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So long, Sollpura: Anthera sacks lead program after dismal 'RESULT'

By Marie Powers, News Editor

Anthera Pharmaceuticals Inc. reported disastrous results from phase III RESULT study of Sollpura (liprotamase), which failed to reach the noninferiority margin of the coefficient of fat absorption (CFA) primary endpoint in individuals with exocrine pancreatic insufficiency (EPI) due to cystic fibrosis (CF). Sollpura did achieve the secondary endpoint of coefficient of nitrogen absorption (CNA), which measures protein absorption. But the findings from RESULT – following a miss in the earlier phase III

See Anthera, page 3

Biogen snaps up Pfizer schizophrenia asset for $75M plus milestones

By Michael Fitzhugh, Staff Writer

Biogen Inc. has moved to buy a midstage neuropsychiatric drug from Pfizer Inc. for $75 million up front, up to $515 million in potential milestones, and tiered royalties in the low to midteens.

The AMPA receptor potentiator, the object of a phase II Pfizer study that was terminated prematurely in a portfolio shakeup, is expected to enter phase IIb testing under Biogen's sponsorship in the second half of this year. Analysts suggested the move would help diversify Biogen's pipeline.

Anirvan Ghosh, Biogen's head of research and early development, told *BioWorld* that, while a number of treatments are available for some symptoms of schizophrenia, cognitive and negative symptoms remain largely unmet needs that Biogen has taken an interest in exploring.

Schizophrenia is characterized by positive, negative and cognitive symptoms. Positive

See Biogen, page 4

BIO-Europe Spring

Spotting opportunities in the gaps: From Brexit to maintaining innovation

By Cormac Sheridan, Staff Writer

AMSTERDAM – Dutch delegates to international biotech conferences routinely express their ebullient sense of identity by attaching their conference badges to their own orange-colored lanyards. Everyone is an honorary Amsterdammer for the duration of the 2018 BIO-Europe Spring meeting, which opened Monday at the RAI conference center in the southern quarter of the city. The official conference lanyard is a vivid

See Brexit, page 5

BIO-Europe Spring

'Think about China earlier' for recruiting trials, global expansion and innovation

By Karen Pihl-Carey, Analyst

AMSTERDAM – As the Chinese ecosystem continues to evolve with an increasing focus on innovative drugs and a rapidly changing regulatory environment, American and European biopharma executives have kept a keen but wary eye on the possibilities.

On one hand, China's massive population presents opportunity for clinical trial recruitment, particularly for patients with no prior treatments. The country also offers Chinese partners with established relationships who can navigate the CFDA's regulatory complexities, opening doors for

See China, page 7

House bill defines who has the 'right to try' unapproved drugs

By Mari Serebrov, Regulatory Editor

Despite warnings of unintended consequences, the U.S. House could take another step this week toward making right-to-try legislation the law of the land.

The House is scheduled to vote Tuesday on a

See Unapproved, page 6

U.K. investing $40M to systemize delivery of cell, gene therapies

By Nuala Moran, Staff Writer

LONDON - The U.K. government has announced a total of £30 million (US$41.7 million) for the formation of three specialist academic centers to work in collaboration with the Cell and Gene Therapy Catapult in laying the groundwork for

See NHS, page 8

With new dedicated info cell, India's drug regulator chases innovation

By T.V. Padma, Staff Writer

HYDERABAD, India – India's drug regulator is working to launch this month a new unit that would facilitate access to regulatory information and, hopefully, shore up the willingness of Indian drug companies to take more risks.

See India, page 9

Financings

BCI Pharma, of Liège, Belgium, said it has received €1.9 million (US$2.2 million) in public funding from the Walloon region and €2 million (US$2.5 million) more from public-private investors. The funds will be used to accelerate and finalize the company's research projects in the fields of cancer, neuropathic pain, inflammation and neuroinflammation, it said. As a first step, it has created a Belgian holding company and, in September 2017, opened a lab at the University Hospital of Liège. The company designs and validates kinase inhibitors libraries (Bikin 1-3).

