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DEAL COULD TOTAL $600M

Pfizer makes $87.5M wager on AM-Pharma's phase II AKI drug

By Nuala Moran, Staff Writer

LONDON – Pending positive results from an ongoing phase II trial of its human recombinant alkaline phosphatase in acute kidney injury (AKI), AM-Pharma NV is to be acquired by Pfizer Inc. for $600 million.

The phase II began in January and is under way in 10 countries, with results expected next year. For now, Pfizer is making a down payment of $87.5 million in return for a minority equity stake and an exclusive option to buy the rest of AM-Pharma.

"I'm very pleased with the agreement," said Erik van den Berg, CEO of AM-Pharma.

See AM-Pharma, page 3

MANO A MANO FROM MILANO

Formula One: CAR-CIK to make queasy riders of others in T-cell race?

By Randy Osborne, Staff Writer

CEO Maurits Geerlings told *BioWorld Today* that Formula Pharmaceuticals Inc. may have found a way around the drawbacks of chimeric antigen receptor (CAR) methods that deploy autologous T cells, thanks to the worldwide exclusive license the firm has gained to

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CHINA

COSTS UNLIKELY TO SKYROCKET?

NDRC: Reforms aimed at removing price caps, boosting local access

By Cornelia Zou, Staff Writer

HONG KONG – In a move that could lead to more and easier access to better medicines at the local level, China plans to eliminate fixed prices for drugs next

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THE BIOWORLD BIOME

HAPPY HOUR

Binge drinking tied to G protein channel subunit

By Anette Breindl, Senior Science Editor

In animal studies, researchers have tied levels of the G protein-coupled channel subunit, GIRK3, in a midbrain area known as the ventral tegmental area (VTA), to the propensity to binge drink.

See Drinking, page 6

IN THE CLINIC

Curemark closes in on gut mechanism in autism with second phase III

By Marie Powers, News Editor

Privately held Curemark LLC launched an additional phase III trial of its chymotrypsin modulator, CM-AT, that will enroll a broad population of children with autism, ages 3 to 8, after a previous phase III of the compound met the endpoints in the same age group of children with autism who had low levels of chymotrypsin, a digestive enzyme. The randomized, double-blind, placebo-controlled study is expected to enroll approximately 300 children with autism, compared with 182 children with autism and low levels of chymotrypsin enrolled in the previous study, to help determine whether CM-AT could potentially benefit a broader population of children with the disorder by targeting the gut.

Patients will be randomized to a single unit dose powder of CM-AT three times

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IN THIS ISSUE

DEALS AND M&A

Ligand broadens royalty rights portfolio after beating Q1 views

By Michael Fitzhugh, Staff Writer

With rising royalty revenue boosting its first quarter earnings, Ligand Pharmaceuticals Inc. added rights to potential future milestone and royalty payments on 15 biologic development

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FINANCINGS

Precision Biosciences Inc., of Research Triangle Park, N.C., closed a $25.6 million series A financing led by Venbio. Fidelity Biosciences, Amgen Ventures, Baxter Ventures, Osage University Partners, the Longevity Fund and unnamed investors also participated in the oversubscribed financing. The company is using its genome-editing technology to enable the production of specific nucleases that can insert, remove and modify DNA in complex genomes. It said the new funding would help it develop its genome-editing platform and accelerate the development of its genome-edited product pipeline.

OTHER NEWS TO NOTE

Audentes Therapeutics Inc., reported that ongoing preclinical studies of AT001 (AAV-MTM1), its experimental treatment for X-linked myotubular myopathy (XLMTM) expanded and confirmed earlier observations, which demonstrated that treatment with a single dose of an adeno-associated virus (AAV) carrying the gene deficient in XLMTM resulted in an increase in muscle strength, improved respiratory function and prolonged survival. It also said the data are the first demonstration of persistent disease correction in a large animal model of a neuromuscular disease through the delivery of a single, intravenous administration of AAV.

Biontech AG, of Mainz, Germany, and **Eli Lilly and Co.**, of Indianapolis, said they entered a research collaboration to discover cancer immunotherapies, aiming to identify and validate tumor targets and their corresponding T-cell receptors (TCRs) in one or more types of cancers. Under the terms, Biontech will get a $30 million signing fee. For each potential medicine, Biontech could receive more than $300 million in development, regulatory and commercial milestones. If successfully commercialized, Biontech would also be eligible for tiered royalty payments up to double digits. In addition, subject to the terms of the agreement, Lilly will make a $30 million equity investment in Biontech's subsidiary, Cell & Gene Therapies GmbH, which specializes in the research and development of TCR and chimeric antigen receptor immunotherapeutics.

Blueprint Medicines Inc., of Cambridge, Mass., said the *Journal of Clinical Investigation* published an overview of the company's kinase drug discovery and development strategy. The article described how the abnormal activation of kinases drives many hallmarks of tumor biology.

Cidara Therapeutics Inc., of San Digeo, said the FDA has designated the company's lead antifungal candidate, CD101 IV, as a qualified infectious disease product with fast track status. Both designations are for the use of CD101 IV in the treatment of candidemia and invasive candidiasis. Cidara plans to file an investigational new drug application and initiate a phase I trial of the drug in the second half of 2015. (See *BioWorld Today*, March 17, 2015.)

Endo International plc, of Dublin, said it will spend about $130 million to buy a broad portfolio of branded and generic injectable and established products focused on pain, anti-infectives, cardiovascular and other specialty therapeutics areas from a subsidiary of Aspen Holdings Inc. The deal adds a product portfolio that generated about $28 million of revenue during the fiscal year ended June 30, 2014, as well as a sizable pipeline of products in various phases of development that are expected to launch over the next several years, Endo said.

