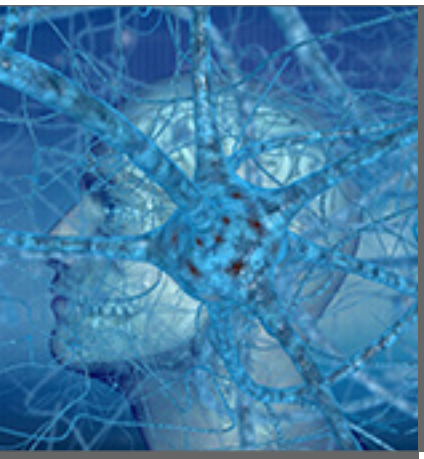
BioWorld

The news source of record covering the development of innovative human therapies
Actionable Intelligence • Incisive Analysis

Clarivate Analytics

March 28, 2019
Volume 30, No. 60



Secondary offering in MS: Novartis' Mayzent cleared with cross-spectrum label

By Randy Osborne, Staff Writer

Trial designer and steering committee member Bruce Cree told *BioWorld* that the FDA made "a very wise decision" in assigning the broad label to Novartis AG's oral sphingosine 1-phosphate (S1P) receptor modulator Mayzent (siponimod) in multiple sclerosis (MS), "covering the continuum from clinically isolated syndrome all the way into active secondary progressive MS [SPMS]."

Mayzent was given the nod for adults with relapsing forms of MS that include SPMS – where it's the

See Novartis, page 3

Drug price reforms advance in U.S. House despite debate on 'nuclear' provisions

By Mari Serebrov, Regulatory Editor

When the marketplace doesn't work anymore, Congress and government have to step in. This is one of those times, Rep. Frank Pallone (D-N.J.) said Wednesday as the House Energy and Commerce Subcommittee on Health began to mark up six bills aimed at increasing competition in the prescription drug market and lowering prices.

There was bipartisan agreement on the need to step in, as well as on four of the bills being considered. But what some considered "nuclear" provisions in legislation that would stop pay-for-delay patent settlements and require innovators to provide samples to would-be competitors had Republicans worrying about the unintended consequences, while most of the Democrats on the panel shrugged off the what-ifs and constitutional questions in their push to advance the bills to the full committee.

See Reforms, page 4

Expert pitches controversial approach to tackle drug-resistant infections: government control

By Nuala Moran, Staff Writer

LONDON – The author of an influential U.K. government review on tackling drug-resistant infections globally has decried the vapid response of the pharma industry and suggested there should be moves to form a public utility-like

See AMR, page 5

Lilly deepens commitment to immunology with Immunext deal

By Lee Landenberger, Staff Writer

Eli Lilly and Co.'s new partnering deal with privately-held Immunext Inc. to research and globally license an antibody to treat certain autoimmune diseases is another sign that Lilly is deepening its commitment to the immunology space.

See Immunext, page 7

Big 'diff' separating drugs from FMT; FDA expected to offer guidance clarity

By Randy Osborne, Staff Writer

With further FDA guidance yet to come on how fecal microbiota transplants (FMTs) to treat *Clostridium difficile* (*C. diff*) infections will be regulated, investors continue to weigh the odds of drugs vs. the controversial but popular therapy.

C. diff can cause symptoms ranging from diarrhea to life-threatening inflammation of the colon, and illness from the bug most commonly affects older adults in hospitals or in long-term care facilities, typically occurring after use of antibiotics, according to the Mayo Clinic. But "studies show increasing rates of *C. diff* infection among people traditionally not considered high risk, such as younger and healthy individuals without a history of antibiotic use or exposure to health care facilities," researchers add. Each year in the U.S.,

See FMT, page 6

The BioWorld Biome

Undruggable, for now

New target surfaces for KRAS-driven cancers

By Anette Breindl, Senior Science Editor

By investigating the "surfaceome," the group of proteins that move to the cell surface in response to KRAS signaling, researchers have identified a protein, Syndecan-1, that is critical for KRAS-driven cancer cells to obtain nutrients from the environment.

See KRAS, page 8

BIO Europe Spring 2019

Transformation and translation: Evotec's Lanthaler urges biopharma to rethink its model

By Jennifer Boggs, Managing Editor

VIENNA – After nearly three days of partnering meetings and sessions touting the latest therapeutic advances such as cell and gene therapy and the microbiome, along with presentations depicting the unprecedented level

See BIO, page 9

Appointments and advancements

Abingworth LLP, of London, appointed Bali Muralidhar partner.

Akorn Inc., of Lake Forest, Ill., appointed Dandy Dorado-Boladeres executive vice president of global quality.

Albireo Pharma Inc., of Boston, appointed Pamela Stephenson chief commercial officer.

Algernon Pharmaceuticals Inc., of Vancouver, British Columbia, appointed Arun Sanyal to its medical and scientific advisory board.

Aprea Therapeutics AB, of Solna, Sweden, appointed Eyal C. Attar senior vice president and chief medical officer.

Ascension Healthcare plc, of London, appointed Mark Turrell national accounts and sales director.

Athenex Inc., of Buffalo, N.Y., appointed John Moore Vierling and Stephanie Davis to its board.

Axcella Health Inc., of Cambridge, Mass., appointed Shreeram Aradhye executive vice president, chief development officer.

Biocorrx Inc., of Anaheim, Calif., appointed Balbir S. Brar senior vice president of drug development.

Cognition Therapeutics Inc., of Pittsburgh, appointed Lisa Ricciardi to its board.

Dermavant Sciences Inc., of Phoenix, a subsidiary of Roivant Sciences Ltd., appointed Cyril Allouche chief financial officer.

Enterprise Therapeutics Ltd., of Brighton, U.K., appointed Amit D. Munshi non-executive chair of its board.

Forma Therapeutics Inc., of Watertown, Mass., appointed Frank D. Lee CEO. Founder and former CEO Steve Tregay will serve as senior advisor to the CEO.

Imara Inc., of Cambridge, Mass., appointed Willem H. Scheele chief medical officer.

Interna Technologies BV, of Utrecht, the Netherlands, appointed Andrea van Elsas to its scientific advisory board.

Intra-Cellular Therapies Inc., of New York, appointed John A. Bardi senior vice president for market access, policy and government affairs.

Iteos Therapeutics SA, of Gosselies, Belgium, appointed Joanne Jenkins Lager chief medical officer, effective April 1.

Menlo Therapeutics Inc., of Redwood City, Calif., appointed Elisabeth Sandoval to its board.

Mesoblast Ltd., of Melbourne, Australia, appointed Joseph R. Swedish non-executive chair of its board.

Mirum Pharmaceuticals Inc., of San Diego, appointed Chris Peetz CEO. Former CEO Mike Grey will serve as executive chairman of its board.

Oasmia Pharmaceutical AB, of Uppsala, Sweden, appointed Joakim Lindén acting chief financial officer.

Ocular Therapeutix Inc., of Bedford, Mass., appointed Leslie J. Williams to its board.

Ovid Therapeutics Inc., of New York, appointed Thomas Perone senior vice president, general counsel and corporate secretary.

Recro Pharma Inc., of Malvern, Pa., appointed Arnaud Ajdler to its board.

Rubius Therapeutics Inc., of Cambridge, Mass., appointed Natalie Holles to its board and Greg Whitehead senior vice president and chief quality officer.

Sienna Biopharmaceuticals Inc., of Westlake Village, Calif., appointed Alexander Azoy chief financial officer and Sean Andrews vice president, investor relations.

BioWorld

BioWorld (ISSN# 1541-0595) is published every business day by Clarivate Analytics.

Opinions expressed are not necessarily those of this publication. Mention of products or services does not constitute endorsement.

