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Celgene, Agios Pharmaceuticals win FDA approval for IDH2-targeting Idhifa in AML

By Michael Fitzhugh, Staff Writer

A new therapy for certain adults with relapsed or refractory acute myeloid leukemia (AML), developed by Celgene Corp. and Agios Pharmaceuticals Inc., has won earlier-than-expected FDA approval following a priority review.

The oral therapy, Idhifa (enasidenib), is the first and only one the agency has approved to address AML patients with an isocitrate dehydrogenase-2 (IDH2) mutation, a group accounting for between 8 and

See Idhifa, page 3

One shoe's already dropped as Janssen's RA drug steps into adcom

By Mari Serebrov, Regulatory Editor

A look at the FDA's briefing document for Wednesday's Arthritis Advisory Committee (AAC) meeting suggests the other shoe could drop on Janssen Biotech Inc.'s sirukumab.

The FDA let the shoe fly when it raised safety concerns about a trend of a greater risk of death with sirukumab over placebo due to cardiovascular events, infection and malignancies. Proposed to treat adults with moderately to severely active rheumatoid arthritis (RA) who had an inadequate response or are intolerant to disease-modifying anti-rheumatic drugs (DMARDs), sirukumab was associated with an increased risk of serious infection in clinical development, with reports of opportunistic infection and tuberculosis, the FDA said.

Although the agency will ask the AAC to discuss the adequacy of a phase II dose-selection study and the use of

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'We can do both,' CEO says

Extended family: Series B relates $83.5M for vectors to Homology, near clinical

By Randy Osborne, Staff Writer

Homology Medicines Inc. CEO Arthur Tzianabos told *BioWorld* that the new $83.5 million in series B money should let the firm "move our lead program all the way through a phase I/II proof-of-concept trial" while edging toward the clinic with the AMEnDR (AAV-Mediated Editing by Direct Homologous Recombination) platform at the same time. "The reason we can do both is because essentially this is a new family of adeno-associated virus [AAV] vectors," he said.

See Homology, page 5

Milestone makes ready for phase III with $55M series C

By Marie Powers, News Editor

Milestone Pharmaceuticals Inc. collected its biggest raise to date, completing a $55 million series C led by Novo Holdings A/S that included new investors Forbion Capital Partners and funds managed by Tekla Capital Management. Existing investors Domain Associates, Fonds de solidarité FTQ, BDC Capital, Pappas Capital and GO Capital also participated. Milestone, based in Montreal with a U.S. subsidiary in Charlotte, N.C., will use the proceeds to advance its short-acting calcium channel inhibitor, etripamil (previously MSP-2017), into a pivotal phase III program, to

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Invitae Corp. acquires Good Start and Combimatrix in combo stock, cash deal

By Katie Pfaff, Staff Writer

Genetic information firm Invitae Corp. plans to acquire both Good Start Genetics Inc., a molecular diagnostic company for preimplantation and carrier testing of inherited diseases, and Combimatrix Corp., a prenatal and pediatric diagnostic company, putting itself at the front of the family genetics space. San Francisco-based Invitae entered definitive agreements with the two companies, which are contingent on several conditions.

The sale is a combination of common stock, cash and payment of debt. Invitae has agreed to pay

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Newco News

Good drugs for bad bugs: Startup Bugworks gets grant for superbug drug development

By David Ho, Staff Writer

HONG KONG – To speed up biopharmaceutical research on fighting superbugs, the Combating Antibiotic Resistant Bacteria Biopharmaceutical Accelerator (CARB-X) recently awarded grants to a number of biopharma firms, among them a 3-year-old startup aptly named Bugworks Research India Pvt. Ltd., which received $2.6 million.

"The initial investment of $2.6 million from CARB-X

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Regulatory front

Spurred by **Sanofi SA's** refusal to agree to fair pricing for a Zika vaccine, U.S. Sen. Bernie Sanders (I-Vt.) and Rep. Peter DeFazio (D-Ore.) reintroduced an amendment this week that would require federal agencies and federally funded nonprofits to secure reasonable pricing agreements from manufacturers before they grant exclusive rights to make drugs, vaccines or other health care products that were developed with taxpayer funding. The agreements would tie the allowable U.S. price to the price in other members of the Organization for Economic Co-Operation and Development. In proposing the bill, which made its first appearance 20 years ago, Sanders noted that U.S. taxpayers spent more than $1 billion on Zika research and prevention efforts, including $43 million paid directly to Paris-based Sanofi to develop a vaccine. Another $130 million in federal funding is still to come for the drug company. "Yet they have rejected the U.S. **Army's** request for fair pricing. That is simply unacceptable," Sanders said, adding that Sanofi is not unique. He pointed to **Pfizer Inc.**'s prostate cancer drug, Xtandi (enzalutamide), which was developed at the University of California-Los Angeles with taxpayer-funded research grants and support from the Army and the NIH. While patients in the U.S. are charged $129,000 for a one-year treatment of Xtandi, those in Canada pay $30,000, the senator said.

The **EMA** is seeking public comments on a reflection paper on how drug companies can better address the needs of older patients. Although older people take more drugs than the rest of the EU population, "medicines are rarely developed or packaged to take into account their specific needs," the EMA said. The reflection paper describes factors drug sponsors should consider when designing medicines for older people – appropriate routes of administration and dosage forms, dosing frequency, excipients, container closure systems, devices and technologies, and user instructions. The EMA is inviting comments on the accuracy of tablet breaking, the administration of drugs through feeding tubes, and multiple compliance aids and drug dispensing systems. Comments on the paper, which may be used in developing future guidance, are due Jan. 31, 2018.

The **FDA** finalized a 2013 draft guidance on developing new antibacterial drugs to treat serious bacterial diseases in patients with an unmet medical need. The guidance outlines approaches for streamlined development programs that are consistent with the FDA's regulatory flexibility regarding the evidence needed to support drug approval for patient populations with serious disease and limited or no treatment options, according to a notice slated for publication in Wednesday's *Federal Register*.

Financings

Innoviva Inc., of Brisbane, Calif., said it plans to offer $175 million of convertible senior notes due in 2025 in a private placement. The purchasers will also have a 30-day option to purchase up to an additional $17.5 million of the notes. Innoviva plans to use the proceeds to refinance a portion of its 9 percent fixed rate term notes due in 2029 and may also purchase shares of its common stock in privately negotiated transactions. Shares of Innoviva (NASDAQ:INVA) lost 44 cents to close at $13.28 on Tuesday.

Appointments and advancements

Arix Bioscience Ltd., of London, added Meghan FitzGerald to its board, and appointed her to the audit committee.

CTI Biopharma Corp., of Seattle, added Laurent Fischer to its board.

Dimension Therapeutics Inc., of Cambridge, Mass., appointed Mary Thistle principal financial and accounting officer.

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Idhifa

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19 percent of AML patients, or about 1,200 to 1,500 individuals in the U.S. Alongside it, the FDA green-lighted an Abbott-developed companion diagnostic that can detect IDH2 gene mutations, which runs on Abbott's m2000rt Realtime System, a PCR testing automation system.

Agios had previously worked with Foundation Medicine Inc. to find patients most likely to respond to its IDH1 and IDH2-targeting candidates and "to develop and potentially commercialize diagnostic products" for those programs, but picked Abbott as its commercial partner in October 2016. Agios spokeswoman Holly Manning said the Foundation collaboration was "more focused on using their platform in our clinical trials."

Though a relatively small market for Celgene, analyst forecasts compiled by Cortellis project the therapy could generate $100 million in 2018 sales, peaking in 2021 with $456 million in annual revenue, a ramp-up likely tied to expectations that the partners could expand into first-line treatment of AML.

Mutations in IDH2, a critical metabolic enzyme, result in elevated levels of the oncometabolite 2-hydroxyglutarate (2HG), which prevents differentiation of myeloblasts, leading to tumor formation and progression. By inhibiting IDH2, Idhifa (formerly AG-221) aims to reduce 2HG levels and restore myeloblast differentiation. (See *BioWorld Today*, April 8, 2014.)