STOCK MOVERS 5/11/2015

Company	Stock in $	Change in %
Nasdaq Biotechnology	+$2.14	+0.06%
Keryx Biopharmaceuticals	+$1.38	+14.81%
La Jolla Pharmaceuticals	+$1.97	+11.95%
Plasmatech Biopharma	+$2.46	+33.51%
Radius Health Inc.	+$3.49	+9.19%

Biotechs showing significant stock changes Monday

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AM-Pharma

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"Pfizer is becoming a minority shareholder and has the option to buy the remainder of the shares, based on the phase II. All trial sites are up and running, so Pfizer gets to decide in the later part of 2016," he told *BioWorld Today*.

While the deal is specifically tied to the outcome of the current phase II in AKI caused by sepsis, Pfizer will get rights to recombinant alkaline phosphatase in other indications, which include ulcerative colitis and the ultra-rare disease hypophosphatasia.

Beyond the $87.5 million up-front payment, the balance of $512.5 million will be staged across the exercise of the option and subsequent milestones. The product must get to market for Bunnik, the Netherlands-based AM-Pharma to get the full $600 million.

The deal is just reward for shareholders in privately held AM-Pharma, who in September 2011 made a show of faith by investing $40 million to fund development of a human recombinant form of alkaline phosphatase. That followed a decision to halt phase II development of a bovine version of the enzyme. (See *BioWorld Today*, Sept. 14, 2011.)

The round was led by Ysios Capital Partners and Kurma Life Science Partners, with backing from the corporate venture arms of Shire plc and Abbvie Inc. along with BB Biotech Ventures, Idinvest Partners, Forbion Capital Partners and Inventages Venture Capital.

At that point, AM-Pharma had amassed a body of positive phase II data in ulcerative colitis and AKI, where the bovine version improved renal function, reduced the length of stay in intensive care and was safe and well tolerated.

It was to take AM-Pharma two years to develop the recombinant product and get back into phase I safety studies, and a further year to restart patient trials. The pause provided the opportunity for the company to increase understanding of the mechanism of action of the enzyme, which is found in the epithelial cells of the gastrointestinal tract, the kidney, liver and lungs.

In the treatment of AKI, alkaline phosphatase acts by dephosphorylating pro-inflammatory substances, including lipopolysaccharides and extracellular adenosine triphosphate (ATP) that are released as a result of gram-negative sepsis or tissue necrosis. In addition, the adenosine that results from dephosphorylation of ATP has an anti-inflammatory effect.

AM-Pharma also demonstrated that the recombinant product, which is based on two isoforms of human alkaline phosphatase, has improved physical characteristics, with a much longer half-life than the bovine counterpart.

The company decided to focus on development of alkaline phosphatase in AKI because of the high level of unmet medical need, with hospital-acquired AKI affecting roughly 2 million patients per annum in the U.S., Japan and Europe. There are 700,000 deaths as a result.

In the U.S., $10 billion per year is spent on managing the condition. With no approved drugs the only treatment is dialysis and best supportive care. AM-Pharma estimated that scenario translates into potential annual sales of $2 billion for a drug labeled for AKI.

PREPARING FOR PHASE III

While other companies have drugs in phase II development for preventing AKI, AM-Pharma said it has the only product that aims to treat the problem once it occurs.

Given that, there were no existing regulatory guidelines and AM-Pharma has had to negotiate with the FDA and the EMA. "We tailored the phase II design to the needs of both regulators, but they were in fact remarkably aligned," van den Berg said.

The primary endpoint in phase II is creatinine clearance as a direct marker of kidney function. Secondary endpoints include improvements in kidney capacity, reduction in hospital days and the level of requirement for dialysis.

"We will, in addition, evaluate progression to chronic kidney disease over a long period of time," said van den Berg. While it awaits the phase II results and the possible triggering of the option, AM-Pharma will continue to operate as a standalone independent company. "We will progress as planned. We can't predict [the outcome], though Pfizer has done extensive due diligence and clearly has a lot of confidence," he noted.

Progressing as planned includes preparing the ground for phase III, which AM-Pharma will do in discussion with Pfizer. "If successful in phase II, this means we can be faster to market, which will benefit patients, shareholders and [Pfizer]," said van den Berg.

Mikael Dolsten, president of worldwide R&D at Pfizer, said the clinical data demonstrate the potential to treat AKI caused by sepsis. "We aim to accelerate the development of recombinant alkaline phosphatase into a potential first-in-class treatment," he said. //

OTHER NEWS TO NOTE

Glaxosmithkline plc, of London, and the University of North Carolina at Chapel Hill, created the HIV Cure center and a jointly owned new company that will focus on discovering a cure for HIV/AIDS. That public-private partnership is designed to redefine the traditional way of conducting research and create a new model to seek the breakthroughs needed to tackle a challenging global health issue, they said, and the center will be located on the university's campus.

Hemispherx Biopharma Inc., of Philadelphia, said the EMA issued a positive opinion on its application to the Committee on Medical Products to secure orphan status for the development of double-stranded RNA therapy Ampligen (rintatolimod) for the treatment of Ebola. The company submitted in vitro and in vivo data on the drug's efficacy, and clinical safety information was included in the application. (See *BioWorld Today*, Feb. 3, 2015.)

Formula

Continued from page 1

an allogeneic, nonviral CAR platform that leverages instead cytokine-induced killer (CIK) cells as immune effectors.

"This is a mixed cell population, whereby 95 percent of the cells carry the CD3-positive phenotype, which makes them T cells," Geerlings said. "But a large portion of these cells also carry the CD56-positive phenotype, which gives them natural killer [NK] cell-like features

Developed over the past seven years at the Research Center Fondazione M. Tettamanti, a University of Milano-Bicocca affiliate in Italy, the technology comes aboard as Formula completes a private investment of an undisclosed amount.