Our newsroom

Lynn Yoffee (News Director), Jennifer Boggs (Managing Editor), Peter Winter (*BioWorld Insight* Editor), Michael Fitzhugh (News Editor), Anette Breindl (Senior Science Editor), Mari Serebrov (Regulatory Editor), Amanda Lanier (Managing Editor), Karen Pihl-Carey (Analyst), Ann Marie Griffith (Production Editor)

Staff writers: Randy Osborne, Shannon Ellis, John Fox, Nuala Moran, Brian Orelli, Alfred Romann, Tamra Sami, Cormac Sheridan

Practical information

For sales inquiries: https://clarivate.com/products/bioworld/.
In North America, call: 1-855-260-5607. Outside of the U.S. and Canada, call +44-203-684-1797.

For customer service support: https://support.clarivate.com/LifeSciences.
In North America, call: 1-800-336-4474. Outside of the U.S. and Canada, call: +44-203-684-1796.

For ad rates and information, contact Adam Lubas at (929) 246-3800, or email Adam.Lubas@Clarivate.com.

For photocopy rights or reprints, contact Adam Lubas at (929) 246-3800, or email Adam.Lubas@Clarivate.com.

Send all press releases and related information to newsdesk@bioworld.com.

Business office

John Borgman (Director of Commercial Competitive Intelligence), Donald Johnston (Senior Marketing Communication Director, Life Sciences)

Contact us

Jennifer Boggs, (770) 880-3631 | John Borgman, (831) 462 2510 | Anette Breindl, (770) 810-3134 | Michael Fitzhugh, (770) 810-3064 | Donald Johnston, (678) 641-0970 | Nuala Moran, 44-7778-868-579 | Randy Osborne, (770) 810-3139 | Mari Serebrov, (770) 810-3141 | Cormac Sheridan, 353-87-6864323 | Peter Winter, (770) 810-3142 | Lynn Yoffee, (434) 964-4011

Novartis

Continued from page 1

first and only therapy – as well as relapsing remitting disease. "There really is only one other drug that has SPMS mentioned in its indication and that's a drug we no longer use in treatment for MS patients called mitoxantrone," which has "fallen by the wayside because of its toxicity profile," said Cree, clinical research director in MS at the University of California San Francisco School of Medicine. SPMS afflicts about 40 percent of patients, he said, though "different studies will give different point estimates. A lot of it has to do with where you decide to draw the cutoff between relapsing MS and secondary progression." Figuring out which patients are "beginning to insidiously worsen" is tricky, he added, and "it's been, at least in the U.S., in some ways discouraged because it takes treatment options away from patients."

Basel, Switzerland-based Novartis won Mayzent's approval based on the phase III trial called Expand, the largest-ever controlled clinical experiment of SPMS patients, which proved that the treatment significantly reduced the risk of disease progression, including impact on physical disability and cognitive decline. Patients enrolled in Expand represented the typical SPMS population. At the start of the study, patients had a mean age of 48 years and had been living with MS for about 16 years. More than half chalked a median Expanded Disability Status Scale score of 6 and relied on a walking aid. Mayzent showed it can significantly reduce the risk of three-month confirmed disability progression (the primary endpoint, with a 21 percent drop vs. placebo, p=0.013, and a 33 percent reduction vs. placebo in patients with relapse activity in the two years prior to screening, p=0.0100). Under the terms of the marketing clearance, patients on Mayzent won't require a first-dose observation (i.e., cardiac monitoring when they start on the drug) unless they have pre-existing heart conditions. (See *BioWorld*, Aug. 26, 2016.)

Jefferies analyst Peter Welford called the Mayzent approval "widely expected" and pointed to the SPMS label as especially important. In a report, he cheered the compound's "much less onerous first-dose monitoring requirements," also called first-dose observation (FDO), as compared to Novartis' Gilenya (fingolimod), already entrenched in the MS market. He predicted $1.25 billion in worldwide peak Mayzent sales. "We forecast Gilenya U.S. generics from around mid-2023, reflecting the midpoint of 'worst case' August 2019 entry if [Novartis'] dosage '405 patent is ruled invalid and perhaps 'best case' December 2027 when this patent expires," Welford wrote.

Cree said the FDO requirement with Gilenya is "something that's been worked out pretty well over the years. Many patients can have the FDO conducted in the privacy of their home. If the FDA had decided everybody needed an FDO, we would just do it," he added, calling the procedure "more of a nuisance for providers and patients" than anything else. "It's nice to see the FDA is willing to consider the data as is, rather than simply say, 'OK, this is what we did for Gilenya so this is what we have to do with Mayzent.'" Such is an indication of "how carefully considered the FDA is these days with neurology indications," he said.

No 'rush,' analyst says

Reports of Mayzent's $88,500 annual cost cited by Welford – about 11.5 percent less than Gilenya – brought comparisons as well to Basel, Switzerland-based Roche Holding AG's MS therapy Ocrevus (ocrelizumab), which targets CD20-expressing B cells and goes for about $65,000 per year, a price tag that led the U.K.'s National Institute for Health and Care Coverage to recommend against coverage last September. Ocrevus was approved in the EU in January 2018. It won the go-ahead from the FDA two years ago for relapsing forms of MS and primary progressive MS, and was the first drug to gain the marketing nod in the latter indication.

The regulatory win by Novartis comes on the heels of the filing this week by Celgene Corp., of Summit, N.J., of the NDA for S1P receptor modulator ozanimod in relapsing MS. Ozanimod is under consideration by European gatekeepers, too. Ozanimod "also has certain advantages," Cree said, including a good safety profile, though the compound "at least at this point has only been investigated in patients with relapsing MS. The FDO data for ozanimod looks very clean as well." Last year the FDA issued a refuse to file letter for ozanimod, the crown jewel in Celgene's $7.2 billion acquisition of Receptos Inc., which had a five-year consensus sales forecast of $1.63 billion, according to Cortellis Competitive Intelligence. (See *BioWorld*, March 1, 2018.)

Guggenheim analyst Yatin Suneja said the approval of Mayzent likely will have an effect on Cambridge, Mass.-based Biogen Inc.'s MS sales, "given off-label use of Tecfidera [dimethyl fumarate] and Tysabri [natalizumab] in SPMS," adding in a report that the FDA go-ahead "could potentially raise the commercial bar" for ozanimod. "While the majority (64 percent) of Biogen's revenue comes from their MS franchise ($8.6 billion, down 4.3 percent year over year in 2018), we view the impact of Mayzent on Biogen as moderate given that MS patients routinely switch drug classes (e.g., CD20s, interferons, S1P1s, etc.) as they develop a tolerance to a certain type of drug, reducing its efficacy on their symptoms, and that a S1P1 modulator (Gilenya) already exists on the market, so this is a drug type that patients have already had access to in the past, and hence will not generate a 'rush' of new patients seeking to switch to a new class of therapy," in Suneja's view.

Shares of Novartis (NYSE:NVS) closed Wednesday at $95.11, up 9 cents. Biogen's stock (NASDAQ:BIIB) ended at $229.95, down $2.96. ♦

Appointments and advancements

Sygnature Discovery Ltd., of Nottingham, U.K., appointed to its drug metabolism and pharmacokinetics (DMPK) department: Stuart Best, associate director of DMPK; Hayley Butler, principal scientist; Daniel Weston, associate director; and Bodo Spöri, senior director of business development.

Synspira Inc., of Framingham, Mass., appointed Robert Gallotto president and CEO and to its board.

Verona Pharma plc, of London, appointed Martin Edwards to its board, effective April 1.

Reforms

Continued from page 1

The debate over the Protecting Consumer Access to Generic Drugs Act, H.R. 1499, centered on a provision that would deem as anticompetitive all patent settlements involving any kind of reverse payment since the Supreme Court's 2013 ruling in *FTC v. Actavis*. In that ruling, the court refused to draw a bright line on the legality of such agreements. Rather than presuming the agreements are anticompetitive on their face, the Supreme Court told lower courts they have to dive into the details of each challenged settlement. (See *BioWorld Today*, June 18, 2013.)