Patients in the pivotal study were treated with Idhifa for a median of 4.3 months. At a monthly wholesale acquisition cost of $24,872, that would equate to a cost of about $107,000 per patient.

Celgene spokesman Greg Geissman said the company is proactively working with U.S. payers on patient-centric agreements designed to provide immediate access to the medicine with no out-of-pocket costs for eligible patients, other than those covered by federal health care programs.

Summit, N.J.-based Celgene, which completed its new drug application in late December 2016, licensed Idhifa from Cambridge, Mass.-based Agios as part of a 2010 collaboration agreement. The oral medicine, the first to emerge from the partnership, works by blocking several enzymes that promote cell growth.

Celgene has worldwide development and commercialization rights for Idhifa. Agios is eligible to receive up to $120 million in payments assuming achievement of certain milestones and royalties on net sales. Both companies will work to market the drug in the U.S., though Celgene will reimburse Agios for costs incurred for its part of those efforts.

The approval was based on the results of a single-arm trial of 199 patients with relapsed or refractory AML who had IDH2 mutations as detected by the Realtime IDH2 Assay. The study measured the percentage of patients with no evidence of disease and full recovery of blood counts after treatment, or complete remission (CR), as well as patients with no evidence of disease and partial recovery of blood counts after treatment, called CR with partial hematologic recovery, or CRh, the FDA said.

With a minimum of six months of treatment, 19 percent of patients experienced CR for a median 8.2 months, and 4 percent of patients experienced CRh for a median 9.6 months. Of the 157 patients who required transfusions of blood or platelets due to AML at the start of the study, 34 percent no longer required transfusions after treatment with Idhifa, according to the agency.

Common side effects of Idhifa include nausea, vomiting, diarrhea, increased levels of bilirubin and decreased appetite.

The approved label includes a boxed warning that an adverse reaction known as differentiation syndrome can occur and can be fatal if not treated. The agency also advised pregnant or breastfeeding women against taking the therapy due to risks of harming a developing fetus or newborn baby.

Idhifa received both FDA fast track and orphan status for AML. It also has EMA orphan status.

About 21,380 people are expected to be diagnosed with the fast-progressing bone marrow cancer this year. Despite treatment, the majority of them will eventually experience relapse. Both induction and consolidation therapies typically include chemo, though at differing doses. Allogeneic or autologous stem cell transplants are also used during consolidation therapy for younger patients. About 10,590 people with the condition are expected to die of the disease in 2017.

Even after Tuesday's approval, Celgene and Agios still have a significant slate of partnered assets in development. First, they're working to expand the number of patients – and, of course, the market – addressable by enasidenib, testing it in combination with Vidaza (azacitidine) and, separately, with a standard chemotherapy regimen of cytarabine and daunorubicin, in newly diagnosed AML patients. They're also studying the orally available IDH1 inhibitor ivosidenib (AG-120) in a variety of cancers that harbor an IDH1 mutation, including front-line and relapsed/refractory AML. Another candidate, the pan-IDHm inhibitor AG-881, is under investigation for the treatment of glioma with IDH mutations.

Other companies are also working on precision treatments for AML. Astellas Pharma Inc., of Tokyo, is investigating gilteritinib in various patient populations through several planned and already started phase III trials, including the registrational Admiral experiment in relapsed/refractory FLT3-positive AML. Glycomimetics Inc., of Rockville, Md., is advancing GMI-1271, an E-selectin antagonist for relapsed/refractory AML. And, in May, Novartis AG, of Basel, Switzerland, gained FDA approval for Rydapt (midostaurin), a therapy for people with newly diagnosed AML positive for FLT3 mutation. A positive opinion recommending approval of the medicine in Europe arrived in July. (See *BioWorld Today*, May 1, 2017.)

Shares of Agios (NASDAQ:AGIO) closed Tuesday at $58.65, up $2.71, while shares of Celgene (NASDAQ:CELG) closed at $135.18, down 23 cents. ♦

Janssen

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long-term, placebo-controlled trials in people with RA, it said the ultimate focus of the meeting will be the efficacy and safety findings, as well as the overall benefit-risk profile, of sirukumab dosed at 50 mg every four weeks via a subcutaneous injection.

The first shoe dropped on the drug last week when London-based Glaxosmithkline plc (GSK) announced it was terminating its partnership with Janssen, part of Johnson & Johnson, of New Brunswick, N.J., to develop the monoclonal antibody (MAb) that inhibits interleukin (IL)-6. The move will enable GSK to prioritize its strongest assets by shifting resources away from those that "offer more limited opportunities," the company said in its second-quarter earnings report.

If sirukumab were to be approved, it would step into a field crowded with multiple small-molecule drugs and biologics that are considered DMARDs in treating RA. However, the FDA said another treatment option would be desirable, given that RA is a chronic progressive disease associated with morbidity and mortality.

First-line treatments for patients with RA are nonbiologic DMARDs. The second-line of DMARDs consists of tumor necrosis factor-alpha (TNF-alpha) antagonists such as Humira (adalimumab, Abbvie Inc.), Remicade (infliximab, Janssen) and Enbrel (etanercept, Amgen Inc.). Between 30 percent to 40 percent of patients fail to respond or become intolerant over time to the TNF-alpha drugs, the FDA said. The options then are to switch to another TNF-alpha antagonist or try a drug with a different mechanism of action.

Sirukumab, which would be marketed as Plivensia, would compete with two other MAbs that target the IL-6 pathway – Roche Holding AG's Actemra (tocilizumab) and the recently approved Kevzara (sarilumab), partnered by Sanofi SA and Regeneron Pharmaceuticals Inc. Sirukumab's mechanism of action is a bit different, though, as it targets IL-6, whereas the other two target an IL-6 receptor.

Analysts are predicting that sirukumab, if approved, would trail the other two IL-6 drugs. According to a consensus forecast in Clarivate Analytics' Cortellis, sales for Actemra, which was first approved in 2010, are expected to peak at $3.346 billion by 2022. In comparison, Kevzara, approved in May, is forecast to peak at $736 million by 2022, and Plivensia, if approved this year, is projected to peak at $507 million in 2020.

GSK's step-away from its rights to the biologic in the Americas could raise some uncertainty for future development of sirukumab.

According to Clinicaltrials.gov, GSK was still recruiting last month for a phase III trial of the molecule in giant cell arteritis, and Janssen was recruiting for a phase II study of the drug in major depressive disorder. GSK suspended a phase IIa asthma trial last November. Meanwhile, the FDA granted sirukumab orphan drug designation last month for juvenile idiopathic arthritis. ♦

Financings

Reata Pharmaceuticals Inc., of Irving, Texas, said it closed its public offering of about 3.7 million shares of its class A common stock, which included 487,500 shares sold pursuant to the underwriters' full exercise of their option to purchase additional shares, at a price of $31 per share. The gross proceeds are expected to be about $115.9 million. Reata will use funds for working capital and general corporate purposes, which include advancing the development of bardoxolone methyl through a phase II/III program in chronic kidney disease caused by Alport syndrome, phase II programs in additional renal indications and phase II programs in PH-ILD, and the development of omaveloxolone in Friedreich's ataxia and mitochondrial myopathies. Jefferies LLC, Leerink Partners LLC and Stifel, Nicolaus & Co. Inc. acted as joint book-running managers. Robert W. Baird & Co. Inc. and Ladenburg Thalmann & Co. Inc. acted as co-managers.