The Berwyn, Pa.-based company said it believes its platform could improve over CAR approaches using autologous T cells, with safety and efficacy advantages, since it doesn't require apheresis, and can be prepared with small amounts of peripheral blood samples. Nonviral transfection, through a method that the company also has not disclosed, could make scale-up manufacturing more practical and cost-effective as compared to viral transfection methods, too.

Formula's approach is "not proven in the context of CAR in patients," but the idea is "established preclinically and we are now working on the GMP manufacturing side," Geerlings said. "It's hypothesis driven, but with some clinical experience nonetheless with unmodified CIK cells that have been extensively used in something like 45 trials. Some of these trials used allogeneic CIK; most used autologous."

Geerlings noted that in "CAR data that have reported with the CD19 target, there has been for a reasonably sizeable amount of patients, relapse reported as early as six months. Then you look at the limitations of T cells that are major histocompatibility complex restricted. Beyond the mechanism through CAR, these T cells don't have a way of recognizing the tumor as a foreign body, hence they don't have a triggering mechanism. In that context, you would want to have an antitumor response that is independent of CAR and supplementary to CAR, meaning a broader antitumor response mechanism than what T cells can provide through CAR."

Allogeneic T-cell-induced graft-vs.-host disease (GVHD) is a big problem in CAR immunotherapy. For many patients, autologous blood used in existing experimental therapies could lead to suboptimal CAR outcomes because of previous chemotherapy, bone-marrow transplantation or co-morbidities. "We look at the cells from another perspective," Geerlings said. "If you want to work with allogeneic-sourced cells, T cells have always been a burden," and using the CIK methodology, GVHD could show a "significantly reduced incidence and risk compared to T cells." The CIK weaponry devised by Formula represents "a special mix, because it's not something you would naturally see in the human body," he added.

The GMP manufacturing activities under way for Formula's lead CAR CIK immunotherapy program are expected to lead to the first clinical trials next year. Formula plans to develop proprietary and licensed targets in hematologic oncology and solid tumor indications on its own and in partnership with others.

"Various groups have proposed NK cells as an alternative to CAR," Geerlings said. "The limitation of true NK cells is that they are short-lived. They do not have the kind of persistence that you would need to see in order to provide a durable antitumor response in patients." CIK technology, by contrast, may offer "a broader immune response than T cells can provide, hence the potential to eliminate the minimal residual disease that is left over in those patients who, through CAR alone, would not be fully rendered into molecular remission."

DOSING GUARANTEE?

In the allogeneic NK space, the main non-academic player is Cardiff-by-the-Sea, Calif.-based Conkwest Inc., which late last year garnered $50 million in class A stock sale money, including $48 million from Nantworks Inc. founder and well-known biotech entrepreneur Patrick Soon-Shiong plus $2 million from Sorrento Therapeutics Inc., of San Diego. The firm had been privately financed the previous April, and had deliberately stayed under the rader until the organization could be further built out. (See *BioWorld Today*, Dec. 26, 2014.)

Conkwest aims to integrate its NK bid with fully human antibody libraries from Sorrento, and take advantage of Culver City, Calif.-based Nantworks' Nantomics proteomics platform, as well as a cell production method and technology that allows for gene transfer without the need for lentivirus insertion. Neukoplast, a line of NK cells also known as NK-92, has reached the phase II stage.

"We have not even spoken about all the other subtypes of phenotypes that apply to the differentiation between T cells used for CAR T purposes and the kind of T cells that we have now in a mixture," Geerlings said. "Our process, the protocol by which we create CIK cell population, polarizes the cells in a different direction than the peripheral blood mononuclear cells [PBMC] that are stimulated with other cytokines" in CAR T efforts. Thus, Formula "starts with the same PBMC source," but ends up with a different outcome, he said.

"This is applicable as broadly as CAR T would be," Geerlings said. "We have already ongoing discussions with prospective collaborators for some tumor targets." He reiterated a special potential benefit for patients "at the level of the prescriber, the physician, who has a choice to use either autologous CAR T, or an allogeneic source. The problem is that a sizeable percentage of patients that could quality for CAR T simply cannot generate a sufficient starting dose with their own blood. The PBMCs have been compromised."

It's a problem that "in theory, we hope to overcome," Geerlings said. "When we work with healthy donor material, we can provide sufficient and healthy enough PBMCs. That could open the market, if you will, the access to care for those patients

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NDRC

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month. And, despite public concerns, the regulator said drug prices will not shoot up even after price caps are taken away.

The National Development and Reform Commission (NDRC) recently released a public notice saying the government would no longer set the highest out-of-factory prices and retail prices for most drugs in the country.

"It sounds like an interesting measure that could really help local access and encourage developers to launch better medicines," said Steven Bradshaw, European director of consulting firm Market Access Solutions. "The initial impact is going to be difficult to ascertain, as around 75 percent of drugs in China are sold through the hospitals rather than retail, and so local tendering helps to control local prices."

The planned price reform will see the government loosen its grip on all drugs except for narcotics and psychotropic substances. Health insurance departments will map out payment standards, including processes, reference and methods for drugs that are covered by national health care insurance schemes.

Patented drugs or drugs manufactured under exclusive arrangements will be priced through transparent negotiations.

Prices for blood products not covered by insurance along with nationally purchased preventive products, free antiviral therapies for HIV/AIDS and birth control drugs will be decided through bidding or negotiation. Owners will price other products based on the manufacturing and operational costs and market demand.

"The government's price ceiling is no longer adaptable to the current situation because first, it doesn't reflect and guide the market supply and demand in time; second, it overlaps with the centralized tender purchasing system; third, it has smaller and smaller influence on the drugs' actual transaction prices," said the NDRC in a statement following the official announcement. "It is inevitable and at the right timing to eliminate the retail price ceiling of drugs and reform the pricing system."