Subsequently, "*Actavis* has not put an end to anticompetitive behavior in the marketplace," Pallone said. He noted that while pay-for-delay settlements have decreased since that June 17, 2013, decision, the number of other kinds of settlements has dramatically increased.

Those settlements may "bring an additional product to market sooner, but they still insulate the branded drug from true competition," allowing companies to continue selling the branded drug at artificially high prices, Pallone said. Such practices pervert the intent of the Hatch-Waxman Act, which opened the door to robust generic competition, and twists its incentives to extend drug monopolies, he added.

"We need to pass this legislation to clarify the rules of the road, to deter detrimental pay-for-delay settlement agreements, to prevent monopolization and bring back competition," Pallone said of the bill sponsored by Rep. Bobby Rush (D-Ill.).

Republicans had no issue with those sentiments, but they questioned the constitutionality of retroactively making a legal agreement illegal. Rep. Morgan Griffith (R-Va.) also warned that it could lead to brand companies nullifying the deals and forcing generics, which had relied on those agreements, off the market.

Experts testifying earlier this month during a subcommittee hearing on the legislation expressed similar concerns. Many companies have made irrevocable decisions based on agreements that were legal at the time they were signed, Jeff Kushan, a partner at Sidley Austin LLP, said as he warned the subcommittee that voiding the agreements would have consequences. (See *BioWorld*, March 14, 2019.)

At the markup, Rep. John Sarbanes (D-Md.) defended the retroactive provision, saying it's simply meant to give the FTC the authority to review existing agreements to see whether they're anticompetitive and to take action if they are. Pallone added that the existing agreements are what's delaying generic competition today.

An amendment, offered by Rep. Fred Upton (R-Mich.) to remove the retroactive language, failed on party lines. However, several Democrats, including Sarbanes and Rush, agreed that the concerns about the retroactive provision need to be addressed before the markup in the full committee.

Going nuclear

The other debate Wednesday was over the penalties provision in the House version of the Creating and Restoring Equal Access to Equivalent Samples (CREATES) Act, H.R. 965, which would require the manufacturers of reference drugs to supply samples, at market price, to would-be generic and biosimilar competitors.

> *"I don't care if we go nuclear. The American people are going into bankruptcy because of the cost of their drugs.*
>
> Rep. Debbie Dingell (D-Mich.)

The Senate version of the bill would set penalties based on the greater of profits or treble damages. The House version calls for penalties that could be equal to the revenue the reference drug generated in a period beginning 31 days after the sample request was received and ending the date the samples were delivered.

Rep. Peter Welch (D-Vt.), one of the bill's sponsors, said he based the penalties on advice from the FDA and FTC. The idea is to create a clear deterrent, so monetary penalties aren't just considered the price of doing business.

Sarbanes pointed out that the revenue language is a cap. The courts would have discretion in setting penalties in individual instances. He also reminded his colleagues that profits can be manipulated, whereas revenue is a specific number.

Saying that Republicans on the subcommittee agreed with the underlying principle of the CREATES Act, Rep. Greg Gianforte (R-Mont.) offered an amendment to align the penalties with the common legal practice of the greater of profits or treble damages. Basing the penalties on revenue would be unprecedented, he said, and could stifle innovation by encouraging frivolous lawsuits.

It also could present problems if a company were sued by several competitors. And if a company had only one drug on the market, a penalty based on revenue could wipe it out, Gianforte added.

"If it's one company with one drug that's ripping off consumers, no sympathy from me on that," Welch responded.

Citing case law in which penalties are based on profits or treble damages, Rep. Greg Walden (R-Ore.) said, "Going to revenues is the equivalent of going nuclear, and not tactically."

"I don't care if we go nuclear," Rep. Debbie Dingell (D-Mich.) said. "The American people are going into bankruptcy because of the cost of their drugs. . . . I will go nuclear."

Although the amendment failed on a voice vote, the penalty issue likely will surface again. If the Senate sticks with its version of the bill, the two chambers would be forced to reconcile their differences for CREATES to become law.

Moving on

The other drug-related bills the subcommittee advanced Wednesday include:

- the Payment Commission Data Act, H.R. 1781, which would provide the Medicare Payment Advisory Commission and the Medicaid and CHIP Payment and Access Commission with drug pricing and rebate data under Medicaid and Medicare Parts B and D so they can use the information in their analyses;
- the Bringing Low-cost Options and Competition while Keeping Incentives for New Generics (BLOCKING) Act, H.R. 938, which would discourage the "parking" of 180-day

See Reforms, page 7

AMR

Continued from page 1

company to buy up relevant assets and fill the gap.

Jim O'Neill, former chief economist at Goldman Sachs, former government treasury minister and now chair of the London-based think tank Chatham House, railed at "the amount of nonsense that gets spewed out of pharma companies about their commitment," saying "if the industry delivered only 10 percent of what it promised, things would be better."

Since he filed his report in May 2016, Novartis AG and Sanofi SA have transferred antimicrobial R&D to third parties, leaving only three large pharma companies active in the field.

And there has been little evident progress with the industry's Jan 2016 AMR (antimicrobial resistance) declaration, in which, among other measures, pharma committed to take action by increasing investment in R&D and making improvements in how research is conducted. (See *BioWorld Today*, Jan. 21, 2016.)

"Some more radical means of changing the risk/reward [profile] need to be further explored," O'Neill said.

For him, the modern pharma business is too rigid, and it is impossible for antibiotic programs to beat the return on investment rules. But noted O'Neill, many other products they develop depend on antibiotics being available and to carry on working. If there are high levels of hospital-acquired infections, there is not a safe environment for other therapies to be used effectively.

Cancer treatments, for example, are failing not because oncology drugs do not work, but because patients with weakened immune systems succumb to antibiotic-resistant infections.

Given this, pharma companies should think about spreading the costs of producing antibiotics across their business lines, because they need them to underpin other products, O'Neill said. "If [pharma companies] don't change their business structure, policymakers and society will have to force them."

The U.K. government AMR review pushed the subject up the agenda and it was discussed at three G20 meetings. But said O'Neill, "Unless you follow up by doing something, it's empty words."

For example, one mechanism he suggested, play or pay, in which companies that do not invest in antimicrobial research would pay a levy to fund those that do, has not been taken up, despite, said O'Neill, pharma companies he has spoken to appearing to be receptive.

A second suggestion, of incentivizing research by paying $1 billion to $1.5 billion market entry awards, payable on approval of a product, also died on the vine.

Diagnostics lag, too

There has been a similar lack of activity around the recommendation that development of new diagnostics should be incentivized, and that the U.K. should set a target

> *"Some more radical means of changing the risk/reward [profile] need to be further explored.*
>
> Jim O'Neill, former chief economist at Goldman Sachs, former government treasury minister and now chair of Chatham House

that by 2020 antibiotics will be prescribed only against a diagnosis of a specific infection.

"Getting new drugs is not as important as reducing inappropriate demand. Most important is the growing role of diagnostics in forcing medical practitioners to apply some objectivity," said O'Neill. "Without that, even if we get new drugs, in 10 years' time we will be in the same position in terms of resistance."

Around four weeks into conducting the U.K. government AMR review, and as he got a feel for the subject, O'Neill said it seemed evident to him that the problems could be overcome by creating a government-owned entity that was not seeking private sector returns.

"I was told I was naïve, so I backed off," O'Neill said. However, he has become more and frustrated by the lack of progress. Although he does not have a precise model to propose, O'Neill noted early stage programs are undervalued, and with pharma divesting and disinterested, it would be possible to acquire the resources as the basis of an antibiotics utility.