Other news to note

Aicuris Anti-infective Cures GmbH, of Wuppertal, Germany, said the FDA granted fast track status to oral pritelivir, the firm's lead candidate for the treatment of acyclovir-resistant mucocutaneous herpes simplex virus (HSV) infections in immunocompromised adults. A small-molecule helicase-primase inhibitor with what Aicuris described as a novel mode of action, the candidate is undergoing a phase II study called PRIOH-1 in the U.S. to evaluate efficacy and safety compared to intravenous foscarnet, a virostatic agent used mainly for the treatment of herpes viruses resistant to other antiviral drugs. In a prior phase II study, oral pritelivir significantly improved the suppression of viral shedding compared to nucleoside analogue valacyclovir, the current standard of care for genital HSV-2 infections. Those results were published in the *Journal of the American Medical Association* earlier this year.

Astrazeneca plc, of London, said the FDA granted breakthrough designation to acalabrutinib for the treatment of patients with mantle cell lymphoma who have received at least one prior therapy. Acalabrutinib is described as an investigational, highly selective, potent BTK inhibitor in development for the treatment of multiple B-cell cancers. U.S. regulators granted the designation based on the totality of clinical data from the acalabrutinib development program, including data from the phase II ACE-LY-004 trial in patients with relapsed or refractory disease.

Bristol-Myers Squibb Co., of New York, said the FDA approved Opdivo (nivolumab) injection for intravenous use for the treatment of adult and pediatric (12 years and older) patients with microsatellite instability-high or mismatch repair deficient metastatic colorectal cancer that has progressed following treatment with fluoropyrimidine, oxaliplatin and irinotecan. Approval was granted under the accelerated pathway based on overall response rate and duration of response. The recommended dose is 240 mg administered as an intravenous infusion over 60 minutes every two weeks until disease progression or unacceptable toxicity. The PD-1-blocking antibody for the treatment of advanced melanoma and non-small-cell lung cancer gained its first approval in late 2014.

Homology

Continued from page 1

Bedford, Mass.-based Homology's flagship drug candidate would treat a disease caused by an inborn error of metabolism, though Tzianabos declined to be more specific. "Because we've been in the rare disease drug development business for a long time as former Shire executives, we're very careful about naming exact lead indications right out of the gate until we have feedback from regulatory agencies on our approach," he said. Instead, it's best to "be surefooted about not naming your lead indication and whipping up a frenzy around it before you really know that you've got a path to the clinic."

The company was formed in 2015, and the following year made known the closing of a $43.5 million series A preferred stock financing co-led by 5AM Ventures and Arch Venture Partners, with participation from Singapore-based investment firm Temasek along with Deerfield Management and Arch Overage Fund. Tzianabos had spent about nine years directing discovery, research and early development programs at Dublin-based Shire plc before moving to Ovascience Inc., of Waltham, Mass., and then taking the top spot at Homology. (See *BioWorld Today*, May 2, 2016.)

Sam Rasty, who worked with Tzianabos as vice president and head of new products in Shire's Rare Diseases Business Unit, joined Homology as chief operating officer. Albert Seymour came over from Shire to serve as chief scientific officer.

> *"One of the things we've learned about new technologies, particularly the CRISPRs, is that you're getting ahead of yourself a little bit when you start naming IND filing dates.*
>
> Arthur Tzianabos
> CEO, Homology Medicines

Homology's gene editing and gene therapy technologies are based on the research of Saswati Chatterjee, professor of virology at the Beckman Research Institute at the City of Hope. Chatterjee and her team led the first studies of AAV vector-mediated gene transfer into hematopoietic stem cells (HSC), next identifying and isolating a series of naturally occurring AAVs from human CD34+ cells.

"Nobody had really looked at human stem cells as a reservoir for AAVs, but she comes from one of the major stem cell transplant centers in the world" and had good access to pursue the idea, Tzianabos said. "Based on what the DNA payload looks like, you can say this is going to be a gene transfer vector or this is going to be a gene editing/gene correction vector."

Gene editing at the company starts with designing homology sequence arms that are highly specific to a region of the human genome, and results in a permanent therapeutic correction in the DNA when delivered to cells by AAVHSC vectors that travel to the cell's nucleus and bring about homologous recombination directed repair.

Preclinical work is underway that would enable an investigational new drug (IND) application with the product candidate, but Tzianabos wouldn't speculate about timing. "When you say that [enabling work is ongoing], you're definitely in development mode and not too far away from the clinic," he said, but "one of the things we've learned about new technologies, particularly the CRISPRs, is that you're getting ahead of yourself a little bit when you start naming IND filing dates. We're already seeing some of these companies having to push back timelines. We want to be very careful about how we lay out our plans publicly and be respectful to patients who are waiting for this type of treatment."

Partners? Maybe, but first . . .

Game-changing biologics such as monoclonal antibodies and RNA interference "can take as long as 20-plus years" to traverse the path from lab bench to market, Tzianabos said, citing Cambridge, Mass.-based Alnylam Pharmaceuticals Inc. in the latter field. Gene therapy is finding its feet similarly, "albeit with a history where it went up fast and came back to earth" gradually, as people understood the research would not yield drugs overnight, he said. "We're seeing traction with a number of companies now," notably Spark Therapeutics Inc., of Philadelphia, and San Rafael, Calif.-based Biomarin Pharmaceutical Inc.

"We always thought privileged areas of the body – the eye, the brain – where you can do drug delivery is probably the best place to start," Tzianabos said. "In fact, that's what you're seeing with Spark and their LCA2 program [in Leber congenital amaurosis]. It looks like they're really going to hit it out of the park."

In central nervous system disorders, he called out Voyager Therapeutics Inc., of Cambridge, Mass., which late last year scored solid phase Ib data with VY-AADC01 for Parkinson's disease. Last month, the company dosed the first patient in a phase I trial aimed at further optimizing surgical delivery. The study explores a back of the head surgical delivery approach, compared to cohorts one, two and three from the phase Ib experiment using transfrontal delivery into the putamen. (See *BioWorld Today*, Dec. 9, 2016.)

On the other hand, "people have been a little bit wary of peripheral diseases" in gene therapy, Tzianabos said, even as inroads are being made. He pointed to phase I success by Chicago-based Avexis Inc., which last month disclosed its "alignment" with the FDA on the company's manufacturing process for AVXS-101, the gene therapy for spinal muscular atrophy type 1. Avexis' progress "really does bode well for branching out and going after some of these diseases that are multi-organ," he said. (See *BioWorld Today*, Nov. 3, 2016.)

Asked about partnering, Tzianabos said Homology's "approach has been to validate the platform and be extremely efficient about [making a beeline] to the clinic to show that the platform has validity to it, and has legs. Then, at the same time, you can think about partnering out areas of the platform that are noncore to your business – [other] therapeutic areas, for example. You can't do everything."

Validating the platform in-house "with our own programs

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Milestone

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produce clinical and commercial supplies and to begin pre-commercialization activities.

Not a bad start for Joseph Oliveto, late of Chelsea Therapeutics International Ltd., who was named the company's president and CEO in March after an informal advisory role during the preceding six months.

Oliveto had been kicking around for opportunities after Chelsea, of Charlotte, N.C., went to H. Lundbeck A/S in 2014 following the hard-fought battle for approval of Northera (droxidopa) to treat neurogenic orthostatic hypotension, or NOH. The deal by Lundbeck, of Valby, Denmark, was valued at $530 million up front, with another $128 million tied to milestones for Northera's commercial performance. (See *BioWorld Today*, Feb. 19, 2014, and May 9, 2014.)

Last year, Oliveto was approached by Scott Weiner, a Milestone board member and partner at Pappas Ventures, where Oliveto had worked as an executive in residence. Philippe Douville, who founded Milestone and shepherded the company through its first decade, was seeking to slide into the role of chief scientific officer. He wanted to find a CEO with development and commercialization experience as etripamil, designed to treat episodes of paroxysmal supraventricular tachycardia (PSVT), rounded the bend toward late-stage development.

When Oliveto talked with other Milestone board members and executives, he saw a lot to like.

"I saw similarities between the lead program and Northera and similarities between NOH and PSVT," he told *BioWorld*. "This was in my sweet spot."