The commission stressed that eliminating the price ceiling does not mean that the government will no longer manage drug prices. Rather, it represents a shift in the way it does it.

Borrowing a page from other countries with mature pricing and health care systems, China decided to move away from its traditional approach to price controls, which it said is representative of more immature health care systems or of countries without universal coverage. A better approach, said the commission, is to strengthen the supervision of health care, purchases and price behavior.

The NDRC also said that restrictions built into the bidding system would prevent drug prices from climbing rapidly.

"But we don't rule out the possibility of price rises of some of the drugs caused by costs and market supply and demand," said the NDRC.

China's move could have influence beyond its shores, particularly in countries that use China as a reference for their own drug prices.

"Australia and Philippines reference China, so there may be some repercussions on a global pricing level, but until we have a test case it is difficult to predict whether the ripple effect will be positive or stormy," said Bradshaw.

The system also could help eliminate, or at least tackle, a longstanding lack of transparency at multiple levels of the drug marketing process that is troublesome for multinational pharmaceutical companies trying to tap into Asian markets. Many governments have introduced measures to slow down the growth of spending on drugs as well as price volume agreements linked to new therapies. A case in point is South Korea's Health Technology Assessment.

And issues remain, not the least of which is the reality that manufacturing costs are going up and they would necessarily translate into higher drug prices. Companies need to mark up prices to cover shipping and distribution costs as well as work with local partners. In China's case, the money paid to distributors and hospitals is the reason some drugs are sold at such high prices.

"Also, the profit margin between national prices and locally negotiated discounts means that there isn't necessarily an incentive locally to push prices down," said Bradshaw.

Sometimes biopharmaceutical therapies fall under the radar of payers given the small number of patients involved, he added.

"There are incentives to develop and launch therapies for rare and orphan diseases in some markets, especially those conditions with high unmet need," said Bradshaw. "However, despite this, advanced biologics are often not reimbursed in markets such as China and adoption rates are very low." //

OTHER NEWS TO NOTE

Imago Pharmaceuticals Inc., a Bay Area biotech, said the Michael J. Fox Foundation for Parkinson's Research acquired a library of research tools from the company around the parkin protein. Those tools, which include cell lines, plasmids and compounds, are aimed at accelerating biological study and drug development against that disease-modification target. Imago purchased those tools as part of a 2014 deal with Dublin-based **Perrigo Co. plc**. They originated at now-defunct biotech Elan Pharmaceuticals plc.

APPOINTMENTS AND ADVANCEMENTS

Biodelivery Sciences International Inc., of Raleigh, N.C., appointed Sarah DeRossett vice president of clinical research and medical affairs.

Celsion Corp., of Lawrenceville, N.J., appointed Harriet Shelare director, communications.

Txcell SA, of Valbonne, France, named Stéphane Boissel CEO and Miguel Forte chief operating officer.

Drinking

Continued from page 1

The results showed, senior author Candice Contet of the Scripps Research Institute told *BioWorld Today*, that "the more GIRK3 you have in the VTA, the less you drink."

Contet and her colleagues published that conclusion, and the data supporting it, in the May 11, 2015, online issue of the *Proceedings of the National Academy of Sciences*.

As far as the work's practical applications go, Contet summarized the simplest possible conclusion about how to harness the results to treat or prevent binge drinking as "let's activate the GIRK3-containing channels."

But, she added, "that being said, it's really not that simple."

Separate experiments have suggested that total currents through GIRK channels are not much affected by the subunit composition, and that the subunits may influence each other's processing and trafficking within cells, so that changes in GIRK3 levels have ripple effects on the overall number and type of GIRK channels that are not necessarily straightforward.

"There's definitely a lot more work to be done," she concluded, "before we can define a strategy."

GIRK is a G protein-coupled channel that is expressed in the brain (though not exclusively so), where its activation inhibits neurons from firing. In the case of GIRK, in cell culture, alcohol can directly open the channels without the need for a G protein-coupled receptor, which is what normally would open the GIRK channel.

Contet and her team wanted to see whether alcohol would have an effect beyond the cell culture, in living animals.

In their studies, the researchers focused on GIRK3 subunits for a combination of reasons.

They are expressed in the brain, and while GIRK2 knockouts show a number of behavioral symptoms, animals lacking specifically the GIRK3 subunit have fewer behavioral changes.

"Their baseline behavior is very normal," Contet said.

However, a few clues suggest GIRK3 may play a role in the response to drugs. For one thing, GIRK3 knockouts will not self-administer cocaine. They also respond somewhat differently to alcohol withdrawal.

Many aspects of their reaction to alcohol were unchanged, including how it was metabolized and what it took for the animals to become intoxicated.

Nor did the knockouts drink more than other mice if alcohol was always available to them – a situation in which animals will sip at alcohol, but very rarely drink enough to become intoxicated.

However, GIRK3 knockouts would drink much more than normal mice if alcohol was only available for two hours at a specific time of day that is a mouse's equivalent of happy hour: a time when they will tend to drink if alcohol is available.

Under those experimental circumstances, the knockouts would binge drink – that is, drink until they were intoxicated.

Contet and her team next wanted to test which particular brain area might be responsible for the knockout's binge drinking propensity. They focused their attention on the ventral tegmental area, a midbrain area that projects to the prefrontal cortex and nucleus accumbens via a dopamine projection.

Previous studies have linked the VTA to reward processing, albeit in a complex way. Contet said that technically speaking, it is responsible for the link between cues that predict rewards, not for the feeling of the rewards itself.