So, problem not solved, but O'Neill did have progress to report on other recommendations, notably in the creation of a $2 billion global innovation fund.

With backing from public and philanthropic funders, the biotech industry has stepped up and is applying the money to populate the discovery end of the antibiotic pipeline.

However, noted Tim Jinks, head of the drug-resistant infections program at the Wellcome Trust, which has made substantial contributions to funding antimicrobial R&D, these companies lack the capacity to get products to market, and with only three large pharmas left with an interest in the area, there is increasingly nowhere for programs to go when drugs complete phase II.

"Science alone can't solve the problem, an economic overhaul is necessary," Jinks said. While small biotechs have become engines of antibiotic discovery, this only goes so far in dealing with the AMR. "We are relying on the depths and capabilities of big pharma. But for them, it's not an attractive business proposition."

Echoing this, Anand Anandkumar, CEO of Bugworks, of Bangalore, India, a small biotech developing a broad-spectrum antibiotic against gram-negative bacteria, said the innovation issues are being solved by small companies.

"The push mechanism has worked. We need pharma to stay at the front end and pull," Anandkumar said. ♦

FMT

Continued from page 1

about a half million people get infected, and recent years have seen the condition become more frequent, severe and harder to treat.

Enter the FMT approach, which transfers healthy, donated fecal matter stored in stool banks to ill patients as a way of rejuvenating microbes in the gut. U.S. regulators have been wrestling with the question of whether the treatment constitutes drug therapy or some other kind of product. Meanwhile, three biotech firms – Roseville, Minn.-based Rebiotix Inc., Seres Therapeutics Inc., of Cambridge, Mass., and Vedanta Biosciences Inc., also of Cambridge – are steering the Microbiome Therapeutic Innovation Group (MTIG), an independent 501(c)(6) outfit for the purpose of "leading the research and development of FDA-approved microbiome therapeutics and microbiome-based products to address unmet medical needs, improve clinical outcomes, and reduce health care costs." According to the group's website, "through a collective voice, the MTIG membership works together to enhance the regulatory, investment, and commercial environment to accelerate microbiome therapeutic drug product development and expand availability of life-changing and life-saving FDA-approved microbiome therapies to patients." MTIG said it's "committed to working with stakeholders who share in our mission and seek to collaborate with patients, patient advocates, professional societies/organizations/public health officials, scientists, government policymakers, health care providers and payers who seek tangible policy and regulatory solutions to issues in the emerging microbiome arena."

U.S. regulators' word on FMT was published in the *Federal Register* in 2016, and was meant to provide "members of the medical and scientific community and other interested persons with notice that, when finalized, we intend to exercise enforcement discretion under limited conditions, regarding the IND requirements for the use of FMT to treat *C. difficile* infection not responding to standard therapies." Gatekeepers intended the guidance to replace an opinion dated March 2014, and said that when finalized, it will supersede guidance from July 2013.

"Centralized manufacturing in stool banks presents safety concerns related to the use of FMT from a limited number of donors administered to multiple patients," the FDA said. "These safety concerns include transmission of infectious agents and potentially other unidentified risks related to changes in the microbiome. Therefore, FDA does not intend to extend enforcement discretion with respect to the IND requirements applicable to stool banks distributing FMT products. The sponsor's compliance with the IND requirements will help to ensure that the stool donor and stool are appropriately qualified by screening and testing, and that centralized processing of FMT adheres to appropriate current good manufacturing conditions."

The agency went on to say that a stool bank sponsor "may identify as the investigator on the IND an individual who is within or affiliated with the stool bank," and "health care providers who receive FMT product from the stool bank may be sub-investigators. Sponsors may request waiver of certain IND regulations applicable to investigators. IND sponsors requesting a waiver of certain investigator responsibilities may also include a request for waiver of those regulations related to sub-investigators."

Stool banks in crosshairs

What will the FDA rule next? That's anybody's guess, and as the wait goes on, the likes of Seres, with *C. diff* drug candidate SER-109, though given breakthrough therapy status and orphan drug designation by the agency, has been facing hurdles in enrolling its phase III study called Ecospor because of FMT use. In its earnings-report press release, Seres nodded to the "uncontrolled practice" of FMT. Seres describes lead candidate SER-109 as an orally administered capsule that may repair the underlying cause of recurrent *C. diff*: dysbiosis, a disrupted state of the microbiome. The compound was developed using computational design insights suggesting that a complex spore ecology includes keystone organisms that could address the underlying dysbiosis and return the microbiome to a healthy state, Seres said, calling the treatment "an ecology of bacterial spores, enriched and purified" from healthy, screened human donors. Ecospor is shooting for 320 participants in the Ecospor experiment, targeting completion in June of this year.

Wainwright analyst Vernon Bernardino likes Seres' candidate. "We expect SER-109 to come out on top when an FDA decision for a regulatory pathway for FMT comes to a head," he wrote in a March 11 report, acknowledging "the competitive threat posed by the potential for FMT to remain in widespread use." He allowed, too, that his firm expects the phase III study in *C. diff* by Rebiotix with FMT-based, enema-delivered RBX-2660, to turn out positive. "However, in our view, SER-109 remains the leading microbiome-directed drug candidate capable of navigating the regulatory pathway for approval," he said. FMT has proven capable of chalking up cure rates nearing 90 percent, but "establishing a regulatory pathway for mass scale use of FMT is currently unfavorable, as the identity of bacterial species, FMT's potency, purity, and safety are difficult to standardize nor been evaluated in large, well-controlled clinical trials."

Seres' expertise gained a strong vote of confidence recently by way of a deal with Astrazeneca plc, of London. The pact will focus on advancing mechanistic understanding of the microbiome in boosting the efficacy of cancer immunotherapy, and the pair will probe potential synergy with Astrazeneca's compounds. Preclinical and early clinical data suggest that the gut microbiome's health may have an impact on response to checkpoint inhibitors. Seres' microbiome therapeutic SER-401 may be studied in combination with Astrazeneca drugs targeting various cancers, the companies said.

Rebiotix, for its part, boasts the MRT, or Microbiome Restoration Therapy, drug platform, which the company said uses controlled manufacturing processes and quality control parameters to assess the impact of human-derived microbiota therapies on health and disease. Specifically, the approach

See FMT, page 8

Immunext

Continued from page 1

A year ago, Lilly acquired Armo Biosciences Inc. and in January it did the same with Loxo Oncology Inc., both dedicated immunology companies. Today's deal includes an upfront payment of $40 million to Immunext and the possibility of receiving about $565 million in development and commercialization milestones, plus tiered royalties ranging from the mid-single to low-double digits on product sales. Lilly gets an exclusive, worldwide license to develop and commercialize the drug target. (See *BioWorld*, May 11, 2018 and Jan. 8, 2019.)

Lebanon, N.H.-based Immunext specializes in developing immunotherapy compounds for cancer and autoimmune diseases.

Lilly and Immunext plan a three-year study with this collaboration. Specific details about the milestones are confidential, said Immunext spokeswoman Gayle Gosselin, who added, "Jay Rothstein, chief science officer of Immunext, has been working on this target for many years. Immunext will continue its work on other immuno-metabolic targets."

Jay Rothstein, chief science officer of Immunext

Validation studies, ex vivo and with small animals, according to Immunext, show the target to operate independently and upstream of known immune checkpoint regulators. It also asserts that therapies targeting a transporter target are shown to regulate immune cell metabolism.

Rothstein said the collaboration will "bring forward a first-in-pathway antibody that specifically targets the metabolism of lymphocytes to reprogram rather than suppress the immune system."

Regulating the metabolism of immune cells is a promising approach to treating these diseases, according to Ajay Birula, Lilly's vice president of immunology.

