sanofi SA**, of Paris, calling the offer "opportunistic and grossly inadequate." Since Medivation rejected Sanofi's $9.3 billion offer in March, the French pharma has gone hostile, initiating moves to replace Medivation's board. (See *BioWorld Today*, April 29, 2016, and May 26, 2016.)

Nexus Biopharma Inc., of Montclair, N.J., formerly Plata Resources Inc., said it completed its merger with Nexus Biopharma Inc., a company developing an obesity drug targeting the AMPK metabolic pathway. As a publicly operating company, the life sciences firm said its access to capital markets will enable it to complete drug optimization and pre-investigational new drug application studies to move toward clinical testing.

Oncobiologics Inc., of Cranbury, N.J., said the 5.8 million units issued in its IPO will separate in accordance with their terms. Each unit consists of one share of common stock, one-half of a series A warrant and one-half of a series B warrant. The biosimilars maker closed its IPO last month, generating net proceeds of about $29.8 million.

Opko Health Inc., of Miami, said it will move it stock listing to Nasdaq from the New York Stock Exchange. Shares are expected to begin trading on Nasdaq June 24 under the ticker OPK.

Prometic Life Sciences Inc., of Laval, Quebec, said the FDA granted fast track designation to the firm's plasminogen drug candidate, in phase II/III testing in patients with congenital plasminogen deficiency. The product previously received orphan designation in both the U.S. and Europe.

Shire plc, of Dublin, said it completed a decentralized procedure to support approval by 17 authorities in Europe for Cuvitru (IG 20mg/ml solution for subcutaneous injection), a treatment for pediatric and adult patients with primary and certain secondary immunodeficiency disorders, a group of disorders in which part of the body's immune system is missing or does not function properly. Cuvitru is an IG treatment that does not contain proline. Local marketing authorizations in Europe are expected to begin later in 2016.

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NEWS FROM THE ADA

The following data were released at the American Diabetes Association Scientific Sessions in New Orleans:

Amarin Corp. plc, of Dublin, reported additional data on Vascepa (icosapent ethyl) supporting its efficacy in reducing concentrations of potentially atherogenic lipoproteins in patients with type 2 diabetes and persistent high triglyceride (TG) levels despite statin therapy. The ANCHOR study investigated Vascepa as a treatment for patients with residual high TG (≥200 and <500mg/dL) despite statin-induced control of LDL-C. The study enrolled 702 patients, of which the majority (73 percent) had type 2 diabetes. The primary endpoint was percent change in TG levels from baseline to 12 weeks compared with placebo in subjects treated with placebo or Vascepa at 2 or 4 g/day. The data presented are an analysis of NMR measurements providing the concentration and size of lipoprotein particles (VLDL, LDL and HDL) in ANCHOR subjects with type 2 diabetes, and comparing the results of subjects taking 4 g/day Vascepa (n=160) to those taking placebo (n=154). The analysis showed that, compared with placebo, Vascepa significantly reduced the median concentration of: total (-11.3 percent; p=0.004), large (-48.9 percent; p<0.0001), and medium (-12 percent; p=0.02) VLDL particles; total (-7.4 percent; p=0.009) and small (-13.1 percent; p<0.0001) LDL particles; and total (-7.5 percent; p<0.0001) and large (-29.7 percent; p<0.0001) HDL particles.

Astrazeneca plc, of London, presented results of two pooled analyses involving more than 4,600 patients with type 2 diabetes. In one analysis of patients with type 2 diabetes and renal impairment, Farxiga (dapagliflozin) reduced body weight and systolic blood pressure regardless of baseline estimated glomerular filtration rate (eGFR), when compared to placebo. Additionally, it reduced urine albumin to creatinine ratio (UACR) in patients with a baseline UACR ≥30 mg/g when compared to placebo, including in patients with mild renal impairment (eGFR ≥60 to <90 ml/min/1.73m2). The compound is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes. The second analysis examined the effects of Farxiga vs. placebo in patients treated with potassium-sparing agents. When co-administered with potassium-sparing agents, the compound resulted in lower A1C, body weight and systolic blood pressure, with no evidence of increase in serum potassium.

Boehringer Ingelheim GmbH, of Boehringer Germany, and **Eli Lilly and Co.,** of Indianapolis, reported that new analyses of data from the EMPA-REG OUTCOME trial showed that risk reductions were consistent across age groups for cardiovascular outcomes, including CV death, with Jardiance (empagliflozin) compared with placebo when added to standard of care in adults with type 2 diabetes and established CV disease. In addition, the companies said results from the MARLINA-T2D trial showed that Tradjenta (linagliptin) reduced blood sugar in adults with type 2 diabetes (T2D) at risk for kidney impairment, with a renal safety profile similar to that seen in other trials. MARLINA-T2D examined the safety and efficacy of Tradjenta compared to placebo in 360 patients with T2D and albuminuria. At 24 weeks, Tradjenta was associated with a 0.6 percent reduction in A1C compared to placebo, although change in albuminuria was not significant.

Dynavax Technologies Corp., of Berkeley, Calif., announced preliminary results from a pivotal phase III trial demonstrating that Heplisav-B vaccine provided a significantly higher rate of seroprotection than Engerix-B, an approved hepatitis B vaccine, in adults with type 2 diabetes. The study compared two doses of Heplisav-B with three doses of Engerix-B in adults ages 18 to 70. Among the over 8,000 randomized participants, there were 1,144 adults with type 2 diabetes of whom two-thirds had diabetes for five years or more. Results showed that Heplisav-B provided seroprotection in 90 percent of participants with diabetes compared with 65.1 percent for Engerix-B - a statistically significant difference of 24.9 percent. Larger differences were observed in participants ages 60 to 70, with the vaccine demonstrating an 85.8 percent rate of seroprotection compared with 58.5 percent for Engerix-B. The FDA has established Dec. 15, 2016, as the Prescription Drug User Fee Act action date for the Heplisav-B biologics license application.