Contet and her team used a virus to restore GIRK3 in the VTA of their knockouts. In a separate set of experiments, they used the same virus to give mice that had natural GIRK3 expression an extra dose of the subunit, leading to high levels of GIRK3-containing channels in their VTA.

The results showed that more GIRK3 in the VTA was tied to less drinking. Restoring GIRK3 in the knockouts reversed their propensity to binge drink, and animals overexpressing GIRK3 drank still less.

The team next wanted to see whether GIRK3 drove animals to drink because it made the VTA more active, or less so.

In principle, Contet explained, either would be possible. A lack of GIRK3 could make the reward pathway function better, so that "whenever [the GIRK3 knockouts] drink, it feels really good."

On the other hand, if the pathway did not work as well in the knockouts, they might drink more to compensate.

In experiments using brain slices, the team found that not only did the VTA pathway fire less in response to alcohol in the knockout mice – it did not fire at all, "which was really surprising to us."

Even with amounts of alcohol that could only be reached in an animal if that animal were drinking enough to die of alcohol poisoning, the slices remained unresponsive.

The team confirmed their findings in vivo by looking at the other end of the pathway, measuring the dopamine levels in the prefrontal cortex after administration of alcohol directly into the VTA.

In those experiments, alcohol led to rises in dopamine level in normal mice but not in the knockouts, confirming the finding that "ethanol was not doing anything to the VTA neurons."

Of course, if alcohol cannot engage the VTA pathway, one prediction might be the opposite of what the team observed – namely, that such mice would have no reason to drink at all, since it does not make them feel good.

Contet said that paradox is resolved because the VTA is not the only reward pathway in the brain.

"What that tells us is that there are other pathways," she said, and that "these mice probably drink more to engage those alternative circuits."

The difference between the overall reward circuitry for alcohol and other drugs may also reconcile the increase in binge drinking Contet and her team observed with the previous findings that GIRK3 knockouts will not self-administer cocaine. //

Curemark

Continued from page 1

daily for 90 days or placebo on the same dosing schedule, according to Cortellis Clinical Trials Intelligence (CTI). The primary endpoint is efficacy compared to placebo based on changes in the aberrant behavior checklist subscale for irritability/agitation, or ABC-I, between baseline and week 12. Secondary endpoints include measurements of changes in the aberrant behavior checklist subscale for lethargy/social withdrawal, or ABC-L, between baseline and week 12.

The phase III, which will be conducted at 20 U.S. centers, is expected to report data in the second half of 2016, according to Cortellis CTI.

Rye, N.Y.-based Curemark submitted its rolling new drug application (NDA) for CM-AT in 2013 under the FDA's fast track designation.

The company has not disclosed the active ingredient in CM-AT except to describe the compound as an enzyme replacement therapy targeting protein digestion that has been in use for four decades. Cortellis CTI describes CM-AT as a pancreatic enzyme concentrate. Based on the compound's safety record, the company was not required to do toxicology studies, so all three trials of CM-AT were designed primarily as efficacy studies in children with autism.

Certain patients enrolled in the previous phase III study, completed in December 2011, were offered enrollment into an open-label extension study of CM-AT that is fully enrolled and expected to be completed this year, according to Cortellis CTI.

A spokesman for the company said Joan Fallon, Curemark's founder and CEO, and other members of the management team were not available for additional comment on the new trial or the company's regulatory strategy.

Fallon, a former biology professor at Yeshiva University and private practice clinician specializing in pediatric development, formed Curemark a decade ago with support from angel investors and a dip into her own retirement savings. The company completed a $6.5 million series A round in 2009 that was filled by high net worth individuals. (See *BioWorld Today*, Oct. 16, 2009.)

In October 2013, the company closed an $18.5 million equity financing led by an undisclosed European institutional investor. All told, Curemark has raised more than $50 million, mostly from individuals, eschewing venture capital, Fallon said during an independent TED event last year. (See *BioWorld Insight*, Nov. 18, 2013.)

Along the way, the company collected dozens of patents on its enzyme delivery system, according to Fallon, covering CM-AT as well as discovery-stage assets CM-4612, a small-molecule psychomodulator, and CM-182, a small-molecule antipsychotic, which target attention deficit hyperactivity disorder and schizophrenia, respectively. The company also has discovery-stage programs in Parkinson's disease and addiction.

'WE'RE REALLY NEW AT LOOKING AT AUTISM IN THIS WAY'

Curemark's drug delivery technology involves the application of a lipid coating that behaves as a solid, even at body temperature, enabling the drug formulation to be released for maximum action at the site where proteins are most actively digested in the body. The technology also masks any taste and is produced in a size-controlled fashion so that the texture in the mouth is smooth and unnoticeable – features that Curemark maintains are important for physiological effectiveness as well as patient compliance and safety.

The company's platform technology is focused on the role of exocrine pancreatic deficiencies, or dysfunctions in the way the body digests food, including defects in the secretion of the proteases trypsin, chymotrypsin and elastase, which help the body obtain essential amino acids from food. Amino acids are needed to build new proteins – including neuroreceptors – that turn genes on and off and regulate important metabolic functions. Curemark's thesis is that enzyme deficiencies play a role in the pathology of neurological disease.

In advancing CM-AT, "we disrupted a medical paradigm, where digestion is digestion and brain function is brain function and never the twain shall meet, even when the byproduct of protein digestion is the very building block of amino acids – of neurotransmitters like serotonin and dopamine, all of which have major, major actions in the brain," Fallon said during last year's TED talk.

In 2013, *Science* proclaimed microbiome research a scientific breakthrough of the year, citing as one such advance the expanded understanding of how physiology is influenced by microbes in the gut. For example, a 2013 paper published in *Cell* showed that, in a mouse model of autism spectrum disorders (ASD), treating dysbiosis by oral administration of probiotics improved behavioral symptoms. (See *BioWorld Today*, Dec. 30, 2013.)