Corvus Pharmaceuticals Inc., of Burlingame, Calif., completed its previously announced underwritten public offering of about 8.1 million shares of its common stock, including the exercise in full of underwriters' options to purchase about 1.1 million shares. The offering generated about $64.8 million in net proceeds for Corvus. Credit Suisse and Jefferies acted as joint book-running managers for the offering.

Global Blood Therapeutics Inc., of South San Francisco, said the underwriter exercised its full option to purchase an additional 600,000 shares, which brings total proceeds from the firm's recent public offering to about $248.4 million. Funds will be used to support clinical development of voxelotor for the treatment of sickle cell disease, including the ongoing phase III HOPE Study and ongoing phase IIa HOPE-KIDS 1 Study, as well as future clinical trials; to build and expand its commercial organization in preparation for the potential approval and launch of voxelotor; to fund its other research and development activities; and for working capital and general corporate purposes. Wells Fargo Securities LLC is the sole book-running manager. (See *BioWorld*, March 12, 2018.)

Humacyte Inc., of Research Triangle Park, N.C., said the company raised $75 million in a series C preferred stock financing, led by a global consortium of existing private investors and new investors, including Pointstate Capital. The company has received more than $330 million in total funding to date, including a $150 million series B round in October 2015. The funding is expected to support the company's ongoing Humanity study, a pivotal phase III trial assessing the human acellular vessel, or Humacyl, an alternative to current dialysis access products that can act as a conduit for hemodialysis in patients with end-stage renal disease who are not candidates for fistula placement. The company also intends to use the funds to complete the development, testing and qualification of a Durham, N.C.-based bioprocessing system planned to manufacture Humacyl. In September 2017, Humacyte announced the completion of enrollment of 350 evaluable subjects and expects 12-month post-implantation patient data from the study to be available during the third quarter of this year. (See *BioWorld Today*, Oct. 21, 2015.)

Immutep Ltd., of Sydney, raised about A$6.9 million (US$5.4 million) through an institutional placement of shares (ASX:IMM) intended to help fund the company's ongoing and planned immuno-oncology clinical development programs and its preclinical program in autoimmune disease. Platinum Asset Management, Australian Ethical Investment, Ridgeback Capital Investments and former Immutep chairman, Lucy Turnbull, participated in the financing. The offering placed about 326.2 million new ordinary shares at an issue price of A$0.021 (US$0.02) each. U.S.-based shares of the company (NASDAQ:IMMP) gained 30 cents, or 16.5 percent, on Monday to close at $2.13.

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Anthera

Continued from page 1

SOLUTION trial in CF patients with EPI – prompted Anthera to suspend development of the recombinant pancreatic enzyme replacement therapy (PERT), halting the 20-week extension period of RESULT, the SIMPLICITY study in children 28 days to <7 years of age assessing Sollpura powder for oral solution and the long-term safety EASY study.

The program's termination left Anthera, of Hayward, Calif., on life support. Shares (NASDAQ:ANTH) fell Monday to an all-time low of 40 cents as the company acknowledged that it was evaluating "all strategic alternatives." The stock closed at 50 cents, a decline of $2.14, or 81 percent. Nearly 39.6 million shares were exchanged, or about 24 times the stock's average daily volume.

In a five-minute conference call in which the company took no questions from analysts, Craig Thompson, president and CEO, essentially recited details from an issued statement. RESULT's design, he explained, was based on the outcome of the phase III SOLUTION study and included a higher starting dose and more aggressive dose optimization based on clinical signs and symptoms of malabsorption.

Findings from SOLUTION, reported in December 2016, showed a narrow top-line miss. After a three-week run-in period on Creon or Zenpep (pancrelipase, Allergan plc) to establish baseline CFA, 126 patients enrolled in SOLUTION were randomized to Sollpura or Pancreaze (pancrelipase, Janssen Pharmaceuticals Inc.), with the primary endpoint set at noninferior CFA measured after eight weeks. The main mark was margin in the primary modified intent-to-treat (mITT) analysis, which fell just short. Researchers did find that, by additional pre-specified analyses of CFA (mITT-baseline observation carried forward and per protocol), Sollpura hit the noninferiority goal. The study also confirmed that the ratio of the three enzymes in Sollpura turned up appropriate response in the CNA. (See *BioWorld Today*, Dec. 29, 2016.)