The $8 billion Loxo deal brought Lilly targeted cancer assets that include Vitrakvi (larotrectinib), approved in December to treat adult and pediatric patients with solid tumors that have a neurotrophic receptor tyrosine kinase gene fusion without an acquired resistance mutation, along with other promising candidates in Loxo's pipeline.

In May 2018, Lilly bought Armo for about $1.6 billion in an all-cash transaction bolstering its immuno-oncology program through the addition of Armo's lead candidate, pegilodecakin, a pegylated interleukin-10. Pegilodecakin, also known as AM-0010, has demonstrated clinical benefit as a single agent and in combination with both chemotherapy and checkpoint inhibitors across several tumor types, Lilly said. It's currently being studied in a phase III trial in pancreatic cancer, as well as earlier stage trials in lung and renal cell cancer, melanoma and other solid tumor types.

The compound is a long-acting form of human IL-10, a naturally occurring immune cell growth factor that's critical for the proliferation and cytotoxic activity of tumor-specific CD8+ T cells. Armo's scientists increased the size of IL-10 by linking it to polyethylene glycol to prolong its circulation time in the body to maximize its activation of antitumor CD8+ T cells. So far, it has been studied in more than 350 people with cancer across more that 14 tumor types. In a phase I/Ib trial, the company has observed objective tumor responses, including partial and complete responses.

Immunext's partners in other deals include Janssen Biotech Inc., Roche Holding AG and Sanofi SA. It has a clinical-stage program with V-region immunoglobulin-containing suppressor of T-cell activation (VISTA), a negative checkpoint regulator for cancer immunotherapy, along with preclinical programs to develop antibodies targeting immune-metabolic proteins. In late 2016, the company cut a deal with F. Hoffmann-La Roche Ltd. and Hoffmann-La Roche Inc. to develop therapeutics to modulate the immune system in treating autoimmune diseases and inflammation. Immunext granted Roche worldwide, exclusive license to develop and commercialize therapeutics to agonize the VISTA signaling pathway. In that deal, potential payments to Immunext include those for achieving certain preclinical, development and commercial milestones, which could total more than $400 million. It is also eligible to receive tiered royalties up to double digits on sales of products. Roche is responsible for clinical development and commercialization of all products under the agreement.

Two months later, Immunext and Sanofi agreed to develop an antibody that could treat a range of autoimmune diseases, including lupus and multiple sclerosis. Immunext granted Sanofi an exclusive worldwide license to develop and commercialize a CD40L monoclonal antibody, INX-021, in preclinical development that suppresses the activity of a cellular pathway. The two companies planned to begin a research collaboration to support clinical trials.

Potential milestone payments to Immunext could total $500 million. It could also receive tiered royalties up to double digits on product sales.

Lilly stock (NYSE:LLY) closed Wednesday at $128.77 per share, down 1.72 percent. ♦

Reforms

Continued from page 4

exclusivity by a first generic applicant;

- the Purple Book Continuity Act, H.R. 1520, which would require the online Purple Book to be in a searchable format and direct the FDA to consider the types of patents that should be listed for biologics and biosimilars included in the "book;"
- the Orange Book Transparency Act, H.R. 1503, which would ensure that the Orange Book is up-to-date by requiring manufacturers to share complete and timely information with the FDA. It also would require that patents invalidated by the courts or the Patent Trial and Appeal Board be removed promptly, and it directs the FDA to reconsider the types of patents that should be listed in the Orange Book. ♦

KRAS

Continued from page 1

The process controlled by Syndecan-1, called macropinocytosis, is not specific to KRAS-driven tumors, or to tumor cells at all. It is a specialized form of endocytosis, the process by which cells take up various substances through pinching off parts of their membrane into endocytic vesicles.

Immune cells, for example, use macropinocytosis to take up antigens. Tumor cells, including KRAS-driven tumor cells, use it to supply themselves with nutrients including amino acids.

Though it is not unique to tumor cells, the dependence on macropinocytosis is "a critical vulnerability" for tumor cells, Giulio Draetta told *BioWorld*, because they badly need nutrients to fuel their growth.

Draetta is the chief scientific officer and professor of genomic medicine at the University of Texas MD Anderson Cancer Center. He is also the senior author of the paper reporting on the role of Syndecan-1, which appeared in the March 28, 2019, issue of *Nature*.

In their studies, the authors used inducible mouse models of KRAS-driven pancreatic cancers and pancreatic cancer cell lines to identify Syndecan-1 as a protein that moved to the cell surface in response to KRAS signaling. They then showed that Syndecan-1 was critical for the initiation of macropinocytosis.

Syndecan-1, which also goes by CD138, is overexpressed in a number of solid tumors. Antibody-drug conjugate indatuximab ravtansine (BT-062, Biotest AG) and separate CAR T cells being developing by the University of North Carolina and The Sixth Affiliated Hospital of Wenzhou Medical University target CD138. Those approaches are currently in early stage clinical trials.

Draetta was nevertheless circumspect about the work's clinical prospects. "No more than maybe one percent of the fundamental findings we make are translated," he pointed out. "We will of course engage in evaluating antibodies… but this is so early."

Whatever the specifics of targeting Syndecan-1, however, the work published in *Nature* is "a solid finding that is there to stay," and represents another step in the long road to making KRAS druggable.

KRAS at AACR

Moving KRAS to the druggable column could transform the outlook for a number of cancers. Pancreatic cancer, with a five-year survival rate of less than 10 percent, is one of them. Other tumor types with both high death tolls and frequent KRAS activation are non-small-cell lung cancer and colorectal cancer. Overall, KRAS-activating mutations are present in roughly 20 percent of all solid tumors.

At the upcoming annual meeting of the American Association for Cancer Research, researchers from both academia and industry will report on new insights into what drives tumors with activated KRAS, hopefully uncovering their vulnerabilities along the way.

In a NextGen Stars spotlight that will also focus on macropinocytosis, assistant professor Cosimo Commisso from the Sanford Burnham Prebys Institute for Medical Discovery will report new insights into how nutrient stress induces macropinocytosis in RAS-driven cancers. Frank McCormick, from the University of California at San Francisco, will give an overview of RAS inhibitors in a Monday session on The NCI RAS Initiative.

And in addition to dozens of abstracts in the regular program, no fewer than three late-breakers will also report new data on fighting KRAS-driven tumors.

In a Monday late-breaking poster session, researchers from Eli Lilly and Co. will present an abstract titled "Combination of an ERK1/2 inhibitor (LY3214996) with pan-RAF inhibitor enhances anti-tumor activity in KRAS mutant colorectal cancer (CRC) and non-small-cell lung cancer (NSCLC)."

And on Wednesday, Mirati Therapeutics Inc. and Array Biopharma Inc. will present "Insight towards therapeutic susceptibility of KRAS mutant cancers from MRTX1257, a novel KRAS G12C mutant selective small molecule inhibitor," while researchers from the University of North Carolina and G1 Therapeutics Inc. will report on "Combination therapies with CDK4/6 inhibitors to treat KRAS-mutant pancreatic cancer." ♦

FMT

Continued from page 6

delivers live, human-derived microbes into a sick patient's intestinal tract. RBX-2660 is the first formulation to emerge from MRT; the second is called RBX-7455, described as the first of its kind – a non-frozen, room-temperature stable, orally delivered microbiota-based product. The phase III effort with RBX-2660, called Punchcd3, is signing up 270 subjects and should complete around the end of this year.

Vedanta has phase II-stage oral VE-303, described as a rationally-defined bacterial consortium candidate being developed for the prevention of recurrent *C. diff.* It consists of eight types of clonal human commensal bacteria strains selected for their ability to provide colonization resistance to *C. diff.* and manufactured under GMP conditions, the company said. A study called Consortium is enrolling 146 participants and is expected to finish in another year or so.