Eiger Biopharmaceuticals Inc., of Palo Alto, Calif., presented positive results of a study evaluating subcutaneously administered exendin (9-39), a 31-amino acid peptide that selectively targets and blocks GLP-1 receptors, in post-bariatric surgical patients who experience dangerously low, postprandial blood glucose levels (hypoglycemia) known as post-bariatric hypoglycemia (PBH). The study used a single ascending dose design to examine the pharmacokinetics, pharmacodynamics, and local tolerability of three escalating doses of subcutaneous exendin (9-39). Eight subjects suffering from PBH were enrolled and administered oral glucose tolerance tests (OGTT) with and without subcutaneous exendin (9-39). Hypoglycemia was defined as a plasma glucose level of 50 mg/dl or less during OGTT. Prevention of hypoglycemia and reduction in hypoglycemic symptoms was achieved in all eight subjects at all dose levels of subcutaneous exendin (9-39). Conversely, without subcutaneous exendin (9-39), all eight subjects became hypoglycemic and required rescue during baseline OGTT when plasma glucose reached 50 mg/dl.

Fate Therapeutics Inc., of San Diego, reported preclinical data demonstrating that a single administration of Toleracyte, its programmed CD34-positive immuno-regulatory cell product candidate, can result in durable correction of type 1 diabetes in a well-established non-obese diabetic (NOD) mouse model. Research also showed that a single administration of programmed cells significantly delayed the onset of type 1 diabetes in NOD mice. Fate is advancing Toleracyte in late-stage preclinical development through a collaboration with Boston Children's Hospital.

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NEWS FROM THE ADA

Intarcia Therapeutics Inc., of Boston, reported that during the Freedom-2 phase III trial of ITCA 650, the continuous delivery exenatide system demonstrated superior efficacy to Januvia (sitagliptin, Merck & Co. Inc.) in reducing HbA1c and body weight in patients with poorly controlled type 2 diabetes on metformin following one year of treatment, meeting all primary and secondary trial endpoints. Significantly more patients on ITCA 650 60 mcg vs. Januvia 100 mg achieved the ADA-recommended HbA1c target of <7.0 percent (61 percent vs. 42 percent; p<0.001), the company said. In the composite endpoint of HbA1c reductions of greater than or equal to 0.5 percent and weight reductions of 2 kg (4.4lbs) or greater, 61 percent of patients using ITCA 650 achieved the endpoint vs. 28 percent of those who received Januvia (p<0.001). The study was one of four phase III studies in the Freedom program, all of which successfully met their primary endpoints. Intarcia expects to file an application for approval of ITCA 650 by the end of the third quarter 2016, slightly later than its original estimate. (See *BioWorld Today*, Aug. 20, 2015.)

Janssen Research & Development LLC, of Raritan, N.J., a unit of Johnson & Johnson, reported the outcomes of multiple studies of its sodium glucose co-transporter 2 inhibitor canagliflozin. In one series of studies, Janssen said that it found that people with type 2 diabetes treated with Invokana (canagliflozin) achieved greater blood glucose control and were more likely to stay on therapy than were those treated with dipeptidyl peptidase-4 inhibitors, a common class of medicines for type 2 diabetes that includes Januvia (sitagliptin, Merck & Co. Inc.). Separately, a phase II study of patients treated with a combination of canagliflozin and phentermine, found that the combination was effective for weight loss in overweight or obese non-diabetic adults. At 26 weeks, patients in the canagliflozin with phentermine arm experienced a significant placebo-subtracted reduction in systolic blood pressure (-4.2 mmHg; p = 0.015) and demonstrated statistically superior weight loss compared to placebo, with the canagliflozin with phentermine, phentermine, canagliflozin and placebo arms producing weight decreases of 7.5 percent, 4.1 percent, 1.9 percent and 0.6 percent compared to baseline respectively (p <0.001). Additionally, among the patients observed throughout the 26 week duration of the study, significantly more achieved ≥5 percent weight loss in the canagliflozin with phentermine arm vs. placebo (66.7 percent vs. 17.5 percent; p <0.001). Janssen also reported the results of a phase II, randomized study showing glycemic improvements in adults with type 1 diabetes mellitus treated with canagliflozin. The 18-week study evaluated 351 adults with inadequately controlled T1DM who were administered canagliflozin 100 mg, canagliflozin 300 mg or placebo as an add-on to insulin. At the end of the study, canagliflozin 100 mg and 300 mg were associated with a 11.6 percent and 10.1 percent increase in the time patients spent within target glycemic ranges (glucose >70 to ≤180 mg/dL) and showed comparable reductions in time spent above target (glucose >180 mg/dL) vs. placebo. But there were no meaningful changes in the time patients spent below target (glucose ≤70 mg/dL) across groups.

New data from a completed phase III trial showed that Indianapolis-based **Eli Lilly and Co.**'s Trulicity (dulaglutide) 1.5 mg significantly reduced hemoglobin A1c (A1C) and body weight as an add-on to insulin glargine without increasing the risk of low blood sugar after 28 weeks compared to placebo plus insulin glargine, Lilly reported. After 28 weeks of treatment, Trulicity 1.5 mg plus insulin glargine significantly reduced A1C from baseline (1.44 percent) compared to placebo with insulin glargine (0.67 percent), the company said.

Mannkind Corp., of Valencia, Calif., reported data from additional analyses of its inhaled insulin product, Afrezza (insulin human), that showed faster onset of action and shorter duration than rapid-acting insulin analogs in patients with diabetes mellitus. In a randomized, controlled, six-treatment, crossover dose-response study comparing Afrezza to the rapid-acting insulin analog, lispro (Humalog, Eli Lilly and Co.) in 30 patients with type 1 diabetes, Afrezza's onset of action occurred within 16 to 21 minutes compared to 45 to 52 minutes for subcutaneous insulin across the studies. Afrezza's duration of action at clinically relevant doses was consistently shorter by two to three hours. In addition, Mannkind reported that Afrezza's labeled dose overestimated its effect, emphasizing the need for appropriate dose titration.