In the randomized, open-label, assessor-blind, noninferiority, active-comparator RESULT study, which enrolled 140 patients, those randomized to Sollpura received a starting dose that was approximately 25 percent higher than their pre-study porcine PERT dose, and 59 percent received additional dose adjustments designed to simulate "real-life" conditions, yielding a mean Sollpura dose of 8,673 (range 2,925-14,941) lipase units/kg/day, which was substantially higher than the comparator Pancreaze mean dose of 6,527 (range 2,358-10,253) units/kg/day and higher than the mean Sollpura dose of 7,286 (range 4,478-10,000) units/kg/day in SOLUTION.

"Although a proportion of patients randomized to Sollpura maintained or improved their CFA from baseline, a higher proportion of patients [in RESULT] experienced a worsening," Thompson said. The mean treatment difference in CFA change from baseline was 14.3 percent, with upper and lower 95 percent confidence intervals of -18.22 and -10.39.

The treatment difference in CNA change from baseline (-1.53 percent) was within the 15 percent noninferiority margin. In comparison to the earlier SOLUTION study, the presence or absence of concomitant gastric acid suppressants had no meaningful effect on CFA (mean changes from baseline in CFA of -15.06 percent and -16.58 percent, respectively).

RESULT also was modified from SOLUTION to provide a shorter treatment duration of four weeks, with three weeks of dose optimization and one week of stable dosing. The trial design was discussed with FDA officials prior to administration and was approved by the Cystic Fibrosis Foundation Therapeutics Development Network (CFFTDN) protocol review committee and the European Cystic Fibrosis Society Clinical Trial Network executive committee, according to Anthera.

In December 2017 and again in January, prespecified interim futility analyses were conducted by a data monitoring committee comprising experts appointed by the CFFTDN when approximately 25 percent and 50 percent of patients, respectively, completed the four-week treatment period. In both instances, the committee recommended the study continue to completion.

'There may be some interest' in assets

With Sollpura at the end of the road, Anthera has its back to the wall. Its other asset, blisibimod, fell short in the phase III CHABLIS-SC1 study testing the selective peptibody antagonist of the B-cell activating factor cytokine against systemic lupus erythematosus, or SLE. (See *BioWorld Today*, Nov. 11, 2016.)

Although prospects initially looked brighter for blisibimod in the phase II/III BRIGHT-SC study in individuals with IgA nephropathy, slow recruitment forced the company to convert BRIGHT-SC to a phase II study. In August 2017, Anthera reported positive top-line data and said it planned to meet with the FDA to discuss a phase III program, but those trials never began, according to Cortellis Clinical Trials Intelligence. (See *BioWorld Today*, Dec. 8, 2016.)

Piper Jaffray's Edward Tenthoff voiced surprise at the RESULT findings, given the protocol amendment, as he downgraded Anthera's shares to "underweight" from "overweight" and lopped the price target to 10 cents from $4.

Likewise, Jefferies Group LLC analyst Matthew Andrews offered scant encouragement. Although, based on positive phase II blisibimod data in IgA nephropathy and intellectual property, manufacturing and CMC know-how for Sollpura, "there may be some interest from pharma/biotech in these assets," he wrote, Andrews nevertheless knocked the stock's price target down to 50 cents from $2 based on the risks of raising additional capital and remaining a "going concern."

Anthera finished 2017 with cash and equivalents of $2.2 million. In January, the second closing of a PIPE transaction generated net proceeds of $11.1 million. During the first quarter, the company also received $3.1 million from the exercise of warrants and sale of shares in relation to an equity purchase agreement. ♦

Biogen

Continued from page 1

symptoms, which include auditory hallucinations, disorganized or bizarre thoughts, delusions and irrational fears, are largely treated with antipsychotic dopamine antagonists. But those same drugs have little effect on negative symptoms, such as affective blunting, emotional withdrawal, anhedonia, poverty of speech and apathy, and cognitive impairment.