Etripamil was developed as a fast-acting nasal spray that can be administered by a patient to terminate PSVT episodes wherever and whenever they occur. Northera targets NOH, a sudden drop in blood pressure when a patient stands, an orphan indication that often results from underlying neurological disorders along with lower synthesis and/or release of norepinephrine.

Oliveto began advising Milestone in October 2016 and participated in the company's meetings with the FDA in advance of the data readout from the company's phase II NODE-1 trial. Those findings, reported in May during a late-breaking oral presentation at the Heart Rhythm Society's Annual Scientific Sessions in Chicago, showed statistically significant efficacy for etripamil compared to placebo in acute termination of PSVT induced in an electrophysiology laboratory.

The trial enrolled 104 patients expecting an ablation procedure, who were randomized into one of four etripamil treatment groups (35 mg, 70 mg, 105 mg or 140 mg) or placebo. After 15 minutes, PSVT conversion rates were higher in the patients who received etripamil 70 mg (87 percent; 20/23), 105 mg (75 percent; 15/20) and 140 mg (95 percent; 20/21) compared to placebo (35 percent; 7/20), with "p" values of less than 0.001, 0.05 and 0.001, respectively, compared to placebo. The conversion rate for patients who received etripamil 35 mg was 65 percent (13/20), considered not significant. The median time to PSVT conversion ranged from 1.82 to 3.03 minutes across the four etripamil treatment arms.

'We will run a global trial'

By then, plans for the series C were well underway, with an initial goal of $45 million to fund the phase III program fully. The clamor for participation by quality investors convinced Milestone to upsize the round to provide room for pre-commercialization activities and strategic hires in marketing and medical affairs. Even then, at the end of a fast and furious process, "we had to tell people to put their pencils down so we could close the round," Oliveto said.

Joseph Oliveto

The size of the round – nearly twice the amount of the company's $13 million series A and $17 million series B, combined – spoke volumes about investor confidence in Milestone's progress to date. (See *BioWorld Today*, June 14, 2011.)

"As important as the size of the financing is the credibility of the people who came to the table," Oliveto added.

In conjunction with the financing, Nilesh Kumar, partner at Novo Ventures U.S. Inc., which provides consulting services to Novo Holdings A/S, and Marco Boorsma of Forbion will join Milestone's board, while Daniel Omstead of Tekla will serve as an observer.

> *"We had to tell people to put their pencils down so we could close the round.*
>
> Joseph Oliveto
> President and CEO, Milestone Pharmaceuticals Inc.

Oliveto singled out Novo as an early member of the syndicate, citing Kumar's "understanding of the indication and the opportunity," and pointed to support by publicly held Tekla, which gravitates more toward big biotech, as helping to position Milestone should it make a run at the public markets.

"Front and center" now are plans to discuss with the FDA and EMA the phase III design and the production of trial and commercial material, according to Oliveto. Because PSVT must be treated at the time of an episode, Milestone proposes to enroll a minimum of 300 patients with confirmed diagnosis of atrioventricular nodal reentrant tachycardia or atrioventricular re-entry tachycardia, supply them with the study drug and then send them home to wait for events, which can last minutes to hours. The study will require about 100 to 120 events to determine a statistically significant difference between the treatment arm of 70 mg of etripamil and placebo.

If successful, etripamil could reduce the burden on patients with PSVT, caused by an abnormality in the electrical system of the heart, and also potentially reduce the frequency and

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Combimatrix

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$18.3 million in cash to alleviate Cambridge, Mass.-based Good Start's secured debt, pay $6 million to cover pre-closing and closing liabilities for the company, and issue Good Start 1.65 million shares of common stock – though that amount may vary based on indemnification liabilities.

Invitae has agreed to pay Mukilteo, Wash.-based Combimatrix $27 million of its common stock shares, or 2.85 million shares subject to net calculation for the company at the acquisition date. The stock will be paid for outstanding shares of Combimatrix stock, outstanding restricted stock and in-the-money options. Though specifics are yet to be hammered out, the agreement also includes a possible exchange offer for $6 million in Invitae shares (0.63 million shares) for outstanding Combimatrix series F warrants, based on agreement from 90 percent of series F shareholders. Depending on exchange, exercise of warrants or inclusion within the acquisition, series F warrants may reach $15 million worth of Invitae shares, or about 1.58 million shares. If all warrants were exercised, that could reach $10.7 million, and the company would become a wholly owned Invitae subsidiary.

"This is a transformative moment for Invitae, for our industry, and importantly for patients," said Invitae CEO Sean George. "By acquiring Good Start and Combimatrix, Invitae intends to create the industry's first comprehensive genetic information platform providing high-quality, affordable genetic information coupled with world-class clinical expertise to inform health care decisions throughout every stage of an individual's life."

Comprehensive platform

Invitae said in a presentation that the acquisition of Good Start would build on the latter company's relationship with customers and clinicians, reimbursement success and add to Invitae's sales teams with the approximately 500 IVF clinics the company works with across the U.S. The companies have similar infrastructure, according to the presentation. Additionally, Combimatrix will add to Invitae's commercial footprint, cytogenetic capability, sales force in perinatal testing and help Invitae move into next-generation sequencing (NGS) testing in perinatal and pediatric diagnostics.

"While we need to learn more, the company has clearly taken necessary steps to evolve strategically and address a financial overhang while continu[ing] to execute well relative to core targets," said Cowen and Co., in comments regarding the sale and a private placement of stock, reported July 31. The company entered a definitive agreement to sell $73.5 million in stock to existing and new investors. The funding agreement will include 8.7 million shares sold at $8.50 each and is expected to close Aug. 3. The company was expected to need the additional cash infusion, which increases the firm's cash balance, according to Cowen.

Genetic testing

The companies' genetics platforms are intended to complement each other, creating a comprehensive suite of tests for various life stages. Good Start specializes in embryo tests, preimplantation and carrier testing so that parents and their doctors can use the information to make decisions and form treatment plans.

"Our companies share a belief in the power of genetic information to transform people's lives and a common commitment to making that information affordable and available to all," said Jeffrey Luber, president and CEO, Good Start. "Today, we are thrilled to bring the momentum we've built in IVF to Invitae. Together we will enhance our combined offerings in this important category and bring that comprehensive solution to our customers for the benefit of growing audiences everywhere."

Good Start, which has run more than 1.7 million tests since it began commercial launch in 2012, markets testing in three areas. These include its Genevu clinic-based screening for inherited genetic diseases, Veriyou inherited disease screening that can be collected at home, and can be purchased through Amazon.com, and Embryvu preimplantation genetic testing for parents. Embryvu is based on licensed technology from Johns Hopkins University School of Medicine. Each set of tests uses an NGS platform to streamline workflow and provide the screening at reduced costs. Genetic counseling also is available to customers who undergo testing.

Combimatrix further rounds out the genetic screening portfolio, according to Invitae, "establish[ing] a category-leading menu with the breadth and depth needed to provide comprehensive support for women, their partners and clinicians" in family and reproductive care. "The information that we will be able to provide as a combined entity will enable clinicians to help guide women through some of the most important health decisions they make along the continuum of care in family planning," says Mark McDonough, president and CEO, Combimatrix. "We are eager to combine our complementary product portfolio, expertise and relationships to create the market leader in family health genetics." Combimatrix provides analysis after a miscarriage and screens for genetic anomalies for additional use in preimplantation genetic testing, testing for genetic carriers, and diagnoses for prenatal and pediatric developmental disorders.

Financial outlook

Financial advisers are somewhat cautious with the potential value of the sale given the market it serves. "Our best guess is that Good Start is being sold for ~1x 2017E sales and Combimatrix is being sold for ~2-2.5x 2017E sales," suggested Cowen. "On the surface these seem like reasonable multiples. However, the areas of focus are very competitive with many established commercial and academic participants, and there does seem to be some overlap between Good Start and Combimatrix. Additionally, it is not clear how big the market opportunities are as currently built." Cowen cautioned Invitae has market hurdles to overcome, namely that the market for the companies may be small, about 350,000 patients who seek IVF, and a U.S. market of about $300 million to $500 million. Cowen estimates patients pay about $1,000 per test.