Merck & Co. Inc., of Kenilworth, N.J., announced results from two phase III studies evaluating MK-1293, Merck's investigational, follow-on biologic insulin glargine candidate for the treatment of people with type 1 and type 2 diabetes. In both studies, MK-1293 achieved its primary endpoint by demonstrating non-inferiority in change from baseline A1C (a measure of average blood glucose) and similar safety to Lantus (insulin glargine) after 24 weeks in patients with type 1 and type 2 diabetes. In both studies, MK-1293 met its pre-specified secondary efficacy endpoints of statistical A1C equivalence to Lantus, a measure used to show that an investigational treatment is similar, within an acceptable range, to a current therapy.

Merck & Co. Inc., of Kenilworth, N.J., and **Pfizer Inc.**, of New York, said the phase III VERTIS Mono and VERTIS Factorial studies of ertugliflozin, an oral SGLT-2 inhibitor designed to treat patients with type 2 diabetes, met their primary endpoints. The 26-week VERTIS Mono study, which evaluated ertugliflozin as monotherapy, showed that patients randomized to ertugliflozin 5 mg and 15 mg had A1C reductions of 0.99 percent and 1.16 percent, respectively, compared with placebo (p<0.001, for both comparisons). In addition, more patients taking ertugliflozin 5 mg and 15 mg achieved the A1C treatment goal of less than 7 percent (28.2 percent and 35.8 percent, respectively) compared with placebo (13.1 percent) (p<0.001, for both comparisons). In VERTIS Factorial, a 26-week study that evaluated the co-administration of ertugliflozin and

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NEWS FROM THE ADA

Merck's dipeptidyl peptidase-4 inhibitor, Januvia (sitagliptin), greater reductions in A1C were observed in patients who took ertugliflozin in combination with sitagliptin compared to ertugliflozin or sitagliptin alone. In addition, co-administration of the agents was more effective than either alone in achieving the A1C treatment goal of less than 7 percent. Specifically, 52.3 percent of patients who took ertugliflozin 5 mg in combination with sitagliptin 100 mg and 49.2 percent of patients who took ertugliflozin 15 mg in combination with sitagliptin 100 mg reached an A1C goal of less than 7 percent. In comparison, 26.4 percent achieved this A1C goal with ertugliflozin 5 mg, 31.9 percent with ertugliflozin 15 mg, and 32.8 percent with sitagliptin 100 mg ($p<0.001$ for both combinations vs. individual treatments in model-based tests).

Melior Pharmaceuticals I Inc., of Exton, Pa., and **Bukwang Pharmaceuticals Co. Ltd.**, of Seoul, South Korea, said their phase IIa proof-of-concept study evaluating MLR-1023 in patients with type 2 diabetes met its primary endpoint of lowering post-prandial plasma glucose as evaluated in a mixed meal tolerance test. The four-week study, which enrolled 130 patients across 19 sites in the U.S. and Korea, also achieved statistically significant reduction of fasting plasma glucose after 28 days of treatment in the 100 mg, once-daily treatment group (-38.5 mg/dL) and suggested positive effects on lipid levels and body weight. The companies said the treatment was generally well-tolerated.

Novo Nordisk A/S, of Bagsvaerd, Denmark, reported that patients with type 2 diabetes in the phase IIIa SUSTAIN 2 trial who received 0.5 mg and 1 mg semaglutide, administered once weekly, showed improved glycemic control at 56 weeks from a mean baseline HbA1c of 8.1 percent, achieving reductions of 1.3 percent and 1.6 percent, respectively, compared to 0.5 percent for those treated with sitagliptin (Januvia, Merck & Co. Inc.) 100 mg. In the 56-week SUSTAIN 3 trial, adults with type 2 diabetes and a mean baseline HbA1c of 8.3 percent achieved HbA1c reduction of 1.5 percent when treated with 1 mg semaglutide compared to 0.9 percent for those treated with 2 mg exenatide ER ($p<0.0001$), when added to one or two oral antidiabetics. More adults with type 2 diabetes achieved the HbA1c target of less than 7 percent when treated with 0.5 mg and 1 mg semaglutide compared to sitagliptin in SUSTAIN 2 (69 percent and 78 percent vs. 36 percent) and with 1 mg semaglutide vs. exenatide ER in SUSTAIN 3 (67 percent vs. 40 percent). The most common adverse events (AEs) in patients treated in SUSTAIN 2 and SUSTAIN 3 were gastrointestinal. Novo Nordisk also reported tht its two phase IIIb SWITCH trials showed Tresiba (insulin degludec injection U-100) demonstrated lower rates of overall, nocturnal and severe hypoglycemia vs. insulin glargine U-100. In SWITCH 1, patients with type 1 diabetes who received Tresiba showed a rate reduction of 11 percent in overall symptomatic blood glucose (95 percent confidence interval [CI]: 0.85; 0.94), a rate reduction of 36 percent in nocturnal symptomatic hypoglycemic episodes (95 percent CI: 0.56; 0.73) and a rate reduction of 35 percent severe or symptomatic hypoglycemia (95 percent CI: 0.48; 0.89), compared with insulin glargine U-100 during the maintenance period. In SWITCH 2, patients with type 2 diabetes who took Tresiba experienced a rate reduction of 30 percent in overall symptomatic hypoglycemic episodes (95 percent CI: 0.61; 0.80) and a rate reduction of 42 percent in nocturnal symptomatic hypoglycemic episodes (95 percent CI: 0.46; 0.74), compared with insulin glargine U-100.