According to the National Institute of Mental Health, about 1.1 percent of Americans adults have schizophrenia. Worldwide, there are more than 20 million people living with schizophrenia, Biogen said, noting that the majority of them live with some degree of cognitive impairment attributable to the disease.

The Pfizer candidate that Biogen is acquiring, still known as PF-04958242 for now, is an alpha-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) receptor potentiator. AMPA receptors mediate fast excitatory synaptic transmission in the central nervous system, a process that can be disrupted in a number of neurological and psychiatric diseases, including schizophrenia, Biogen said.

Pfizer had plans to test a capsule-formulated version of the drug in a randomized, 12-week, double-blind, placebo-controlled phase II study slated to include about 250 participants with cognitive impairment associated with schizophrenia (CIAS). However, in September 2016, the trial was terminated prematurely following an internal portfolio prioritization, according to Clarivate's Cortellis Competitive Intelligence. It was noted that the termination was not due to any safety concern or change in the company's assessment of the drug's risk-benefit profile.

Though that study wasn't completed, data from two other randomized, double-blind, placebo-controlled studies suggested promise for the program. The data, presented at the 55th American College of Neuropsychopharmacology's annual meeting in December 2016, was drawn from testing in 69 subjects. After two weeks of dosing with PF-04958242, the participants who received it experienced statistically significant dose-related improvements on the MATRICS Consensus Cognitive Battery, a commonly used metric in studies of drugs for schizophrenia.

"While the data are early, we believe the deal helps BIIB diversify its high-risk high-reward pipeline, which is increasingly important in light of recent enrollment changes to aducanumab's pivotal program," Suntrust Robinson Humphrey analyst Yatin Suneja wrote, referring to the company's recent upsizing of its pivotal phase III studies of experimental Alzheimer's disease therapy due to "more variability on the primary endpoint than assumed."

Meanwhile, it appears that the company will have little trouble arriving at a solid design for a proof-of-concept study of its new asset. Ghosh said while Biogen has yet to finalize the design of its planned phase IIb test of PF-04958242, the field of neuroscience has done a good job of developing ways to probe subdomains of cognition, allowing for very refined read-outs of efficacy.

AMPA receptor modulators have been explored in a variety of other indications, including depression, partial-onset seizures and drug dependence. Biogen's focus is firmly on CIAS at first, but the company will also look at data from other areas carefully to determine whether it would make sense to consider additional indications, Ghosh said.

At least for now, it doesn't appear that Biogen will face much competition from other candidates in the class. The highest-profile recent entrant in the space, Takeda Pharmaceutical Co. Ltd., withdrew development of TAK-653, for treatment-resistant depression, in February. ♦

Financings

Kiadis Pharma NV, of Amsterdam, said it launched a private placement of about 2.6 million shares to institutional investors, representing about 14.8 percent of the firm's current issued share capital. Funds will be used to continue phase III development of allodepleted T-cell immunotherapy product ATIR-101 in the U.S., Canada and Europe, as well as to support manufacturing and commercialization efforts and other corporate activities. The subscription price and number of shares will be determined through a bookbuilding process. Jefferies International Ltd. is acting as sole bookrunner, Canaccord Genuity Ltd. as lead manager, Chardan as co-lead manager and Lifesci Capital LLC as co-manager.

Race Oncology Ltd., of Victoria, Australia, completed a placement of about 9.9 million shares priced at A32 cents (US25 cents) apiece for gross proceeds of about A$3.2 million. In addition to operational funding, proceeds will be used to fund manufacturing of Bisantrene for U.S. registrational trials and for expansion of the named patient program. Bisantrene is a small-molecule chemotherapy drug related to anthracyclines and is initially being pursued in relapsed/refractory acute myeloid leukemia. Race is seeking approval via the 505(b)(2) pathway in the U.S.