Acquisition of Good Start is expected to close in August. Subject to stockholder approval, the sale of Combimatrix is expected to close in the fourth quarter. ♦

Bugworks

Continued from page 1

will be used to get us through the preclinical development stage of our novel first-in-class broad-spectrum antibiotic," Anand AnandKumar, co-founder and CEO of Bugworks, told *BioWorld*.

A further $3.6 million in potential option payments will be used to bring the drug through phase I trials.

Since its founding, the Bengaluru-based drug discovery firm has been hard at work on finding a solution to antibiotic-resistant superbug infections. Its antibiotic platform is designed to kill multidrug-resistant gram-negative bacteria.

More specifically, the company's drug can fight the following ESKAPE pathogens: Enterococcus faecium, which causes neonatal meningitis; *Staphylococcus aureus*, which leads to respiratory infections; *Klebsiella pneumonia*, which weakens the immune system; *Acinetobacter baumannii*, which also weakens the immune system; *Pseudomonas aeruginosa*, which causes pneumonia; and *Enterobacter*, which causes urinary infections.

"Ninety-five percent of nosocomial infections in the world are attributed to these six bacteria," AnandKumar cited as the reason for focusing on the ESKAPE pathogens.

Roughly 700,000 deaths worldwide are recorded annually due to drug-resistant strains of infections. Given that need, AnandKumar said he is looking at quickly bringing the unnamed drug through phase II trials and to market about "three years from today."

Bugworks' lead compound, a gyrase-topoisomerase inhibitor, is also being developed as an intravenous and oral treatment for multidrug-resistant infections, such as the sexually transmitted disease gonorrhea.

According to AnandKumar, it comes with a low risk of developing resistance because it "hits pathogens in two spots, like a sledgehammer" by inhibiting two essential targets in the replication machinery, and it has been designed to bypass efflux resistance mechanism of the bacteria. Because of that, he estimated that it could last between 15 and 20 years without pathogens developing a resistance to it.

Bugworks was formed in February 2014 by three colleagues at Cellworks Group Inc. The company is currently conducting a series A funding. AnandKumar will be meeting investors in "the U.S., India and potentially China" to seek $5 million to $10 million in funding.

Global commitment

CARB-X recently funded seven antibiotic projects in a $17.6 million round of funding. Bugworks is the only company in Asia to make it on that list of seven. The other projects are from the U.K., France, Ireland, Switzerland and two from the U.S.

"Drug-resistant infections are complex and developing new antibiotics is challenging, timely and costly. But restoring the R&D pipeline is vital to address the seriously increasing threat of superbugs which have become resistant to existing drugs. This is a global problem and CARB-X is a critical part of the global solution," said Kevin Outterson, executive director of CARB-X.

> *"Bugworks' lead compound 'hits pathogens in two spots, like a sledgehammer.*
>
> Anand AnandKumar
> Co-founder and CEO, Bugworks

"We are looking to support the best potential new treatments and diagnostics across the world. But we need greater global support from governments, industry and civil society to get the new treatments the world urgently needs."

A public-private initiative, CARB-X aims to fund scientists from around the globe in a bid to eradicate serious bacterial threats by accelerating antibacterial product development. The initiative was formed in July last year as a partnership between the U.K.-based charity Wellcome Trust and the U.S. Department of Health and Human Services Biomedical Advanced Research and Development Authority, part of the Office of the Assistant Secretary for Preparedness and Response, and the National Institute of Allergy and Infectious Diseases, part of the NIH. (See *BioWorld Today*, July 29, 2016.)

"Antibiotics are fundamental to modern medicine but overuse and inappropriate use have led to dangerous bacteria developing deadly resistance. Drug discovery must also go hand-in-hand with concerted action to ensure antibiotics of last resort are reserved for patients where first-line treatments will not work," said Tim Jinks, head of drug-resistant infections at Wellcome. "And we must ensure these treatments can be made available in all countries for those who need them."

The latest funding is part of an overall commitment of up to $455 million by the U.S. government and Wellcome over a five-year period and follows the announcement in March of the first 11 projects to receive funding – eight in the U.S. and three in the U.K. (See *BioWorld Today*, April 3, 2017.)

The projects were selected from among 368 applications from around the world. CARB-X expects to make further funding announcements later this year. ♦

Homology

Continued from page 5

is important, but at the same time, we've had a number of conversations with big pharma, big biotech" about working with them.

Exactly when the company may need to raise more money is "hard to say," Tzianabos said. "Deals always can change that horizon very quickly. Our goal right now is to use this money to get into and through the clinic and proof of concept with our lead program. Then we can think about what the next tranche of money looks like."

Deerfield Management led the series B round. New investors include Fidelity Management and Research Co., HBM Healthcare Investments, Maverick Ventures, Novartis AG, Rock Springs Capital, Vida Ventures, Vivo Capital and Alexandria Venture Investments. Also taking part were 5AM, Arch and Temasek. ♦

Milestone

Continued from page 6

associated costs of emergency room visits. PSVT affects an estimated 1.7 million people in the U.S. and results in more than 600,000 health care claims annually, according to Milestone.

The company aims to open enrollment around year-end or early 2018, which would yield top-line results in mid-2019. Recruitment will begin in the U.S. but, because Milestone holds composition-of-matter patents and wants to maximize its worldwide rights to etripamil, "we will run a global trial," Oliveto said.

A potential launch strategy is a little harder to gauge, he acknowledged.

"Most cardio conditions are not conditions that can be launched by a little company," Oliveto said. "But this is a little different. This is a tachycardia, and depending on how we want to go to market, we could key in on specialists with a small sales force. But we also could go broader into PSVT, which is also managed by primary care physicians and non-specialists. So the strategy is a bit open, if you will."

To that end, Milestone already is engaged in discussions with other biopharmas in the cardiovascular space, though Oliveto made clear that, for now, that attention is entirely inbound.

"We're focused on getting this phase III trial started," he said. ♦

Other news to note

Cellectar Biosciences Inc., of Madison, Wis., started a collaboration with **Avicenna Oncology GmbH**, of Basel, Switzerland. The pair will focus on the development of new phospholipid drug conjugates (PDCs) combining Cellectar's phospholipid ether delivery platform with Avicenna's cytotoxic payloads. Avicenna will provide payloads to Cellectar, which will leverage its expertise in chemical conjugation to link the molecules to its phospholipid ether via the PDC platform. Cellectar will oversee the in vitro and in vivo testing of those molecules alongside an antibody-drug conjugate with the same payload. Both companies will have the option to advance the development of any of the newly conjugated molecules. Financial terms were not disclosed.

Cersci Therapeutics Inc., of Dallas, said it received a Direct-to-Phase II Small Business Innovation Research grant totaling more than $650,000 in 2017, with an additional $1 million to follow in 2018, from the National Institute on Drug Abuse. Those funds will support Cersci's IND for lead non-opioid drug candidate CT-044, targeting submission in the third quarter of 2018. CT-044 is an orally bioavailable, peripherally acting, non-metal based catalytic peroxynitrite neutralizer.

Cidara Therapeutics Inc., of San Diego, said data from a study comparing CD-101, a next-generation echinocandin agent, to the current first-line treatment, micafungin, in a mouse model of intra-abdominal candidiasis were published in *Antimicrobial Agents and Chemotherapy*. The study used MALDI-MS imaging to show a dose-dependent four- to sixfold higher penetration into infectious lesions days after the single dose of CD-101 compared to daily micafungin. The level of CD-101 was high enough to prevent mutations leading to antifungal resistance. Data from Cidara's phase II STRIVE trial of CD-101 I.V. are expected in the fourth quarter.