Poxel SA, of Lyon, France, presented preclinical data suggesting the beneficial effect of imeglimin on insulin sensitivity in a streptozotocin-induced diabetic rat model. After both acute and chronic treatment, imeglimin improved glucose tolerance and overall insulin sensitivity during a euglycemic hyperinsulinemic clamp, with a significant effect on hepatic insulin sensitivity, confirming previous results observed in preclinical models and in type 2 diabetes patients. In a second preclinical study, imeglimin increased glucose-stimulated insulin secretion through a mechanism of action targeting synthesis of nicotinamide adenine dinucleotide (NAD). Treatment of isolated islet cells from a diabetic rat model with imeglimin led to an increase in NAD content, a component of mitochondrial function.

Sanofi SA, of Paris, presented additional data from the pivotal phase III Lixilan-O and Lixilan-L trials of its titratable fixed-ratio combination of basal insulin glargine 100 units/mL and GLP-1 receptor agonist lixisenatide (Lyxumia) in adults with type 2 diabetes. Lixilan-O investigated the efficacy and safety of a once-daily single injection of the titratable fixed-ratio combination of insulin glargine 100 units/mL and lixisenatide vs. treatment with either agent, alone, over a 30 week period in 1,170 patients whose type 2 diabetes was not adequately controlled on metformin alone or in combination with a second oral anti-diabetic agent. After 30 weeks, the fixed-ratio combination showed significantly greater reductions in HbA1c from baseline (8.1 percent) vs. insulin glargine 100 units/mL or lixisenatide (-1.6 percent, -1.3 percent, -0.9 percent, respectively; $p<0.0001$), reaching mean HbA1c levels of 6.5 percent, 6.8 percent and 7.3 percent, respectively. Lixilan-L examined the efficacy and safety of the fixed-ratio combination vs. insulin glargine 100 units/mL over a 30-week period in 736 patients whose type 2 diabetes was not adequately controlled at screening. After 30 weeks, the fixed-ratio combination showed reductions in HbA1c from baseline (8.1 percent) vs. insulin glargine 100 units/mL (-1.1 percent vs. -0.6 percent; $p<0.0001$), reaching mean HbA1c levels of 6.9 percent and 7.5 percent, respectively. The most frequent adverse events in both studies were nausea, vomiting and diarrhea. (See *BioWorld Today*, Sept. 15, 2015.)

Takeda Pharmaceutical Co. Ltd., of Osaka, Japan, published a post-hoc analysis from the global EXAMINE (EXamination of CArdiovascular OutcoMes: AlogliptIN vs. Standard of CarE in Patients with Type 2 Diabetes Mellitus and Acute Coronary

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NEWS FROM THE ADA

Syndrome) cardiovascular (CV) safety outcomes trial (CVOT), which suggested that in patients with type 2 diabetes and recent acute coronary syndrome (ACS), the risk of death, including CV death, was not higher with the dipeptidyl peptidase-4 (DPP-4) inhibitor alogliptin compared to placebo during a median follow-up period of 18 months. Trial results reported that in both groups of patients the occurrence of an additional non-fatal CV event, including myocardial infarction, stroke and unstable angina, was common and increased the risk of death, particularly after hospitalization for heart failure.

Zafgen Inc., of Boston, announced new data from the ZAF-203 clinical trial evaluating beloranib, a MetAP2 inhibitor, for the treatment of severe obesity complicated by type 2 diabetes. Data showed that beloranib was associated with improvement in body composition, including a significant decrease in body weight, fat mass, reduction in waist and hip circumference, and improvements in liver fat, as well as glycemic control parameters including HbA1c, fasting plasma glucose, post-prandial glucose, beta-cell function, and insulin sensitivity, when compared to placebo. The ZAF-203 clinical trial achieved its primary efficacy endpoint, as beloranib demonstrated a statistically significant reduction in body weight compared to placebo.

OTHER NEWS TO NOTE

Sirona Biochem Corp., of Vancouver, British Columbia, said **Wanbang Biopharmaceuticals Co. Ltd.**, of Xuzhou, China, confirmed it will proceed with studies to prepare for an investigational new drug application filing for diabetes candidate SBM-TFC-039, an SGLT2 inhibitor. Sirona received a milestone payment of $300,000 under the companies' collaboration.

Syros Pharmaceuticals Inc., of Cambridge, Mass., said that SY-1425, a retinoic acid receptor alpha (RARα) agonist, was observed to inhibit the growth of cancer cells and prolong survival in an in vivo model of acute myeloid leukemia (AML) with an RARA biomarker discovered by the company. Syros also announced that SY-1365, its first-in-class potent and selective cyclin-dependent kinase 7 (CDK7) inhibitor, was observed to selectively kill acute leukemia cells over non-cancerous cells and induce complete tumor regression and a significant survival benefit in in vivo models of AML. These data are being presented this week at the 21st Congress of the European Hematology Association. The presentations highlight the potential of the gene control platform to systematically analyze the non-coding, regulatory region of the genome to advance a new wave of medicines designed to control the expression of disease-causing genes.

Teva Pharmaceutical Industries Ltd., of Jerusalem, said it will voluntarily suspend sales, marketing and distribution of Zecuity (sumatriptan iontophoretic transdermal system) following postmarketing reports of application site reactions described as burns and scars. Zecuity, a treatment for migraine, was acquired in Teva's buyout of Nupathe Inc. in 2014. In separate news, Teva and an affiliate of **Allergan plc**, of Dublin, inked a deal with **Dr. Reddy's Laboratories Ltd.**, of Hyderabad, India, under which Dr. Reddy's will acquire a portfolio of eight abbreviated new drug applications in the U.S. for $350 million in cash at closing. The portfolio consists of products that are being divested by Teva as a pre-condition to its closing of the acquisition of Allergan's generics business. Teva also reported Monday at the U.S. District Court for the District of Delaware ruled in favor of the company's patent infringement lawsuit against Hetero USA Inc., Innopharma Inc., Hospira Inc., Sagent Pharmaceuticals Inc. and Accord Healthcare Inc., regarding Teva's Treanda (bendamustine hydrochloride) for injection. The company expects the court to enter an order enjoining the defendants from launching their respective generic versions of Treanda until patent expiry in 2026. (See *BioWorld Today*, July 28, 2015.)