Other news to note

Alnylam Pharmaceuticals Inc., of Cambridge, Mass., said Sanofi Genzyme, part of Paris-based **Sanofi SA**, has declined its opt-in for the development and commercialization of lumasiran (ALN-GO1), an investigational RNAi therapeutic for the treatment of primary hyperoxaluria type 1. Alnylam now intends to "rapidly advance" lumasiran into a phase III pivotal study in late 2018, it said, and to commercialize it globally, if approved. It also announced that lumasiran has been granted breakthrough status by the FDA. Through the end of 2019 and, potentially through the end of 2021, Sanofi Genzyme retains the right to opt into other Alnylam rare genetic disease programs for development and commercialization in territories outside of the U.S., Canada and Western Europe.

Brexit

Continued from page 1

orange, as the city assumes the role of unofficial headquarters for the European biotech industry over the next three days, during which more than 2,500 delegates from 55 countries will engage in partnering discussions on more than 3,550 assets.

Amsterdam will, of course, soon become a different kind of focal point for Europe's drug industry, when it starts to host the EMA from next year. There was only a passing reference to the EMA's historic shift from London to Amsterdam during the opening plenary, however. The EMA logo did appear in a promotional video setting out the Netherlands' strengths in biopharma, but the Dutch were by no means in a triumphalist mood.

The Brits were, understandably, in a more mournful mood, as evidenced during an afternoon panel on navigating the uncertainties of Brexit, although one tempered by a determination to mitigate the risks and uncertainties of Brexit as best they can.

A particularly sorrowful note was struck during that discussion by Thomas Lönngren, the former executive director (2001-2010) of the EMA, who made a dramatic intervention from the floor. Professing himself to be "very sorry" that what had been "built up so successfully" now has to move, he warned that the EMA is facing severe disruption.

"From a capacity point of view, EMA will lose a lot of good people from the U.K.," he said. But the threat caused by the loss of competence could be even greater, given the U.K.'s influential role in the work of the EMA's working groups and scientific committees – although he expressed his confidence that the agency would overcome those hurdles.

The nature of the future relationship between the U.K.'s Medicines and Healthcare Products Regulatory Agency (MHRA) and the EMA is as yet unclear. In her recent Mansion House speech in London, U.K. Prime Minister Theresa May expressed a willingness to remain part of the EMA and to abide by its rules. (See *BioWorld*, March 5, 2018.)

European Commission officials have yet to make a detailed response on the specific question of medicines regulation but in general reiterated their opposition to what they see as cherry-picking.

"I was a little disappointed by the European response," Lönngren said. "I hope it's a negotiating position."

Even if it is not – and the U.K. finds itself outside the EMA system – the FDA collaboration, which was agreed during Lönngren's term, in 2002, offers a possible model for a future relationship. "That is a very successful collaboration," he said.

He concluded by saying that it is possible to find ways of collaborating without making too much fuss politically – to loud applause from the audience.

Earlier during the same session, Angela McFarlane, market development director at Iqvia, attested to her faith in the life sciences sector deal negotiated last December between the U.K. government and the country's pharmaceutical industry as the best way for the U.K. to maintain its position as an innovator in biopharma. It makes the case for investing in the U.K. and highlights some of its unique strengths.

"The U.K. leads the world in the number of global real-world evidence studies that are being carried out," she said. The U.K.'s National Health Service's anonymized patient-level data is "a fantastic coalfield" that is waiting to be mined.

However, awareness of the accord remains low, while many of those who do know about it are skeptical about its promised benefits, which include commitments to increase the U.K.'s R&D intensity and to strengthen its clinical trials environment.

The looming disruption of Brexit and its myriad uncertainties currently weigh more heavily on global perceptions of the U.K. as a market for products and as a destination for both clinical trials and investment. McFarlane unveiled new survey data, based on responses from 129 U.K., European and global pharma executives. Half of them believe that Brexit has impacted the attractiveness of the U.K. market; 44 percent consider the U.K. less attractive for product launches, and 73 percent of those now see it as a later launch market, one to two years behind the main global markets.

For Steve Bates, CEO of the U.K.'s BioIndustry Association, the U.K. sector's fundamentals remain in place – and they provide the strongest argument for the U.K.'s ongoing participation in EMA.