Emergent Biosolutions Inc., of Gaithersburg, Md., was awarded about $23 million to develop a multidrug auto-injector for nerve agent antidote delivery. Emergent's device is being designed for intramuscular self- or buddy-administration of antidotes for use in military environments and for civilian emergencies. Under the five-year agreement, awarded through the Medical CBRN Defense Consortium, Emergent will develop a device, conduct studies to demonstrate consistent manufacture, functionality and usability of the final device, and complete regulatory activities required to obtain approval of the product by the FDA.

Other news to note

Epizyme Inc., of Cambridge, Mass., and **US Oncology Research,** of The Woodlands, Texas announced a collaboration to screen and identify relapsed or refractory follicular lymphoma (FL) and diffuse large B-cell lymphoma (DLBCL) patients with EZH2 mutations. Once identified, eligible candidates will be directed to Epizyme's ongoing phase II trial of tazemetostat, an EZH2 inhibitor. US Oncology is implementing a separate screening protocol in 68 locations in the U.S. to identify relapsed or refractory FL and DLBCL patients with tumors bearing EZH2 mutations who may be candidates for enrollment in the trial. Sites began screening patients in July.

Integrated Biotherapeutics Inc., of Rockville, Md., said it received a $6.6 million grant from the National Institute of Allergy and Infectious Diseases to develop a vaccine that can protect against all ebolaviruses. Investigators will use EBOV glycoprotein as a basis for the rational design and production of pan-ebolavirus vaccine candidates to promote broadly protective immune responses that target vulnerable structural sites shared among all ebolaviruses. During the five-year funding period, the team will examine the immune response and protection of mice and guinea pigs to select highly active, engineered immunogens and will test selected immunogens in rodents and nonhuman primates to identify candidates for advanced preclinical development.

Isogenica Ltd., of Cambridge, U.K., signed a new licensing deal with **Takeda Pharmaceutical Co. Ltd.**, of Osaka, Japan. Under the terms, Isogenica has granted Takeda licenses to its family of llamdA VHH single-domain antibody libraries for the discovery, development and commercialization of therapeutic products derived from those libraries. Isogenica is entitled to an up-front and annual license payments. If antibodies are advanced into development, Isogenica is entitled to further license fees, milestones and royalties, though the exact terms were not disclosed.

Lexicon Pharmaceuticals Inc., of The Woodlands, Texas, exercised its option under a collaboration and license agreement with Paris-based **Sanofi SA** to co-promote sotagliflozin, an oral dual inhibitor of sodium-glucose co-transporters 1 and 2 (SGLT-1 and SGLT-2), the pair has been testing for the treatment of type 1 diabetes in the U.S. The opt-in decision was based on positive data from three phase III studies, Intandem1, Intandem2 and Intandem3. Sanofi intends to file applications in the first half of 2018 for the EU and U.S. regulatory reviews of sotagliflozin for the treatment of type 1 diabetes, pending the full readout of phase III data. (See *BioWorld Today*, Sept. 12, 2016.)

M Pharmaceutical Inc., of Cincinnati, said it is changing its name to Callitas Therapeutics Inc. The company is working in the areas of weight management and female health.

Mallinckrodt plc, of Staines-upon-Thames, U.K., said the first patient has been included in an investigational registry intended to help assess the use of Inomax (nitric oxide) gas for inhalation for premature neonates with pulmonary hypertension (PH) vs. term and near-term neonates with the condition. The primary outcome measure for the registry will be a comparison of the incidence of neonates with at least a 25 percent improvement in the Oxygenation Index or Surrogate Oxygenation Index, compared to baseline and summarized by gestation age group. Estimated enrollment for the study is 168 patients, with completion expected by 2022. Inomax is already approved by the FDA for use to improve oxygenation and reduce the need for extracorporeal membrane oxygenation in term and near-term neonates with hypoxic respiratory failure associated with PH in conjunction with ventilator support.

MT Pharma America Inc., of Jersey City, N.J., changed its corporate name to Mitsubishi Tanabe Pharma America Inc. It remains a wholly owned subsidiary of Osaka, Japan-based **Mitsubishi Tanabe Pharma Corp.**

SiO2 Medical Products Inc., of Auburn, Ala., and Rockville, Md.-based **Sanaria Inc.** signed an agreement for the development, manufacture and supply of cryogenic vials for Sanaria's malaria vaccine, Sanaria PfSPZ Vaccine. Financial terms of the deal were not disclosed.

Sirnaomics Inc., of Gaithersburg, Md., said it received FDA orphan drug designation for lead candidate STP-705 in primary sclerosing cholangitis (PSC). The company said it plans to file an IND in PSC in the first half of 2018. STP-705 is a siRNA therapeutic designed to have antifibrotic and anti-inflammatory activity.

In the clinic

Acceleron Pharma Inc., of Cambridge, Mass., said the first patient has been treated in a phase II trial testing ACE-083 in patients with Charcot-Marie-Tooth disease. Part one of the trial is a dose-escalation phase that will enroll up to 18 patients to evaluate safety and increases in muscle volume over a three-month treatment period. Part two, which will enroll 24 patients, will compare ACE-083, which is based on the naturally occurring protein follistatin, to placebo, measuring increases in muscle volume, strength and function, as well as safety over a three-month treatment period.

Acelrx Pharmaceuticals Inc., of Redwood City, Calif., reported results from the phase III IAP312 trial testing Zalviso (sufentanil sublingual tablet system) in 320 patients with moderate to severe acute pain in a hospital setting. A device error occurred in 2.2 percent of the patients, lower than the 5 percent limit specified in the study objectives. A previous version of the Zalviso device produced a 7.9 percent rate of errors in the phase III IAP311 trial, which led to a 2014 complete response letter for the drug/device. On measures of efficacy at the 24-hour, 48-hour and 72-hour time points, 86 percent, 89 percent and 100 percent of patients, respectively, recorded "good" or "excellent" ratings on the patient global assessment. Nurses rated pain control as "good" or "excellent" on the health care professional global assessment 91 percent, 95 percent and 100 percent of the time at the same time points. Acelrx plans to resubmit its NDA to the FDA by the end of 2017. Shares of Acelrx (NASDAQ:ACRX) closed down 12.8 percent to $3.40 on Tuesday. (See *BioWorld Today*, July 29, 2014.)

Earnings

Incyte Corp., of Wilmington, Del., reported second-quarter sales of JAK inhibitor Jakafi (ruxolitinib) totaling $276 million, compared to $208 million for the same period in 2016. Net revenues from sales of Iclusig (ponatinib) were $16 million. Royalties on sales of Jakavi, which was out-licensed to **Novartis AG**, of Basel, Switzerland, outside the U.S., totaled $34 million for the quarter. Incyte reported total revenues of $326 million, up from $246 million for the second quarter of 2016. Net loss for the quarter was $12 million, or 6 cents per share, wider than the loss of 3 cents per share analysts had predicted. As of June 30, the company had cash, equivalents and marketable securities of $609 million. Shares of Incyte (NASDAQ:INCY) closed Tuesday at $128.76, down $4.53.

In the clinic

Amygdala Neurosciences Inc., of Palo Alto, Calif., said it started a phase Ib study testing co-administration of ANS-6637 and alcohol. ANS-6637 is a selective ALDH2 inhibitor designed to prevent abnormal dopamine surges in the brain that drive craving, addiction and relapse. The 48-subject, dose-ranging study will evaluate the safety and tolerability of the co-administration in healthy male moderate drinkers. Up to six dose levels of ANS-6637 (25 mg, 50 mg, 100 mg, 200 mg, 400 mg and 600 mg) will be studied in combination with a multiple-drink alcohol challenge.