Titan Pharmaceuticals Inc., of South San Francisco, said it received a $15 million milestone payment from partner **Braeburn Pharmaceuticals Inc.**, of Princeton, N.J., following FDA approval of Probuphine, a subdermal buprenorphine implant, as a six-month maintenance treatment for opioid dependence. Under the firms' licensing deal, Braeburn will pay Titan tiered royalties on net sales in the U.S. and Canada at rates ranging from the mid-teens to low-20s. Titan also is eligible for up to $165 million in milestones based on achievement of certain annual sales targets.

Tolero Pharmaceuticals Inc., of Salt Lake City, Utah, said its lead clinical candidate, alvocidib, demonstrates high synergistic activity with the B-cell lymphoma-2 (BCL-2) inhibitor, venetoclax (ABT-199) in nonclinical models of acute myeloid leukemia (AML) through a mechanism that involves targeting myeloid cell leukemia-1 (MCL-1) expression. The data were presented in a poster at the 21st European Hematology Association (EHA) Congress. Tolero initiated a randomized phase II biomarker-driven clinical trial comparing alvocidib, cytarabine, and mitoxantrone to cytarabine and mitoxantrone in patients with relapsed or refractory AML.

Valeant Canada, of Laval, Quebec, a unit of Valeant Pharmaceuticals International Inc., said it is expanding its Canadian manufacturing and export capacity with an investment of $7 million into its Steinbach, Manitoba, manufacturing plant. That follows an $8 million announcement last week for the transfer of two new technologies to Steinbach's manufacturing facility. Those investments will ensure compliance with U.S. regulatory requirements and maintain the Steinbach plant's North American manufacturing mandates.

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IN THE CLINIC

Acetylon Pharmaceuticals Inc., of Boston, said it presented data from multiple clinical trials evaluating the safety and efficacy of two selective HDAC6 inhibitors in combination with pomalidomide (Pomalyst, Celgene Corp.) and dexamethasone (Dex) for the treatment of relapsed or relapsed-and-refractory multiple myeloma (RRMM) at the European Hematology Association congress. The ACE-MM-102 phase II trial showed positive data for ricolinostat (ACY-1215) in an analysis of 67 efficacy-evaluable patients enrolled at least 6 months prior to the data cut. Overall response rate (ORR) was 46 percent, with a clinical benefit rate of 58 percent, and a disease control rate of 82 percent, nine months duration of response, and seven months progression free survival. These data compare favorably to mature historical data for the MM-002 and MM-003 trials of Pom and Dex alone. Data from a phase 1b ACE-MM-104 trial, a dose-escalation study of an alternative liquid formulation of ricolinostat in combination with Pom and Dex in patients with RRMM demonstrated daily dosing was better tolerated than twice-daily dosing.

Adamas Pharmaceuticals Inc., of Emeryville, Calif., reported positive findings from its phase II proof-of-concept study designed to evaluate ADS-5102 (amantadine HCl) extended-release capsules in individuals with multiple sclerosis (MS) who have impaired walking. Data from the study suggest that ADS-5102 is well tolerated in the MS patient population and has a significant positive impact on walking speed. The 60-patient study evaluated ADS-5102 dosed at 340 mg once daily in an MS population for four weeks. Efficacy analyses were based on a modified intent-to-treat population (n=56). A key walking assessment was the timed 25-foot walk (T25FW) test. An approximately 15 percent placebo-adjusted improvement in walking speed was seen in the T25FW ($p<0.05$). The other walking performance measures used in this trial were directionally consistent. Further analyses are under way related to fatigue, depression and cognition.

Aerpio Therapeutics Inc., of Cincinnati, announced that clinical data from the company's phase IIa study of its lead candidate, AKB-9778, for the treatment of patients with diabetic macular edema (DME) have been published in *Ophthalmology*. Data previously reported showed the combination of AKB-9778 (dosed at 15 mg BID subcutaneously) and Lucentis (ranibizumab injection dosed at 0.3 mg intravitreally) provided a clinically significant benefit in reduction of macular edema, as measured by central subfield thickness (CST), compared to Lucentis alone at month 2 ($p=0.02$) and at end of treatment at month 3 ($p=0.008$). In association with the improvement in CST, the combination therapy showed a trend toward improved visual acuity (proportion of patients achieving improvement of at least three lines in visual acuity) when compared to Lucentis alone.

Agios Pharmaceuticals Inc., of Cambridge, Mass., reported data at the European Hematology Association congress demonstrating that AG-348 achieved proof-of-concept in an ongoing phase II study (DRIVE-PK) of patients with pyruvate kinase (PK) deficiency, a rare, potentially debilitating, congenital anemia. As of a March 27 data cut-off, 18 transfusion-independent patients (13 with at least one missense mutation and five with two non-missense mutations) were treated with twice-daily dosing of AG-348 for up to six months. Treatment resulted in rapid and sustained hemoglobin increases of >1.0 g/dl in nine out of 18 patients (nine of 13 patients with at least one missense mutation), ranging from 2.3 to 4.9 g/dl with a mean maximum hemoglobin increase of 3.4 g/dl. It is estimated that approximately 80 percent of all PK deficiency patients carry at least one missense mutation. Those data support the hypothesis that AG-348 restores metabolic function and has the potential to correct the underlying defect in the red blood cells of patients with PK deficiency. AG-348 is a first-in-class, oral activator of both wild-type and mutated pyruvate kinase-R (PKR) enzymes.