"Our challenge now is to explain the benefit of continued partnership," he said. For Europe, there is an opportunity cost attached to a U.K. exit from the EMA. Without the U.K., Europe is also less attractive as a global market. "This is why we have a shared problem," he said. The danger is that Brexit could trigger disinvestment from Europe as well as from the U.K., he added.

Absence of innovation

Leaving aside the political uncertainties of Brexit, these are among the best of times for European – and global – biotech as the maturation of novel cell and gene therapies, combined with the consistent performance of more mature technologies, notably monoclonal antibodies, helped to propel new drug approvals to a near-record performance in 2017.

However, the FDA's 53 new drug approvals last year mask a worrying absence of innovation in some of the conditions that impose the heaviest health care burden on the U.S., BIO's senior director of industry research and analysis, David Thomas, told delegates during his customary slot during the opening plenary. Drugs for oncology and rare diseases are heavily represented in the class of 2017. Less so are drugs for addiction, psychiatric disease and pain.

Yet oncology and rare disease are commanding far larger amounts of VC funding and are also on the receiving end of far greater M&A activity, evidenced by the Gilead Sciences Inc. and Celgene Corp. buyouts of CAR T-cell developers Kite Pharma Inc. and Juno Therapeutics Inc. for $11.9 billion and $9 billion, respectively, as well as Sanofi SA's acquisition of hemophilia specialist Bioverativ Inc. for another $11.6 billion.

"We seem to have developed a disproportionate level of

See Brexit, page 10

Unapproved

Continued from page 1

revised right-to-try bill similar to S. 204, which the Senate passed last August. Like the Senate bill, the House legislation creates an alternative pathway to the FDA's expanded use process. But it still would be up to sponsors to decide whether to make their investigational drugs available to certain patients outside of a clinical trial.

Both S. 204 and the House bill also restrict the right to try to investigational drugs that have completed phase I testing, are covered by an investigational new drug (IND) application, are in active development and are not on a clinical hold.

The big difference between the Senate bill and the House revision, which was to be formally introduced Monday, is which patients have a right to seek to try an unapproved drug. S. 204 applies to those who have been diagnosed with a "life-threatening disease or condition" and who have exhausted approved treatment options and are unable to participate in a clinical trial involving the investigational drug, as certified by a physician.

The House bill is more definitive. Besides having exhausted approved treatments and being ineligible or unable to participate in a clinical trial for the drug, a patient seeking to try an IND must be at "a stage of a disease or condition in which there is reasonable likelihood that death will occur within a matter of months" or have "a disease or condition that would result in significant irreversible morbidity that is likely to lead to severely premature death," according to the House version.

"This bill has been a long time coming, but in striking the right balance for patients and their safety, the House is on track to deliver hopeful news for patients desperately seeking the right to try investigational treatments and therapies," Energy and Commerce Committee Chairman Greg Walden (R-Ore.) and Health Subcommittee Chairman Michael Burgess (R-Texas) said.

Not everyone agrees with that assessment. Although the House bill makes several improvements to S. 204, Michael Carome, director of Public Citizen's Health Research Group, said it "still has fundamental flaws that would put vulnerable patients at risk and undermine their rights."

For instance, he said, "the bill still would offer false hope to patients by creating a dangerous pathway for access to experimental medications and biological products" by bypassing the FDA's expanded use program and broadly immunizing manufacturers, sponsors, physicians, clinical investigators and hospitals from liability for a range of conduct related to a patient's use of an experimental therapy.

Carome's comments Monday echoed testimony Kenneth Moch, president and CEO of Cognition Therapeutics Inc., gave at an October Health Subcommittee hearing on the right-to-try bill. "This is feel-good legislation, which gives false hope to patients in need without actually helping them," he said. (See *BioWorld*, Oct. 4, 2017.)

At that hearing, Ellen Sigal, founder of Friends of Cancer Research, warned about the unintended consequences of bypassing the FDA. "Any legislation that goes forward cannot circumvent the FDA and must be carefully crafted to ensure that we don't create a loophole for charlatans and snake oil salesmen to take advantage of desperate patients," she said.