On March 14, MTIG voiced its support of the available FDA draft guidance that provides for patient access to FMT treatment through clinical trials or a physician-prepared setting, with donor controls and informed consent. "The [group's] statement is also aligned with FDA's position not to extend enforcement discretion to unregulated commercial-scale FMT stool banks that have not established safety and efficacy through FDA-regulated clinical trials," MTIG noted. ♦

BIO

Continued from page 1

of capital flowing into the sector, it would be easy to think the biopharma industry had reached optimal capacity. But as the BIO Europe Spring meeting came to a close Wednesday, Evotec AG CEO and Austria native Werner Lanthaler suggested that progress and innovation "aren't happening as fast as they should."

Lanthaler, who has helmed the German biotech for the last decade, opened his remarks with a quick look at transformations in the oil, automotive, hotel, entertainment and even tobacco industries. "There's not a single industry that can afford to not think about how transformation can happen." However, in the biopharma space, "there is room for transformation."

"The blockbuster world is over," he added, pointing out that development costs are rising while sales, despite seeing more products being approved than ever before, are declining per product. That's not necessarily a bad thing – it's a sign the industry might finally be aligning with its precision medicine aspirations – but Lanthaler said that shift means biopharma needs "to rethink our models a bit."

Part of the transformation that needs to happen could come from technologies to improve early stage work and translation. "All the technologies are there to make translation faster," he said, citing next-generation sequencing and induced pluripotent stem cells as examples. "We should not accept that 10 years of a-beta research" results in clinical Alzheimer's disease trials in which "we find out, $80 billion later that it is just bad."

Last week, Biogen Inc. and Eisai Co. Ltd. reported they were stopping phase III studies of much-hyped Alzheimer's candidate, aducanumab, after an independent data monitoring committee concluded it's unlikely the trials would meet their endpoints. The miss was only the latest in a slew of amyloid beta-targeting drugs that have failed to stop or even slow progression of the neurodegenerative disease. (See *BioWorld*, March 22, 2019.)

Better – and preferably earlier – understanding is needed, "not just more data but more knowledge," Lanthaler said. He noted the flurry of biopharmas connecting with artificial intelligence (AI) firms in recent deals. Evotec itself is part of that number, adding $6 million to AI firm Exscientia Ltd.'s series B round in January, adding to its initial $17.6 million investment in 2017. He said the firm believes in AI – "it will change our industry, but only if we translate our data into knowledge; otherwise it's only hocus-pocus." (See *BioWorld*, Sept. 29, 2017.)

Lanthaler also pointed to the funding gap – the so-called valley of death – that still exists, despite the amount of money flowing into the sector. Spinning out ideas from academia into companies also runs into trouble due to data reproducibility issues. "We don't want a VC company investing in something that comes out of academia" only to find it doesn't work in clinical trials.

Evotec, which specializes in drug development, has plenty of experience working at the translational level. In the past few years, the firm has introduced its Bridges initiative, which aims to accelerate translational products from the lab to preclinical proof of concept. It has since inked Bridge agreements with the Canada's MaRS Innovation along with Arix Bioscience plc and the Fred Hutchinson Cancer Research Center.

Long-term bet on infectious disease

Another transformation the industry needs to make is its view of the infectious disease space. In his presentation, Lanthaler described going from a "golden age to a discovery void," with pharma's exodus in infectious diseases and overuse of existing antibiotics leading to the antimicrobial resistance (AMR) problem the affecting global population. His comments come as the author of a May 2016 U.K. government review on addressing drug-resistant infections criticized the pharma industry's lack of response in an update this week. (See the AMR story in this issue.)

If faced with drug resistance, "our preparedness level is not there," Lanthaler said. To put it into perspective, he added, "Today, there are 20 times more scientific people in immuno-oncology than in infectious diseases, but you have the same probability to die" of either if you are 65 and older.

The solution is twofold. One is the support of organizations such as the Bill & Melinda Gates Foundation, which has committed millions for work on diagnostics and therapeutics targeting tuberculosis, along with government efforts that align with public health problems. "The second part is whether the pricing is fair for a novel antibiotic – and I'm stressing 'novel'" – or whether new antibiotics are instead priced along the lines of generics, he said. "With fair pricing, the markets will come back and pharma will come back. That's why Evotec is making a long-term bet."

Last year, the company more than doubled its footprint in the anti-infectives research space through a deal with Sanofi SA, under which it will take on a number of early stage programs, including assets targeting gram-negative bacteria, tuberculosis, malaria and viral diseases, as well as a Sanofi research unit in Lyon, France. In exchange, Evotec got $60 million up front plus a commitment for continued funding, while Sanofi retains option rights. (See *BioWorld*, June 19, 2018.)

Evotec's overall business model comprises a range of drug discovery services, as well as preclinical research, process development, and strategic discovery and development in selected indication areas. Over the years, it has amassed a number of capabilities, from small molecules to antibodies and stem cell platforms and, more recently, has moved into genome editing. ♦

Other news to note

Abcuro Inc., of Newton, Mass., a company that has discovered antibodies for blocking the immune inhibitory receptor KLRG1, said that it has developed an in vivo proof-of-concept for the anti-cancer action resulting from blockade of the receptor in mouse syngeneic models. The results, published in the Feb. 15 edition of *Oncotarget*, highlight KLRG1 as an important driver of adaptive resistance to immunotherapy in humans, the company said.

Crown Biosciences Inc. (Crownbio), of San Diego, said that its parent company, JSR Corp., has entered into a strategic partnership with Hubrecht Organoid Technology (HUB), which will provide preclinical oncology drug development and validation services. Crownbio and HUB will also launch a collaborative research and development program to accelerate further development of the organoid technology, which employs adult stem cells. Crownbio will establish a new operations center in Utrecht, Netherlands, where HUB is located.

Destiny Pharma plc, of Brighton, U.K., selected the Surrey, U.K.-based contract research organization **Medpharm Ltd.** as its partner to develop new topical formulations of the company's XF platform compounds, potential new treatments for dermal and ocular infections. Destiny said one product of the platform, XF-73 nasal gel, for the prevention of post-surgical infections, will begin phase IIb testing in 2019.

Eureka Therapeutics Inc., of Emeryville, Calif., highlighted the March 27 publication in *Science Translational Medicine* of the results of a study that it said demonstrated "efficient antigen-specific cytotoxicity in vitro" by GPRC5-targeted CAR T cells "as well as comparable effect in inducing tumor regression and extending survival at different dose levels in vivo" to B-cell maturation antigen-targeted CARs with an identical backbone. The study was led by researchers from Eureka, Memorial Sloan Kettering Cancer Center and Juno Therapeutics, now part of **Celgene Corp.** The article is "GPRC5D is a target for the immunotherapy of multiple myeloma with rationally designed CAR-T cells."

Guardant Health Inc., of Redwood City, Calif., entered a definitive agreement to acquire **Bellwether Bio Inc.**, of Seattle, in a deal expected to close in April 2019. The Bellwether team will join Guardant to further advance its early detection product pipeline. On Sunday at the AACR meeting in Atlanta, investigators from Guardant and the Samsung Medical Center will report results from a pilot study with Guardant's Lunar assay in early stage cancer. The study demonstrates that addition of epigenomics to the assay can potentially lead to significant improvements in sensitivity for stage I and II colorectal cancer.

Juvenescence Ltd., of Cambridge, Mass., disclosed its latest equity investment in **Byomass Inc.**, of Sudbury, Mass., under which Juvenescence will provide up to $6.5 million in equity financing and collaborate with Byomass to advance these programs. Juvenescence said Margaret Jackson, CEO of Byomass, has joined the Juvenescence team as head of preclinical research and development.