Aimmune Therapeutics Inc., of Vienna, released new phase II extended maintenance therapy data from Aimmune's lead product, AR101 for peanut allergy, which showed that the safety and tolerability profile improved with continued treatment, particularly in a low-dose extended maintenance regimen. Patients on the low-dose extended maintenance regimen of 300 mg of AR101 per day experienced few adverse events, which were primarily mild, and no patients discontinued therapy. The results support the CODIT maintenance regimen in the ongoing phase III PALISADE trial of AR101, which is enrolling peanut-allergic patients 4-55 years of age.

Amgen Inc., of Thousand Oaks, Calif., said results presented at the European Hematology Association congress from a post-hoc analysis of the pivotal phase III ASPIRE study highlighted the benefit of continued treatment with Kyprolis (carfilzomib) in combination with lenalidomide and dexamethasone (KRd) in patients with relapsed multiple myeloma. Separate sub-analyses of the phase III ENDEAVOR study further confirmed efficacy and depth of response benefits of Kyprolis plus dexamethasone (Kd).

Results from the ASPIRE analysis showed that cumulative rates of complete response or better (>CR) continued to increase over time in the KRd arm, most quickly in the first 15 months of treatment. In addition, the progression-free survival hazard ratio (HR) at 18 months was 0.58 (95 percent CI: 0.46-0.72), while the overall study HR at 31 months was 0.69 (95 percent CI: 0.57-0.83), possibly related to patients in the KRd arm receiving Kyprolis for a maximum of 18 months. Six additional presented abstracts further demonstrate the benefit of Kyprolis-based regimens across a range of patient populations.

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IN THE CLINIC

Argos Therapeutics Inc., of Durham, N.C., said the independent data monitoring committee for the pivotal phase III ADAPT trial of AGS-003 for the treatment of metastatic renal cell carcinoma recommended the continuation of the trial based on results of an interim data review. That outcome triggers the second tranche of the financing under the firm's March 2016 securities purchase agreement, and Argos will sale about 5.5 million shares and warrants to purchase 4.1 million shares for proceeds of $29.8 million. The next trial review is expected to coincide with the Genitourinary Cancers Symposium in February 2017. Based on the Arcelis platform, AGS-003 is an individualized immunotherapy designed to induce an immune response targeting that patient's particular tumor antigens. Shares of Argos (NASDAQ:ARGS) fell $1.46, or 19.7 percent, to close Monday at $5.95.

Ariad Pharmaceuticals Inc., of Cambridge, Mass., reported, at the European Hematology Association congress, long-term follow-up data from its pivotal phase II PACE trial of Iclusig (ponatinib), its approved BCR-ABL inhibitor, in heavily pretreated patients with resistant or intolerant chronic myeloid leukemia (CML) or Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL). Responses have been maintained long-term in chronic phase CML (CP-CML) patients. The study shows that patients treated with Iclusig continued to demonstrate anti-leukemic activity with a median follow-up of 4 years for CP-CML. Additionally, 96 percent of CP-CML patients who underwent ponatinib dose reductions while in response maintained their responses (MCyR) at the four year point. The efficacy and safety of ponatinib in CML and Ph+ ALL patients resistant or intolerant to dasatinib or nilotinib, or with the T315I mutation, were evaluated in the PACE trial. A total of 449 patients were treated with ponatinib at a starting dose of 45 mg/day. An estimated 93 percent of patients received two or more approved tyrosine kinase inhibitors (TKIs), and 59 percent of all patients received three or more approved TKIs. Enrollment in the PACE trial was completed in October 2011.

Biospecifics Technologies Corp., of Lynbrook, N.Y., reported positive, statistically significant top-line results from a phase II trial of collagenase clostridium histolyticum (CCH) for the treatment of human lipoma. The trial met its primary endpoint of reduction in the visible surface area of the target lipomas relative to placebo, as determined by caliper, at six months post-injection ($p<0.0001$), and also met all secondary efficacy endpoints. There were no serious adverse events reported during the trial.

Bristol-Myers Squibb Co., of New York, reported results, at the European Hematology Association congress, from CheckMate -205, a phase II registrational trial evaluating Opdivo (nivolumab) in patients with classical Hodgkin lymphoma (cHL). The results, from cohort B of the trial, included patients who had relapsed or progressed after autologous hematopoietic stem cell transplantation (auto-HSCT) and post-transplantation brentuximab vedotin (n=80). The primary endpoint of objective response rate per an independent radiologic review committee was 66.3 percent (95 percent CI: 54.8-76.4). Median time to response was 2.1 months, and estimated median duration of remission was 7.8 months (95 percent CI: 6.6-NE). The majority of responses (62.3 percent) were ongoing at the time of analysis.

Catalyst Pharmaceuticals Inc., of Coral Gables, Fla., said it reached agreement with the FDA on a confirmatory phase III study protocol for Firdapse (amifampridine phosphate) for the symptomatic treatment of Lambert-Eaton myasthenic syndrome (LEMS). As part of the clinical protocol, the company expects to initiate a small, single-center study with Firdapse during the second half of 2016.

Fibrocell Science Inc., of Exton, Pa., has started recruiting adult patients for its phase I/II trial of FCX-007 for the treatment of recessive dystrophic epidermolysis bullosa (RDEB), a condition that causes skin to be very fragile and to blister easily. The primary objective of the open-label study is to evaluate the safety of FCX-007 in patients with RDEB. Additionally, the trial will evaluate type VII collagen expression and the presence of anchoring fibrils resulting from FCX-007, as well as evidence of wound healing. Six adults are expected to be treated with FCX-007 in the phase I portion of the trial and six children will treated in the phase II portion. FCX-007 is the company's first genetically-modified drug candidate developed in collaboration with Intrexon Corp. (See *BioWorld Today*, July 21, 2015.)