Aptinyx Inc., of Evanston Ill., said the first patients have been enrolled in its phase II trial testing NYX-2925, a modulator of the N-methyl-D-aspartate receptor, in patients with neuropathic pain associated with diabetic peripheral neuropathy. The approximately 300-patient trial will compare NYX-2925 at multiple doses to placebo, measuring the reduction in average pain intensity on the Numeric Rating Scale as the primary endpoint. The trial will also measure the effects of NYX-2925 on pain characteristics, sleep interference, psychological state, as well as the safety and tolerability of the drug. NYX-2925 is also being tested at two doses in a separate small phase II trial in 24 patients with fibromyalgia.

CTI Biopharma Corp., of Seattle, said the first patient has been enrolled in its phase II trial testing PAC-203 in approximately 105 patients with primary myelofibrosis who have failed prior treatment with Jakafi (ruxolitinib, Incyte Corp.). The trial will test three dose regimens of PAC-203 – 100 mg once-daily, 100 mg twice-daily (BID) and 200 mg BID – measuring safety and spleen volume reduction at 12 and 24 weeks.

Eyegate Pharmaceuticals Inc., of Waltham, Mass., said the first patient was enrolled in its phase IIb trial testing the Eyegate II Delivery System and EGP-437 combination product for the treatment of pain and inflammation in patients having undergone cataract surgery with implantation of a monofocal posterior chamber intraocular lens. The trial will enroll up to 100 patients, measuring the proportion of subjects with an anterior chamber cell count of zero at day seven and the proportion of subjects with pain score of zero at day one.

Valeant Pharmaceuticals International Inc., of Laval, Quebec, has commercial and manufacturing rights to the EGP-437 combination product through a 2015 licensing agreement. (See *BioWorld Today*, July 13, 2015.)

Flex Pharma Inc., of Boston, started its phase II COMMEND trial testing FLX-787, a co-activator of TRPA1 and TRPV1, in patients who suffer from cramps because of motor neuron disease, focused mainly on patients with amyotrophic lateral sclerosis. The 120-patient trial will measure changes in cramp frequency over the 28-day treatment period in patients taking FLX-787 compared to placebo. Top-line results from the study are expected in the middle of 2018. Flex Pharma plans to start another phase II trial testing FLX-787 in patients with cramps due to Charcot-Marie-Tooth this quarter.

Gensight Biologics SA, of Paris, said enrollment was completed in the phase III RESCUE trial testing its gene therapy, GS-010, in 37 patients with Leber's hereditary optic neuropathy. A second phase III trial, REVERSE, completed enrollment of 36 patients in February. The primary endpoint of both trials is the best corrected visual acuity, measured with the ETDRS chart at 48 weeks post-injection. Top-line results of REVERSE are expected in the second quarter of 2018, and results from RESCUE are due in the third quarter of 2018.

Geron Corp., of Menlo Park, Calif., updated clinical development plans for phase II/III IMerge and phase II IMbark trials, testing telomerase inhibitor imetelstat in lower-risk myelodysplastic syndromes (MDS) and relapsed or refractory myelofibrosis (MF), respectively, being conducted by Janssen Research & Development LLC, a unit of New Brunswick, N.J.-based J**ohnson & Johnson**. For IMerge, part one will be expanded to enroll additional patients in a refined MDS population to confirm the clinical benefit and safety observed from current results. As of May, the 13-patient subset who had received prior treatment with either a hypomethylating agent (HMA) or Revlimid (lenalidomide, Celgene Corp.) and did not have a del(5q) chromosomal abnormality showed an increased durability and rate of transfusion independence compared to the overall trial population. Based on those data, the trial's joint steering committee decided to amend part one of the protocol to enroll about 20 additional patients who are non-del5q and naïve to HMA and lenalidomide treatment in order to increase the experience and confirm the benefit-risk profile of imetelstat dosed at 7.5 mg/kg every four weeks in that refined target patient population. Enrollment into the expanded part one is expected to begin in the fourth quarter. For IMbark, the trial design remains unchanged. Geron expects that the IMbark protocol-specified primary analysis, the completion of which triggers a future continuation decision by Janssen, will begin no later than the third quarter of 2018. Shares of Geron (NASDAQ:GERN) fell 41 cents, or 15.5 percent, to close Tuesday at $2.24, with investors looking at a potential delay for further data. Geron hit a 52-week low last fall after an interim update on the two studies was deemed less than encouraging. (See *BioWorld Today*, Sept. 13, 2016.)

In the clinic

Lumosa Therapeutics Co. Ltd., of Taipei, Taiwan, said it enrolled the first subject for the phase I trial of small-molecule candidate LT-3001 for acute ischemic stroke. Up to 80 healthy volunteers will be enrolled in the double-blind, placebo-controlled, single ascending-dose study to evaluate the safety and pharmacokinetics of LT-3001, results of which will determine the doses for subsequent clinical studies in stroke patients. The trial is expected to be completed in the first quarter of 2018. In nonhuman primate stroke models, LT-3001 showed an apparent wider therapeutic time window and a better safety profile than those reported for recombinant tissue plasminogen activator, or rtPA. LT-3001 is a peptide and small-molecule combination designed to induce thrombolysis and dissolve blood clots while limiting oxidative stress and protecting neurons from endothelial cell damage and reperfusion injury.

Madrigal Pharmaceuticals Inc., of Conshohocken, Pa., said it completed patient enrollment of 125 patients, exceeding its targeted enrollment of 117 patients, in its phase II proof-of-concept study evaluating MGL-3196 for the treatment of nonalcoholic steatohepatitis. MGL-3196 is an oral, once-daily, liver-directed, thyroid hormone receptor beta-selective agonist. Top-line 36-week results, which include a final MRI-PDFF and an end-of-study liver biopsy, are expected in the second quarter of 2018.

Mateon Therapeutics Inc., of South San Francisco, said it completed enrollment of more than 80 patients in the phase II portion of its FOCUS study testing CA4P, its vascular disrupting agent, in combination with Avastin (bevacizumab, Roche Holding AG) and physician's choice chemotherapy for the treatment of platinum-resistant ovarian cancer. The next (second) interim analysis of FOCUS is anticipated in mid-August, the third in September and the fourth and final interim analysis in November. The company expects those analyses to provide preliminary information on objective response rate for 40, 60 and all 80-plus patients, respectively, as well as provide early data on progression-free survival, the primary endpoint of the study. The study's final analysis is scheduled to occur when disease has progressed in 75 percent of enrolled patients.

Protalex Inc., of Florham Park, N.J., said following a planned interim analysis of safety and efficacy data from the second dose cohort, the company is escalating the dose of PRTX-100 in its U.S. phase I/II study of the immunomodulatory candidate in adults with persistent/chronic immune thrombocytopenia. One of the three patients treated in the second dose cohort achieved a protocol-defined platelet response. The open-label, dose-escalating study can enroll up to 36 patients in as many as six cohorts, with each receiving four weekly intravenous doses of PRTX-100 with monitoring for up to 48 weeks. The primary endpoint is a platelet response. Secondary endpoints include safety, immunogenicity and pharmacokinetics.

Proteostasis Therapeutics Inc., of Cambridge, Mass., said it completed dosing of 19 patients as part of the ongoing phase I/II study of PTI-428, its CFTR amplifier, administered with background Orkambi (lumacaftor/ivacaftor, Vertex Pharmaceuticals Inc.) or as the only CFTR modulator therapy in cystic fibrosis subjects over a 14-day period (seven-day dosing followed by a seven-day follow-up period). The trial met its primary safety and pharmacokinetic endpoints, confirming PTI-428's safety, tolerability and lack of clinically meaningful drug-drug interaction with ivacaftor and lumacaftor. Proteostasis is now enrolling patients in the phase II safety and efficacy portion of the study, which explores PTI-428 dosed over a 28-day period. Preliminary data are expected in the fourth quarter.