Oragenics Inc., of Orlando, Fla., started a collaboration with Florida International University in Miami to create computational models of the company's lantibiotic compounds interacting with bacterial membranes and Lipid II, the target of Oragenics' compounds with the ultimate goal of expanding the lantibiotic pipeline. Oragenics said it is regularly seeking to optimize treatment with lantibiotic compounds and believes that the deal will help to best understand the way lantibiotics interact with bacteria, enabling the firm to rationally design analogs with improved antimicrobial and/or pharmacological properties. The firm said efforts may include gram-negative infections.

Pain Therapeutics Inc., of Austin, Texas, changed its name to **Cassava Sciences Inc.** in order to better reflect its strategic focus on drug development for neurodegenerative diseases, such as Alzheimer's disease. Starting today the firm will trade on the Nasdaq market under the ticker SAVA.

Proqr Therapeutics N.V., of Leiden, the Netherlands, disclosed the spinout of dystrophic epidermolysis bullosa activities into a newly formed company, Wings Therapeutics. Proqr has a minority stake in Wings and will be eligible for milestone and royalty rights to commercial products. Financial details were not disclosed.

Solentim Ltd., of Dorset, U.K., and **Valitacell Ltd.**, of Dublin, disclosed a total of €3.5 million (US$3.9 million) in funding under the European Commission's H2020 Fast Track to Innovation initiative to produce an integrated platform to deposit, culture, profile and select optimal cells for the manufacture of life-saving biological medicines. Building on the existing partnership between Valitacell and Solentim made public in February 2019, Microcoat Biotechnologies GmbH, of Bernried, Germany, has joined the consortium to further strengthen manufacturing capability and scale, the companies said.

Vital Therapies Inc., of San Diego, asked stockholders who have not yet voted to cast their ballots in favor of the combination with **Immunic AG**, of Planegg, Germany, and other proposals in the company's proxy statement/prospectus for the special meeting of its stockholders to be held next Thursday. More votes are needed to meet the required threshold for the deal to complete, the company said.

Financings

Elicio Therapeutics, of Cambridge, Mass., a new company developing cancer vaccines and immunotherapies for solid and hematologic cancers has formed with initial financing of $30 million from undisclosed institutional and high net worth investors to support the development of a platform designed to target and deliver immunogens directly to the lymphatic system. The company said its lead vaccines, targeting pancreatic, colorectal and head and neck cancers, will enter the clinic in the first half of 2020. The company's CEO is Robert Connelly, the founding CEO of **Glaxosmithkline plc**-acquired Domantis Ltd. and former CEO of **Pulmatrix Inc.** and **Axcella Health Inc.** (See *BioWorld Today*, Dec. 11, 2006.)

American Depository Shares (ADS) of Lille, France-based **Genfit SA** (NASDAQ:GNFT) closed at $22.05 on Wednesday, having risen 8.5 percent following an IPO of about 6.2 million ADSs at $20.32 each, equivalent to the €18 per share pricing of a concurrent private placement of 500,000 ordinary shares the company executed. Together, the financings were expected to raised gross proceeds of $135.1 million. The funds are slated to help Genfit complete its ongoing phase III development of elafibranor for the treatment of nonalcoholic steatohepatitis (NASH); prepare for the potential commercialization of the candidate in NASH; and run a planned global phase III trial of elafibranor for the treatment of primary biliary cholangitis. Some funds will also be devoted to advancing commercial development of the company's in vitro diagnostic test to identify NASH patients and a research program on the use of elafibranor as a potential backbone for combination therapies. SVB Leerink and Barclays acted as joint bookrunners for the ADS offering. Genfit granted underwriters for the offering a 30-day option to purchase up to 997,500 additional ADSs and/or ordinary shares.

Meissa Vaccines Inc., of South San Francisco, closed a $3.4 million seed round to further develop its investigational vaccine for respiratory syncytial virus. The financing, backed in part by undisclosed individual investors, will be used to move the company's RSV vaccine candidate into the clinic, it said. The company's technologies for reverse genetics and human codon deoptimization allow for rapid generation of live attenuated vaccine candidates, which may be safer yet more immunogenic than natural pathogens, the company said.

Moleculin Biotech Inc., of Houston, said it intends to sell a yet-to-be-disclosed number of units, consisting of shares of common stock and warrants, in an underwritten public offering. All units in the offering will be sold by Moleculin. The company said it plans to use net proceeds from the offering for its planned clinical trials, preclinical programs, for other research and development activities and for general corporate purposes.

Myokardia Inc., of South San Francisco, priced an underwritten public offering of 4.93 million shares of its common stock at $51 per share, the proceeds from which it will use to fund trials, preclinical programs, R&D and corporate needs, it said. Oppenheimer & Co. acted as the sole book-running manager. Myokardia shares (NASDAQ:MYOK) fell by $1.10 cents, or 2.1 percent, to $51 on Wednesday.

Neovacs SA, of Paris, will raise up to €10 million (US$11.3 million) through the issuance of notes convertible into new and/or existing shares of the company and/or redeemable in cash. The notes were secured through an agreement with European Select Growth Opportunities Fund. The financing is intended to allow Neovacs to continue its development of interferon-alpha kinoid for lupus following the results of the phase IIb trial and monitors treated patients over a five-year long-term follow-up program. It will also help the company continue development of the preclinical program of interferon-alpha kinoid for type 1 diabetes and IL-4 / IL-13 kinoid for allergies. (See *BioWorld*, July 5, 2018.)

Precision Therapeutics Inc., of Minneapolis, priced a public offering of its common stock and warrants at $0.80 per unit, with each unit consisting of one share of common stock and a warrant to purchase 0.5 of a share of common stock. The offering, expected to raise up to $1.2 million, is expected to close on or about March 29. Dawson James Securities Inc. is acting as exclusive placement agent for the offering. Company shares (NASDAQ:AIPT) fell about 3 cents, or 3.8 percent, to close at $0.77 on Wednesday.

Syndax Pharmaceuticals Inc., of Waltham, Mass., is raising $26.2 million through the sale of about 4.4 million shares of its common stock (NASDAQ:SNDX) to Biotechnology Value Fund L.P. and other life sciences investors, a 30 percent premium to the company's share price as of market close on March 26. The sale also included warrants to purchase up to about 2.2 million shares of common stock in the company at an exercise price of $12 per share and warrants for another 2.2 million shares at an exercise price of $18 per share. Syndax is developing entinostat, a once-weekly, oral, small-molecule, class I HDAC inhibitor, in combination with exemestane and several approved PD-1/PD-(L)1 antagonists. (See *BioWorld*, Oct. 29, 2018.)