Galena Biopharma Inc., of San Ramon, Calif., said that five phase I trials in healthy volunteers and one phase II single arm, open label pilot study in patients with myeloproliferative neoplasms (MPN) found that GALE-401, its controlled release version of anagrelide, is well tolerated. In the phase II study, fewer moderate to severe (grade 3/4) adverse events and fewer AEs per patient (2.3 vs. 3.3) were observed with GALE-401 compared to what has been reported previously with an immediate release (IR) formulation. Additionally, for five of the 18 patients treated in the phase II study who were intolerant to anagrelide IR, GALE-401 appears to offer a longer duration on therapy compared to previous administration of anagrelide IR, Galena said. In light of the results, Galena said that a randomized trial comparing GALE-401 vs. anagrelide IR in anagrelide naive subjects, alternatively or together with a trial evaluating anagrelide IR intolerant subjects is warranted. The data were presented at the European Hematology Association Congress.

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IN THE CLINIC

Janssen-Cilag International NV, of Beerse, Belgium, a unit of Johnson & Johnson, reported that, compared to placebo, patients in the Eprex (epoetin alfa) arm of a randomized, double-blind phase III study demonstrated a statistically significantly higher erythroid response rate in the first 24 weeks of treatment, the primary endpoint of the study (31.8 percent vs. 4.4 percent, p<0.001). Also, significantly fewer patients required transfusion on epoetin alfa (24.7 percent vs. 54.1 percent). The data, along with data from three registry studies from across Europe, have been submitted to the French health authority Agence Nationale de Sécurité du Médicament et des Produits de Santé, as the reference health authority for Eprex within the mutual recognition procedure, to extend the existing marketing authorization in Europe. A decision is expected in the coming months, the company said.

Mabvax Therapeutics Holdings Inc., of San Diego, initiated a second site affiliated with the Sarah Cannon Research Institute in the phase I study of MVT-5873 (Humab-5B1) in patients with locally advanced or metastatic adenocarcinoma of the pancreas or other CA19-9 positive malignancies. The trial is evaluating the safety, tolerability and pharmacokinetics of MVT-5873 as a single agent or in combination with standard-of-care chemotherapy in patients with metastatic pancreatic cancer.

Mallinckrodt plc, of Chesterfield, U.K., said it submitted an investigational new drug application for Synacthen Depot to the FDA. A depot version of Synacthen (tetracosactide), a synthetic 23 amino acid melanocortin receptor agonist, the product is approved and marketed outside of the U.S. for certain autoimmune and inflammatory conditions. Mallinckrodt intends to pursue development in Duchenne muscular dystrophy.

Onconova Therapeutics Inc., of Newtown, Pa., said interim data from the ongoing phase II trial of oral rigosertib in combination with azacitidine in patients with first- or second-line higher-risk myelodysplastic syndromes, presented by collaborators at the Congress of the European Hematology Association in Copenhagen, Denmark, showed an overall response rate of 77 percent, or 23 of 30 patients. The company said study results are being finalized to initiate end-of-phase-II discussions with U.S. and European regulators.

Pfizer Inc., of New York, said findings from the phase III INO-VATE ALL study evaluating the safety and efficacy of inotuzumab ozogamicin compared with investigator-choice chemotherapy in 326 adult patients with relapsed or refractory CD22-positive acute lymphoblastic leukemia were published online in *The New England Journal of Medicine*. The open-label, randomized study showed that patients who received inotuzumab ozogamicin demonstrated improvement over chemotherapy on a number of measures, meeting the first primary endpoint of complete response (80.7 percent [95 percent CI, 72 percent-88 percent] vs. 29.4 percent [95 percent CI, 21 percent-39 percent], p<0.001). Inotuzumab ozogamicin also extended progression-free survival compared to chemotherapy. The second primary endpoint of overall survival favored inotuzumab ozogamicin compared to chemotherapy but did not reach the level of statistical significance for the trial. In the trial, patients treated with inotuzumab ozogamicin achieved high rates of minimal residual disease negativity and experienced a duration of response of 4.6 months (95 percent CI, 3.9-5.4; HR: 0.55; p<0.034). The most common adverse events (AEs) observed for both inotuzumab ozogamicin and chemotherapy were cytopenias, including febrile neutropenia (16 percent vs. 22 percent). Common nonhematologic treatment-emergent AEs with inotuzumab ozogamicin included nausea, headache and pyrexia while patients in the chemotherapy arm experienced nausea, pyrexia and diarrhea. Additionally, veno-occlusive liver disease occurred more frequently in patients treated with inotuzumab ozogamicin compared to chemotherapy (11 percent vs. 1 percent).

Seattle Genetics Inc., of Bothell, Wash., highlighted data at the 21st Congress of the European Hematology Association evaluating vadastuximab talirine (SGN-CD33A; 33A) in combination with hypomethylating agents (HMAs; azacitidine, decitabine) in frontline patients with acute myeloid leukemia (AML) who had declined intensive therapy. 33A is an investigational antibody-drug conjugate targeted to CD33 using Seattle Genetics' newest technology, comprising an engineered cysteine antibody (EC-MAb) stably linked to a highly potent DNA binding agent called a pyrrolobenzodiazepine (PBD) dimer. Based on data from the ongoing phase I clinical trial, a phase III trial, called CASCADE, was recently initiated evaluating 33A in combination with HMAs in previously untreated AML patients not candidates for intensive induction chemotherapy. The current data suggest that the addition of 33A improves the rates of response and durable remissions in comparison to that seen historically from using the current standard of care alone.

Spark Therapeutics Inc., of Philadelphia, released updated results of the first cohort from the ongoing phase I/II trial of SPK-9001, the lead investigational candidate in its SPK-FIX program, which is being studied for the treatment of hemophilia B. Data show that the low dose cohort of four subjects enrolled in the study experienced consistent and sustained factor IX activity levels following a single administration of SPK-9001 at the initial dose level (5 x 1011 vg/kg) studied in the trial.