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>
> Michael Carome, Director
> Public Citizen's Health Research Group

FDA Commissioner Scott Gottlieb also cautioned the lawmakers against creating a framework that would cater to the least promising candidates and allow clinics and individual providers to promote questionable therapies. He noted that although the FDA approves 99 percent of the expanded use applications it receives, 70 percent of the investigational drugs offered under the program are never approved. That means patients are getting access to drugs that ultimately don't work.

Yet several states have passed right-to-try bills and Congress seems determined to follow suit. Because of the changes in the House bill, the Senate would have to vote on it again if the House passes it. If the bill makes it to his desk, President Donald Trump likely will sign it, as he made right to try a health care priority in his State of the Union address in January.

Other legislation in the works

Meanwhile, Congress is working on a raft of drug-related proposals, some of which could be passed as stand-alone bills, while others might catch a ride on spending or other must-pass legislation.

Late last week, a bipartisan group of senators introduced the Preserving Access to Cost Effective Drugs Act to close a loophole that resulted in Allergan plc transferring six Restasis (cyclosporine) patents to the Saint Regis Mohawk Tribe and exclusively licensing them back in perpetuity. The tribe then tried to use sovereign immunity to shield the patents from inter partes review. Although the Patent Trial and Appeal Board determined that tribal sovereign immunity doesn't apply to its proceedings, that question is now on appeal before the Federal Circuit. The sponsors of the bill said it is aimed at what they called "sham transactions" and would not prevent biopharma companies from partnering with tribes for research, development and licensing of drugs. (See *BioWorld*, Feb. 27, 2018.)

Also last week, Sen. Joe Manchin (D-W.Va.) introduced a bill to restore the Drug Enforcement Administration's (DEA) authority to go after pharmaceutical companies that violate the law and flood communities with opioids. The bill would make changes, requested by the Department of Justice, to amend the 2016 Ensuring Patient Access and Effective Drug Enforcement Act

See Unapproved, page 7

China

Continued from page 1

Western companies seeking global expansion.

On the other hand, cultural and language barriers create apprehension between prospective partners. And government policy changes meant to improve and incentivize biopharma drug development in China are fraught with uncertainty, leaving would-be partners hesitant until they see how it all plays out.

Nevertheless, Jonathan Wang, vice president and head of business development for Shanghai-based Zai Lab, has a strong piece of advice for his colleagues in the U.S. and Europe.

"You should think about China earlier," he told them Monday at the RAI Convention Center in Amsterdam on the opening day of the BIO-Europe Spring conference. "Competition is intensifying there."

Zai Lab has taken a leading role in forming partnerships with overseas firms, helping companies like Bristol-Myers Squibb Co. and Five Prime Therapeutics Inc. gain access to the Chinese market.

Wang participated in a session focused on "New Opportunities in China, From Drug Development to Commercialization." Panelists agreed that interest in Chinese partnerships, as well as efforts toward innovation by China-based companies, are growing at a rapid pace.

Linda Pullan, president of Las Vegas-based Pullan Consulting, a company that has helped negotiate several deals between China and Western companies, said the interest is increasing because the opportunities are increasing. The Chinese government's introduction of the Marketing Authorization Holder (MAH) mechanism in 2016, for instance, has made innovation easier for research and development companies in China.

"When one goes to China, to almost any major city in China, it's almost stunning to see the number of young companies going up," she said. "It is an amazing growth pattern."

But the Chinese companies do not necessarily follow the same path followed by young U.S.-based biopharma companies.

"The other parameter that is different in many ways is the lack of historic role models," Pullan said. "If you're in Boston and you're a young biotech company, you see Novartis and you see Roche and there's tremendous cross-fertilization. China does not have that luxury. There's not the company infrastructure. It's still a very young ecosystem."

Founded in 2014, Zai has ramped up quickly, with six clinical programs currently in cancer, infectious disease or autoimmune indications, and a $172.5 million IPO in the U.S. completed last September. It has signed numerous deals with U.S. and European companies, including one with New York-based Bristol-Myers in 2015 to handle development and commercialization in China of brivanib to treat hepatocellular carcinoma. More recently, in December, it signed a deal for Chinese rights to South San Francisco-based Five Prime's FPA-144, a tumor immunotherapy that overexpresses FGFR2b, to treat gastric and gastroesophageal junction cancer. (See *BioWorld*, Dec. 28, 2017.)