Drug development certainly needed a new approach in autism after a litany of failures. In recent years, Neuropharm Group plc, of London, Repligen Corp., of Waltham, Mass., and Seaside Therapeutics Inc., of Cambridge, Mass., halted programs or were shuttered after failures in phase II or III studies. (See *BioWorld Today*, May 29, 2009, March 8, 2011, and Sept. 21, 2012.)

Coronado Biosciences Inc., of Burlington, Mass., made another run at using its Trichuris suis ova (TSO, or pig whipworm eggs), dubbed CNDO-201, to treat children with ASD after the therapy missed the primary endpoint in a phase II study in Crohn's disease. But late last year, Coronado began shifting into cancer therapeutics through the formation of multiple subsidiaries, completing that transformation last month by rebranding itself as Fortress Biotech Inc. The TSO program and autism indication are gone. (See *BioWorld Today*, Oct. 15, 2013, and Dec. 16, 2013.)

Nearly 150 trials of drugs targeting the treatment of autism are under way, according to Cortellis CTI, though all but a dozen

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Ligand

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programs from its existing partner, Selexis SA, for $4 million in cash.

The programs, spanning preclinical through phase III, include a mix of novel biologics and biosimilars, the company said. Though it didn't identify the assets included in the deal, the majority are early stage and all are fully funded by a development partner. the company said.

"This is an efficient transaction that bolts on potentially lucrative economic rights to numerous new programs and follows the positive developments and successes we have realized with our first transaction with Selexis," said John Higgins, Ligand's CEO. With the addition of the new assests, Ligand's portfolio now exceeds 120 fully funded assets, with obligations from more than 70 partners, he said.

The deal builds on an April 2013 agreement, in which Ligand paid Geneva-based Selexis $4.6 million for a portfolio of future milestone and royalty payment rights on a separate set of more than 15 Selexis commercial license agreement programs. Ligand paid Selexis $3.6 million upon closing and an additional $1 million in April 2014. As in that deal, royalty rates in the new agreement are in the low single-digit range, the company said.

Since Ligand struck its first deal with Selexis, portfolio programs included in it have advanced enough to yield milestone payments of nearly 10 percent of the acquisition price, or about $460,000. That deal, the first to take Ligand into the protein-based therapeutics space, has worked well for the company, Nishan de Silva, Ligand's vice president of finance and strategy and its chief financial officer, told *BioWorld Today*.

Prior to the first agreement with Selexis, Ligand didn't have any partnerships around large molecules. "With this second deal, we're building on that," said de Silva.

On Monday, Ligand reported that its total first quarter royalty revenue accounted for $10.3 million of its $14.6 million first quarter revenue, an increase of 31 percent compared with the first quarter of 2014. The increase was largely reflective of higher Promacta (eltrombopag) royalties, which have risen since ownership of that drug was transferred from Glaxosmithkline plc to Novartis AG last year, and higher royalties from Kyprolis (carfilzomib, Amgen Inc.). (See *BioWorld Today*, April 23, 2014.)

The company reported GAAP earning per share of 4 cents in the first quarter. Adjusted earnings per share from continuing operations were 33 cents vs. the average estimate of 27 cents per share, according to Thomson Reuters I/B/E/S.

The company ended the quarter with $191.7 million in cash.

Ligand expects second quarter adjusted earnings per share to rise to between 37 cents and 40 cents on revenue of $17 million to $17.5 million. Analysts are less optimistic, expecting earnings of 35 cents per share on revenue of $16.4 million, according to Thomson Reuters I/B/E/S.

Three of four brokerages covering the stock hold a "buy" rating on its shares, including Roth Capital Partners LLC, which raised its price target on Ligand shares to $127 from $116 in anticipation that current revenue streams from partnered products as well as those in development will drive significant growth for the company. The remaining analyst rates the company's share as a "hold."

Ligand shares (NASDAQ:LGND) rose $3.92, to close at $84.43 Monday. Up to Friday's close, the stock had risen 51 percent this year. //

OTHER NEWS TO NOTE

Isarna Therapeutics GmbH, of Munich, Germany, disclosed preclinical data for its lead candidate, ISTH0036, a locked nucleic acid-modified antisense oligonucleotide, in phase I development for the treatment of advanced-stage glaucoma. ISTH0036 was administered in murine models of glaucoma filtration surgery (GFS) and laser-induced choroidal neovascularization (CNV). In the murine GFS model, upon intraocular administration, ISTH0036 was able to significantly prolong bleb survival, as compared to control oligonucleotide- and saline-treated eyes. In addition, ISTH0036 was able to significantly decrease the extent of fibrosis in the bleb area in a sequence-specific manner. In the CNV model, intravitreal administration of ISTH0036 was able to significantly reduce (40 percent) the process of angiogenesis, as compared to saline- and control oligonucleotide-treated eyes.

Medigene AG, of Martinsried, Germany, said its recent initiation of a phase I/II trial with dendritic cell vaccines for the treatment of acute myeloid leukemia triggers a milestone payment of €700,000 (US$779,809) to former contributing shareholders of Medigene Immunotherapies GmbH (formerly Trianta Immunotherapies GmbH), to be paid within the next five months. Medigene intends to settle that payment through the issuance of new shares from authorized capital, with the number of new shares to be calculated based on the average value of Medigene's share price over the 30 days both before and after the announcement. The milestone payment was an agreed part of the purchase price in the acquisition of Trianta in January 2014. (See *BioWorld Today*, Jan. 28, 2014.)