Spectrum Pharmaceuticals Inc., of Henderson, Nev., said it completed enrollment with 405 patients randomized in the Rolontis (eflapegrastim) phase III ADVANCE pivotal study under an FDA special protocol assessment. The study is evaluating the safety and efficacy of Rolontis in the management of chemotherapy-induced neutropenia in patients with breast cancer. Top-line data are expected early next year. Rolontis is a long-acting granulocyte colony-stimulating factor developed using the Lapscovery platform technology from **Hanmi Pharmaceutical Co. Ltd.**, of South Korea.

TG Therapeutics Inc., of New York, said it reached an agreement with the FDA for a special protocol assessment regarding the design of two phase III trials of TG-1101 (ublituximab), its glycoengineered anti-CD20 monoclonal antibody, for the treatment of relapsing forms of multiple sclerosis (RMS). The program consists of two trials, ULTIMATE I and ULTIMATE II, each of which is a global, randomized, double-blinded, double-dummy, active-controlled study comparing TG-1101 to Aubagio (teriflunomide, Sanofi SA) in subjects with RMS. The primary endpoint for each study is annualized relapse rate following 96 weeks of treatment. Each trial will enroll about 440 subjects, randomized in a 1-to-1 ratio, with about 880 patients to be enrolled across both trials. The first patient is expected to be enrolled before the end of the summer.

Earnings

Lexicon Pharmaceuticals Inc., of The Woodlands, Texas, reported second-quarter U.S. sales of Xermelo (telotristat ethyl), approved in early March for neuroendocrine tumors patients with carcinoid syndrome diarrhea, of $3.6 million. Total revenues for the three-month period were $12.1 million, down from $20.1 million for the same quarter last year, which Lexicon attributed primarily to lower revenues from its collaboration with Paris-based **Sanofi SA**, partially offset by product revenues. Net loss for the quarter was $35.1 million, or 33 cents per share. Analysts had predicted a loss of 44 cents per share. As of June 30, Lexicon had $231.2 million in cash and investments. Shares (NASDAQ:LXRX) closed Tuesday at $16, down 30 cents. (See *BioWorld Today*, March 2, 2017.)

Appointments and advancements

Merrimack Pharmaceuticals Inc., of Cambridge, Mass., appointed Thomas E. Needham Jr. chief business officer.

Neurocrine Biosciences Inc., of San Diego, named Julie Cooke chief people officer, effective September, and appointed her to the management committee.

Oramed Pharmaceuticals Inc., of Jerusalem, named Simon Bruce vice president of medical affairs.

Radius Health Inc., of Waltham, Mass., appointed Jesper Høiland president and CEO.

Relay Therapeutics Inc., of Cambridge, Mass., named Deborah Palestrant vice president of corporate development and strategy.

Sucampo Pharmaceuticals Inc., of Rockville, Md., added Karen Smith to its board.

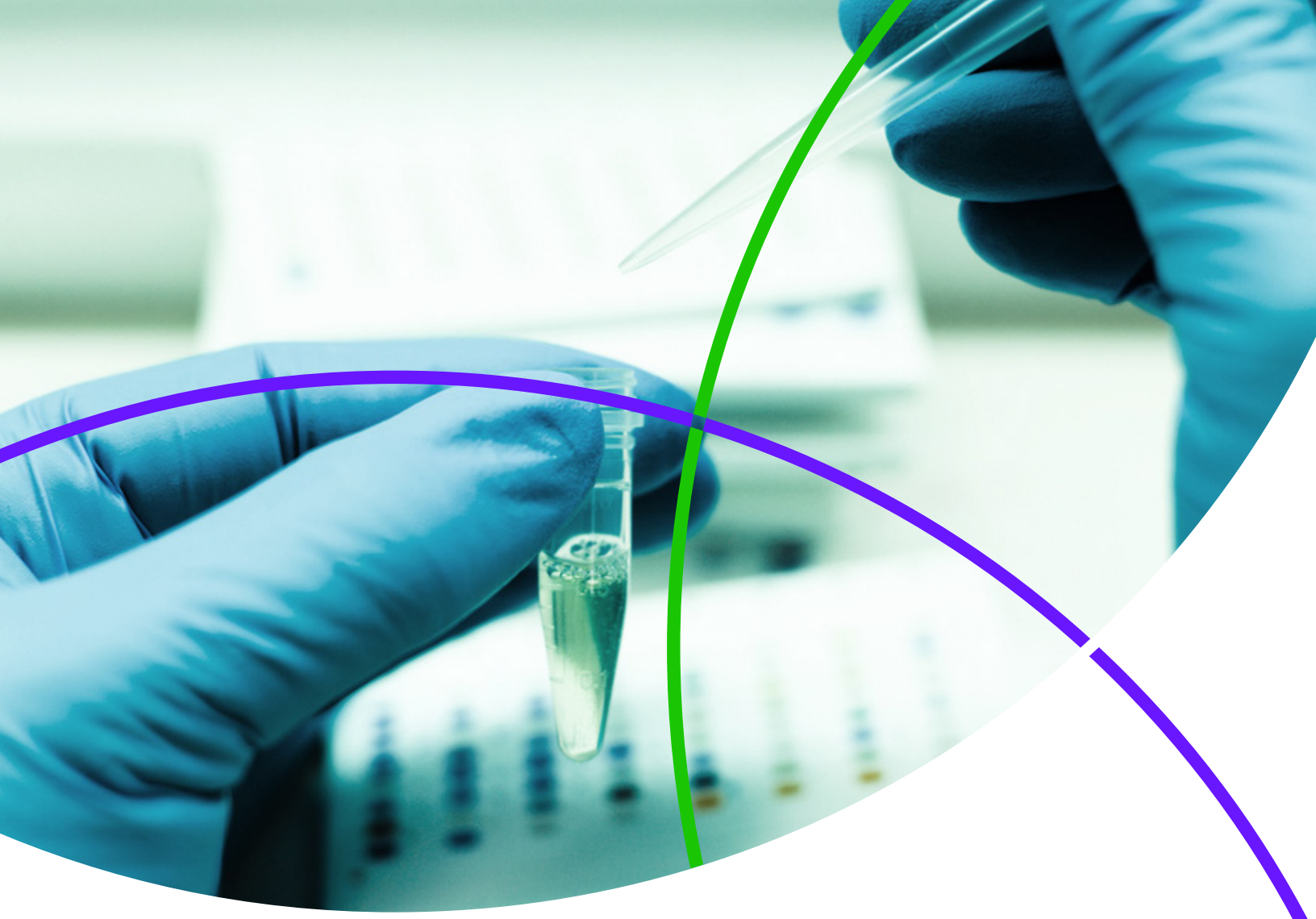
Sutrovax Inc., of Foster City, Calif., added Moncef Slaoui to its board.

Tessa Therapeutics Pte Ltd., of Singapore, appointed Jennifer Butler chief commercial officer.

Vaxil Bio Ltd., of Toronto, appointed Terry Plasse chief medical officer.

In the clinic

Viacyte Inc., of San Diego, said the first patients have been implanted with the PEC-Direct product candidate, an islet cell replacement therapy in development as a functional cure for patients with type 1 diabetes who are at high risk for acute life-threatening complications. The goal of the open-label trial is to evaluate PEC-Direct for safety and definitive evidence of efficacy. The first cohort of patients is receiving multiple small-format cell-filled devices called sentinels in order to evaluate safety and implant viability. Those sentinel units will be removed at specific time points and examined histologically to provide early insight into the progression of engraftment and maturation into pancreatic islet cells including insulin-producing beta cells. A second cohort of up to 40 patients is expected to begin enrolling later this year to evaluate both safety and efficacy. The primary efficacy measurement will be the clinically relevant production of insulin, as measured by the insulin biomarker C-peptide, in a patient population that has little to no ability to produce endogenous insulin at the time of enrollment. PEC-Direct is designed to deliver stem cell-derived pancreatic progenitor cells, called PEC-01 cells, in a device designed to allow direct vascularization of the cells in the device.



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