Sunesis Pharmaceuticals Inc., of South San Francisco, presented updated results from an ongoing phase Ib/II University of Texas MD Anderson Cancer Center-sponsored trial of vosaroxin in combination with decitabine in older patients with previously untreated acute myeloid leukemia and high-risk myelodysplastic syndrome. The results were presented at the 21st Congress of the European Hematology Association. At the optimized induction dose of 70 mg/m2 of vosaroxin, the combination of vosaroxin and decitabine demonstrates a CR/CRp/CRi rate of 76 percent and a median overall survival of 16.1 months. The response rate and survival are significantly better than seen with single-agent decitabine among similar patients.

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IN THE CLINIC

Symbio Pharmaceuticals Ltd., of Tokyo, initiated the phase III trial of SyB P-1501 in Japan. Symbio inked an exclusive agreement with **The Medicines Co.**, of Parsippany, N.J., for development and commercialization rights in Japan for patient-controlled short-term management of acute postoperative pain during hospitalization. The product was approved in the indication last year by the FDA and EMA. (See *BioWorld Today*, May 4, 2015.)

Symic Biomedical Inc., of San Francisco, reported treatment of the first patient in the MODIFY-OA Clinical Trial (Study to Measure the Safety and Efficacy Outcome after Intra-articular Delivery of SB-061 vs. Control in Symptomatic Osteoarthritis Patients) investigating SB-061, a treatment specifically developed for acute management of osteoarthritis (OA) pain. The 12-week, multicenter, double-blinded trial will randomize approximately 90 patients with mild to moderate OA of the knee.

True North Therapeutics Inc., of South San Francisco, reported new clinical data for its lead product candidate, TNT009, which showed encouraging initial results for the first Cold Agglutinin Disease (CAD) patients dosed in the ongoing phase Ib study. These interim data demonstrated a concordant improvement of blood parameters with rapid onset of action in patients with CAD, a form of hemolytic anemia in which autoantibodies target and destroy red blood cells. TNT009 is a first-in-class monoclonal antibody that selectively inhibits the Classical Complement pathway by targeting C1s, a serine protease within the C1-complex in the Complement pathway of the immune system.

Tyme Technologies Inc., of New York, has begun recruiting for a phase Ib/II trial, using its compound, SM-88, to treat prostate cancer. Unlike traditional chemotherapy, SM-88 is designed to target only active cancer cells. The trial is designed to confirm SM-88's earlier reported activity in reducing the Prostate-Specific Antigen without causing the castration-like effects often experienced with the current standard of care.

Uniqure N.V., of Amsterdam, the Netherlands, said additional data from its phase I/II trial of AMT-060 in hemophilia B patients were presented at the 21st Congress of the European Hematology Association. Five patients who received a single administration of the gene therapy, AMT-060, at the initial low dose of 5x1012 gc/kg saw improvements in their disease phenotype and achieved sustained increases in FIX activity, with a median of 5.4 percent (expressed as percent of normal) at six months post treatment. After treatment with AMT-060, total usage of Factor IX concentrate declined substantially, with four patients remaining free of any prophylactic infusions through the April 26, 2016 cut-off date.

Ziarco Pharma Ltd., of Discovery Park, Sandwich, U.K., reported positive, full results from its first phase IIa proof-of-concept study with ZPL-389 in adults. The study demonstrated evidence of efficacy and safety of ZPL-389, a once daily oral histamine H4 receptor antagonist for the treatment of moderate to severe atopic dermatitis, a chronic skin disease with no safe, effective, and well tolerated oral treatments available. In the European multi-country study, 98 subjects with moderate to severe atopic dermatitis (the most common form of eczema) were randomized 2:1 to receive orally either 30 mg ZPL-389 or placebo once daily for eight weeks, respectively. At week eight, ZPL-389 reduced EASI (Eczema Area and Severity Index) by 50 percent (placebo: 27 percent, (p=0.01)). In addition, there was also a statistically significant improvement on SCORAD (SCORing Atopic Dermatitis), with ZPL-389 reducing SCORAD by 43 percent compared to 26 percent for placebo (p=0.004).

FINANCINGS

Antibe Therapeutics Inc., of Toronto, said it closed the first tranche of a non-brokered private placement of units, raising gross proceeds of C$968,500 (US$754,325). Net proceeds will be used for product development and for general corporate purposes.

Celsion Corp., of Lawrenceville, N.J., entered a definitive agreement with a single health care dedicated institutional investor to purchase an aggregate of approximately $6 million of shares of common stock, or pre-funded warrants in lieu thereof, in a registered direct offering. The company agreed to sell an aggregate of approximately 4.4 million shares of common stock, or pre-funded warrants in lieu thereof, at a price of $1.36 per common share or warrant share, respectively, in the registered direct offering. The closing of this offering is expected to take place on or about June 16, subject to the satisfaction of customary closing conditions. H.C. Wainwright & Co. is acting as exclusive placement agent in connection with this offering. The estimated net proceeds to the company from the sale of the shares of common stock or pre-funded warrants in the registered direct offering are expected to be approximately $5.5 million. Celsion said it intends to use the net proceeds for general corporate purposes.

Palo Alto, Calif.-based Vivo Capital closed a new health care venture capital focused fund, the Vivo Panda Fund, at more than $100 million. Vivo plans to invest the capital primarily in innovative early stage health care companies across the industry spectrum, including pharmaceuticals, biotechnology, medical devices and diagnostics.

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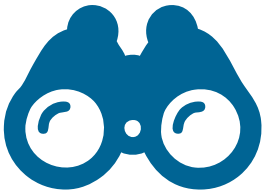

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