Prima Biomed Ltd., of Sydney, disclosed a collaboration with **Nec Corp.**, of Tokyo, and Yamaguchi University in Yamaguchi, Japan, for Orsay, France-based **Immutep SA**'s IMP321 in combination with a peptide vaccine developed by Nec and Yamaguchi University. The study, to be conducted at Yamaguchi University and supported by Nec, will investigate the use of antigen presenting cell activator IMP321 as an adjuvant, together with peptide antigens believed to be involved in hepatocellular cancer.

Roche AG, of Basel, Switzerland, said the FDA approved the cobas KRAS Mutation Test for diagnostic use. The real-time PCR test is designed to identify KRAS mutations in tumor samples from metastatic colorectal cancer patients and aid clinicians in determining a therapeutic path for them.

Curemark

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of those are sponsored by academic institutions or government agencies. Curemark is running two of the 12 trials sponsored by biopharmas.

The effort to target gastrointestinal and pancreatic secretory deficiencies to treat autism and other diseases with dysautonomic components is just beginning. Judy Van de Water, an immunologist and professor at the University of California Davis' MIND Institute and chief scientific advisor of Pediatric Bioscience Inc., of San Diego, which is developing diagnostic tests for autism, said the gastrointestinal tract is a promising mechanism to attack autism because treating a debilitating comorbidity may help a child deal more successfully with other symptoms. Curemark's approach in identifying biomarkers and defining endpoints that are manageable and, perhaps, more achievable also may increase the success rate in autism trials.

But the use of biomarkers is still in its infancy in autism trials. Although dozens of biomarkers have been applied over more than 700 trials in autism, most are standard measurements such as heart rate, total body mass and blood pressure, according to Cortellis CTI, with chymotrypsin among less than a handful of unique biomarkers for late-stage autism studies.

"Biologic and biomedical phenotyping are what's going to help us," Van de Water recently told *BioWorld Today*. "We're really new at looking at autism in this way. Autism just wasn't thought of in the context of biomarkers until the last decade. //

Formula

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that otherwise couldn't use CAR T. That is not to say at all that physicians would say, 'OK, let's first try CAR T, and then try CAR CIK,' because the physician cannot predict whether or not autologous CAR T can generate sufficient dosing. The physician [with the CAR CIK option would have] an alternative, guaranteeing the dosing."

Formula has other opportunities to explore. "You can imagine that we have a very important play also within the context of CD19," Geerlings said, pointing to "four or five players that precede us" in that realm. "Cellectis [SA, of Paris] is the other allogeneic company, and not for nothing have they become very much in the forefront in the news." (See *BioWorld Today*, Feb. 24, 2015.)

CAR T therapy is hotter than ever, turning up at most scientific meetings with regularity. It was a highlight at the Protein and Antibody Engineering Summit 2015 in Boston last week, noted Piper Jaffray analyst Joshua Schimmer, with updates from Santa Monica, Calif.-based Kite Pharma Inc., the University of Pennsylvania and Sloan-Kettering Memorial Cancer Center.

Newsmakers in the space recently include Juno Therapeutics Inc., of Seattle, and San Diego-based Fate Therapeutics Inc., which entered a research and development deal to discover together mechanisms to modulate the properties of Juno's immuno-oncology candidates as a way of improving their therapeutic potential in both the CAR and T-cell receptor cellular immunotherapy programs.

Juno agreed to pay Fate $5 million up front, purchase 1 million of Fate's common shares at $8 apiece and fund activities related to the collaboration through the exclusive four-year research term, which carries a two-year extension option. (See *BioWorld Today*, May 7, 2015.) //

OTHER NEWS TO NOTE

Rxi Pharmaceuticals Corp., of Marlborough, Mass., presented new data on the company's self-delivering RNAi (sd-rxRNA) compounds developed to target tyrosinase and collagenase at the Society for Investigative Dermatology meeting in Atlanta. In vitro data showed that sd-rxRNA compounds, developed to target tyrosinase, lead to a visible reduction in pigmentation in cultured melanocytes.

IN THE CLINIC

Can-Fite Biopharma Ltd., of Petach Tikva, Israel, said it received EMA clearance to begin dosing patients in Europe in its phase II trial of CF102, a small orally bioavailable drug designed to bind to the A3 adenosine receptor, in hepatocellular carcinoma (HCC). The randomized, double-blind, placebo-controlled trial plans to enroll 78 HCC patients with Child-Pugh class B cirrhosis who failed the only FDA-approved drug on the market, Nexavar (sorafenib, Amgen Inc. and Bayer AG). Patients are treated twice daily with 25 mg of CF102, which has been found to be the most efficacious dose in Can-Fite's earlier phase I/II study, resulting in the longest overall survival time. The drug previously received FDA orphan status in HCC and is approved for compassionate use by Israel's Ministry of Health.

Galectin Therapeutics Inc., of Norcross, Ga., disclosed plans for its phase II program with GR-MD-02 for the treatment of nonalcoholic steatohepatitis (NASH) with advanced fibrosis and cirrhosis during its first quarter earnings report. The company said the phase II program will consist of studies in two different NASH fibrosis indications. The NASH-CX trial will enroll 156 patients with NASH cirrhosis and will evaluate 2 mg/kg of GR-MD-02 and 8 mg/kg of GR-MD-02 and placebo, with patients randomized 1-to-1-to-1. The primary endpoint will be change in hepatic venous pressure gradient (HVPG) compared with placebo, and secondary endpoints will include fibrosis stage on biopsy as well as the percent of collagen on biopsy at one year of treatment. Additionally, the HVPG and liver biopsy measurements will be correlated with non-invasive measurements of liver fibrosis and function, including Fibroscan and the 13C-methacetin breath test. Top-line data are expected at the end of 2017. The NASH-FX study, which will enroll 30 NASH patients with advanced fibrosis but not cirrhosis, will be a four-month study, randomizing subjects 1-to-1 to either 8 mg/kg of GR-MD-02 or placebo.