Clinical data for March 27, 2019

Company	Product	Description	Indication	Status
Phase I				
Cellect Biotechnology Ltd., of Tel Aviv, Israel	Apogrft	Stem cells	Acute myeloid leukemia, myelodysplastic syndrome and acute lymphoblastic leukemia	After 180 days of followup, in first 6 patients, there have been no serious adverse events considered related to the treatment; time to engraftment was similar to the standard of care; 8 out of 12 planned patients have been enrolled
Durect Corp., of Cupertino, Calif.	DUR-928	Anti-inflammatory agent	Non-alcoholic steatohepatitis	Started enrollment in the 60-patient, open-label study testing 3 doses of the drug for 28 days; safety, pharmacokinetics and signals of biological activity will be measured; initial data expected in the second half of 2019
International AIDS Vaccine Initiative, of New York	BG505 SOSIP.664 gp140	HIV envelope vaccine	HIV infection prophylaxis	Started the 60-subject IAVI W001 study testing whether the vaccine can create neutralizing antibodies
Vaxart Inc., of South San Francisco	Bivalent norovirus vaccine	Oral norovirus GI.1 vaccine and oral norovirus GII.4 vaccine	Norovirus infection prophylaxis	Completed dosing of open-label, lead-in phase of study; randomized, double-blind, placebo-controlled phase expected to start in April; top-line data expected in the second half of 2019
Tizona Therapeutics Inc., of South San Francisco	TTX-030	Anti-CD39 monoclonal antibody	Advanced cancers	Started enrolling patients in the study measuring safety, tolerability, pharmacokinetics and antitumor activity of TTX-030 as a monotherapy, in combination with an approved anti-PD-1 immunotherapy and in combination with standard chemotherapies
Phase II				
Achillion Pharmaceuticals Inc., of Blue Bell, Pa.	ACH-4471	Factor D inhibitor	Paroxysmal nocturnal hemoglobinuria	Completed enrollment of study testing whether treatment with ACH-4471 plus eculizumab over 24 weeks can increase hemoglobin and reduce transfusions in patients with an inadequate response to eculizumab; data from first 10 patients to be presented at The New Era of Aplastic Anemia and Paroxysmal Nocturnal Hemoglobinuria meeting; end of phase II meeting with regulatory authorities expected in the second half of 2019
Centrexion Therapeutics Corp., of Boston	CNTX-4975	Trans-capsaicin	Severe knee pain associated with osteoarthritis	Data from Triumph study published in *Arthritis & Rheumatology*; CNTX-4975 decreased pain in knee through 12 and 24 weeks ($p<0.0001$ and $p=0.0002$, respectively)
City of Hope, of Duarte, Calif.	Triplex	Multi-antigen broadly recognized vaccine	Cytomegalovirus infection in stem cell and solid organ transplant recipients	In the 102-patient study, patients treated with vaccine had 50% fewer cytomegalovirus events – virus reactivation, antiviral treatment and disease – from day 28 through day 100 compared to patients who received placebo ($p=0.08$)
Orchard Therapeutics Ltd., of Boston	OTL-200	Ex vivo autologous hematopoietic stem cell-based gene therapy	Metachromatic leukodystrophy	All 20 patients had a reconstitution of arylsulfataseA activity in the hematopoietic system within or above the normal reference range within 3 months post-treatment that remained stable throughout the follow-up period; Gross Motor Function Measure (GMFM) total scores in late infantile patients were 72.5% and 73.9% at two- and three-years post-treatment, respectively, compared to 7.4% and 2.4%, respectively, in an untreated age-matched natural history cohort ($p<0.001$ for both); GMFM total scores in early juvenile patients were 76.5% and 71.7% at two- and three-years post-treatment, respectively, compared to 36.6% and 31.3%, respectively, in an untreated age-matched natural history cohort ($p=0.026$ and $p=0.020$, respectively)

Company	Product	Description	Indication	Status
Promethera Biosciences SA, of Mont-Saint-Guibert, Belgium	Hepastem	Liver stem cells	Acute-on-chronic liver failure and acute decompensation	Infusions of 250x10^6 cells (around 3.5x106 cells/kg) caused severe epistaxis in 2 patients; reduction of dose to 0.25x10^6 cells/kg or 0.5x106 cells/kg caused no serious events causally related to treatment; in patients with transplant-free survival at month 3, bilirubin decreased by 80% and Model for End-Stage Liver Disease scores decreased by 50%
Phase III				
Biolinerx Ltd., of Tel Aviv, Israel	BL-8040	Hematopoietic stem cells	Multiple myeloma	All 11 patients in part 1 of the Genesis study treated with BL-8040 and granulocyte colony-stimulating factor (G-CSF) were successfully engrafted; 9/11 patients reached more than 6x10^6 CD34 cells/kg with only one dose of BL-8040 and in up to 2 apheresis sessions; 7/11 patients reached the threshold in a single apheresis session; mobilized cells were observed in all 9 patients for whom there was data
Urovant Sciences Ltd., of Irvine, Calif.	Vibegron	Beta-3 agonist	Overactive bladder in men who are receiving pharmacological treatment for benign prostatic hyperplasia	Following positive data in the Empowur study, company started the 1,000-patient, placebo-controlled Courage study; co-primary endpoints measured at week 12 are the change from baseline in the average number of micturitions per 24 hours and the change from baseline in the average number of urgency episodes per 24 hours; change from baseline in the average number of nocturia episodes per night will be measured as a secondary endpoint
Notes For more information about individual companies and/or products, see Cortellis.				

Regulatory actions for March 27, 2019

Company	Product	Description	Indication	Status
Agios Pharmaceuticals Inc., of Cambridge, Mass.	Tibsovo (ivosidenib)	IDH1 inhibitor	Newly diagnosed acute myeloid leukemia with an IDH1 mutation	FDA granted breakthrough designation for patients who are 75 years or older or who have comorbidities that preclude use of intensive induction chemotherapy
Ampio Pharmaceuticals Inc., of Englewood, Colo.	Ampion	Low-molecular-weight fraction of human serum albumin	Osteoarthritis of the knee	After meeting with the FDA, resubmitted a special protocol assessment; agency expected to respond no later than April 25, 2019
Axsome Therapeutics Inc., of New York	AXS-05	NMDA receptor antagonist	Major depressive disorder	FDA granted breakthrough designation based on data from the phase II ASCEND study
Astrazeneca plc, of Cambridge, U.K.	Forxiga (dapagliflozin)	SGLT2 inhibitor	Type 1 diabetes	The Japanese Ministry of Health, Labour and Welfare approved the drug as an oral adjunct treatment to insulin in adults
Clarus Therapeutics Inc., of Northbrook, Ill.	Jatenzo (testosterone undecanoate)	First-in-class softgel oral formulation of testosterone undecanoate	Testosterone replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone: primary hypogonadism (congenital or acquired) and hypogonadotropic hypogonadism (congenital or acquired)	FDA approval based on phase III Intune trial data, which showed 87% of hypogonadal men treated with Jatenzo achieved a daily average testosterone level in the normal range, with an adverse events profile generally consistent with other testosterone replacement therapies; Jatenzo contains a boxed warning that the drug can cause blood pressure to rise, increasing the risk of heart attack, stroke and cardiovascular death

Company	Product	Description	Indication	Status
Fibrocell Science Inc., of Exton, Pa.	FCX-007	Autologous fibroblasts genetically modified to express COL7	Recessive dystrophic epidermolysis bullosa	Company received feedback on design of its DEFI-RDEB phase III study in a type B meeting with the FDA; study will enroll 15-20 patients with up to 3 pairs of wounds, with one receiving 2 doses of FCX-007 administered four weeks apart and the other wound left as the untreated control; proposed primary endpoint is complete closure of wound at 12 weeks post-administration of the first dose; secondary endpoints include evaluation of the proportion of wounds achieving more than 50% wound closure, a patient reported outcome measure and an analysis of durability out to 24 weeks; study expected to begin in the second quarter of 2019
Genmab A/S, of Copenhagen, Denmark, and Janssen Pharmaceutica NV, a unit of New Brunswick, N.J.-based Johnson & Johnson	Darzalex (daratumumab)	Monoclonal antibody targeting CD38	Multiple myeloma	Submitted a type II variation to the EMA for Darzalex in combination with bortezomib, thalidomide and dexamethasone as treatment for newly diagnosed patients with multiple myeloma who are candidates for autologous stem cell transplant
Silence Therapeutics plc, of London	SLN-124	siRNA targeting TMPRSS6	Beta-thalassemia and myelodysplastic syndrome	CTA submitted to the U.K.'s Medicines and Healthcare products Regulatory Agency
Tetra Bio-Pharma Inc., of Ottawa	PPP-001	Cannabinoid-derived drug	Advanced cancer	Company is ready to submit its pre-marketing application for drug as an herbal medicinal product to the EMA

Notes

For more information about individual companies and/or products, see Cortellis.