IN THE CLINIC

Gemmus Pharma Inc., of San Francisco, said its investigational new drug application for influenza candidate GP1681 was cleared by the FDA. The company expects to start a phase I trial this quarter to identify suitable doses in healthy adults. GP1681 is being developed to alleviate influenza symptoms by reducing, but not eliminating, the viral-induced, exaggerated cytokine response. Gemmus said host-targeted therapy has the potential advantage of being able to treat any influenza virus subtype when flu symptoms are present without concern for the development of viral resistance.

GW Pharmaceuticals plc, of London, said it started a phase III trial of Epidiolex (cannabidiol, or CBD) for the treatment of Lennox-Gastaut syndrome (LGS), a rare and severe form of childhood-onset epilepsy. GW previously received orphan designation from the FDA for Epidiolex for the treatment of LGS. The study will be a randomized, double-blind, 14-week comparison of Epidiolex vs. placebo in a total of 150 patients to assess the dose-ranging safety and efficacy of Epidiolex as an adjunctive antiepileptic treatment. The treatment period will consist of a two-week titration period followed by a 12-week maintenance period, and the study will involve three arms of 50 patients – 20 mg/kg and 10 mg/kg of Epidiolex and placebo. The primary measure will be the percentage change from baseline in number of drop seizures in patients taking Epidiolex vs. placebo. Several additional efficacy and safety secondary outcome measures will be analyzed. GW anticipates that top-line data from the trial will be available in early 2016. The start of the latest trial follows phase III launches in Dravet syndrome. (See *BioWorld Today*, March 10, 2015.)

Heat Biologics Inc., of Durham, N.C., said it launched a phase Ib trial of viagenpumatucel-L (HS-110) in patients with non-small-cell lung cancer, aimed at combining the therapy with multiple immune-modulating strategies. The study will enroll those who have failed one or more prior lines of therapy and will evaluate the safety and efficacy of HS-110 in combination with multiple tumor anti-immunosuppressive agents. The first three combinations to be studied are based on preclinical data showing that reduction of tumor adenosine is highly synergistic with Heat's Impact vaccines, while future cohorts are expected to include combinations with checkpoint inhibitors and T-cell co-stimulators. HS-110 is Heat's first product candidate in a series of Impact drugs designed to direct killer T cells to attack cancer.

Molecular Partners AG, of Zurich, Switzerland, said partner **Actavis plc**, of Dublin, confirmed that the abicipar phase III program is on track to start by the end of this quarter or early in the third quarter. The phase III program will evaluate the safety and efficacy of abicipar and its potential to improve vision gains while reducing the number of treatment injections vs. Lucentis (ranibizumab, Roche AG) in patients with wet age-related macular degeneration. Molecular Partners had partnered on the long-acting mono-Darpin program with Allergan Inc., which merged with Actavis earlier this year. (See *BioWorld Today*, May 5, 2011, and Nov. 18, 2014.)

Myos Corp., of Cedar Knolls, N.J., said it started a dose-response study of Fortetropin in modestly resistance-trained subjects, aimed at examining the effects of Fortetropin supplementation on plasma myostatin levels at various dosing levels. The clinical study is designed to help better define the dose response curve, the minimal effective dose and effects of Fortetropin, a natural myostatin modulator, on serum myostatin. The double-blind, placebo-controlled study will randomize 80 subjects to four groups who will be supplemented with three different doses of Fortetropin and a matching placebo.

Tissuegene Inc., of Rockville, Md., reported phase II data showing that, in a primary analysis, TG-C, an allogeneic cell therapy involving human chondrocytes that have been genetically modified to produce the therapeutic growth factor TGF-beta1, showed a statistically significant improvement over placebo in the change from baseline in both pain and function scores in patients with osteoarthritis. The MRI analysis showed cartilage regeneration evidence in selected TG-C-treated patients. On the basis of those data, Tissuegene said it is preparing to initiate phase III trials of TG-C in patients with osteoarthritis of the knee.

Zafgen Inc., of Cambridge, Mass., reported data from its ZAF-201 phase II study of beloranib, a MetAP2 inhibitor, in obese patients, showing that 12 weeks of treatment led to sustained, progressive and dose-dependent weight loss of up to ~11 kg from baseline. Beloranib treatment also significantly reduced sense of hunger and prospective food intake, and known markers of beloranib response, including major cardiovascular risk factors and markers of inflammation, were also improved at 12 weeks. The study enrolled 147 subjects, with 117 completing the trial. Data also showed significant reductions in total and LDL cholesterol and triglyceride levels and an increase in HDL cholesterol in the beloranib 2.4-mg group, and significant increase in HDL cholesterol and decrease in triglyceride levels was observed with beloranib given at 1.2 mg. Consistent with reduced fat mass and improved adipose tissue function and inflammation, significant ($p < 0.001$) changes in adiponectin, leptin and hs-CRP were observed with beloranib. Data were presented at the European Congress on Obesity meeting in Prague, Czech Republic. The company also presented data from a proof-of-concept study of beloranib in Prader-Willi syndrome, with the drug appearing safe and well tolerated, leading to dose-dependent body and total fat mass reductions despite 50 percent increase in total daily calorie intake.

APPOINTMENTS AND ADVANCEMENTS

Ubivac LLC , of Portland, Ore., appointed Ashok K. Batra and Paul E. Frieman to its advisory board.

Voyager Therapeutics Inc., of Cambridge, Mass., named Jeff Goater senior vice president, finance and business development.

Zogenix Inc., of San Diego, named Stephen Farr CEO, and he will continue as president. Roger Hawley, former CEO, will continue as a member of the board.

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