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> Linda Pullan
> President, Pullan Consulting

"Zai is leading the way in bringing these drugs into China as the partner of choice," said Zai co-founder Marietta Wu, who is also managing director of Quan Capital, a global venture fund that is backed by Zai.

Not only does Zai bring innovation to China through partnering, but Quan Capital looks for investments in "certain capability gaps" or areas in which Chinese companies are not innovating, Wu said. One of those gaps is the cancer immunotherapy space.

"Chinese patients read about the PD-1s" and other innovative products, Wang said, "and they can't get access to that."

Just as Chinese patients are lacking access to innovative drugs, U.S. and European drug developers are failing to recruit certain groups of patients for clinical trials, an area in which China could easily fill a need. The country has large numbers of potential patients for clinical trials focused on Asia-centric diseases, such as gastrointestinal cancers, hepatitis B virus and lupus, Wang said.

But in order for collaborations to work, partners need to rely on quality data. The Chinese government's reforms include the cutting down of wait times for moving into the clinic, "enabling more global participation," Wang said.

Potential partners need to find ways to overcome cultural differences, such as the Chinese tendency to conduct business based on relationships vs. the American way of legal, signed contracts, not to mention time zone barriers and language barriers. Hiring employees who speak the language of the partner is essential, Wang said.

"When you start doing the project you'll be talking with people who are maybe one or two or several levels below the CEO," he said. "They ultimately are the people who have ownership." ♦

Unapproved

Continued from page 6

"to restore DEA's authority to go after bad actors and reduce unnecessary bureaucracy," Manchin said.

On another front, several lawmakers are trying to craft a bipartisan bill to reauthorize pandemic preparedness provisions that are set to expire Sept. 30. Those provisions enable the supply and maintenance of the national stockpile of medical countermeasures and fund the development of treatments for infectious disease outbreaks or other emergencies. ♦

NHS

Continued from page 1

advanced therapies to be applied at scale in the National Health Service (NHS).

The Advanced Therapy Treatment Centers will put in place the integrated processes and systems needed to routinely deliver cell and gene therapies.

That will include elements such as near-patient manufacturing for autologous therapies, traceability and tracking for products and for patient follow-up, and the means to capture real-world evidence to support reimbursement and payment.

The centers will run clinical trials of products in development and also be responsible for establishing best practice in the administration of cell and gene therapies that are starting to come through regulatory approvals.

"The objective over three years is to scale up to 10 times the current number of products coming through clinical trials and also to see the numbers of approved products [administered] increase gradually," said Keith Thompson, CEO of the Cell and Gene Therapy Catapult, the national body that has responsibility for bridging the gap between academia and industry to promote commercialization of advanced therapies.

That will see each center administering 2,000 to 3,000 treatments per annum during the three-year project, whilst building up the capacity to deliver 10,000 treatments a year.

The industry body, the Alliance for Regenerative Medicine, is predicting that over the next three years around 40 regenerative medicine products will get regulatory approval.

"The timing could not have been better: We've been pushing for this for a long time and now it is happening as approvals are coming through. We will be getting the infrastructure in place in advance," said Thompson.

The three centers, based in the regions around Manchester, Birmingham and Newcastle, won the funding in a competition with other university hospitals across the U.K. They already are working to develop a number of advanced therapies with existing networks of collaboration partners.

Thompson said the aim is that they now move on from ad hoc research to routine administration, whilst continuing to be involved in clinical trials. "We are trying to encourage innovation, but we also want to build generic systems," Thompson said.

There are other specialist advanced therapies groups around the country and part of the brief of the Advanced Therapy Treatment Centers is to share the expertise they build as part of the project. "Therapies won't get out to large-scale national adoption unless there is a whole process from manufacture to delivery," said Thompson.

The Cell and Gene Therapy Catapult's job is to provide the glue that holds everything together. "Our role is to bring cohesiveness, to provide the interface to regulators, to [health technology assessment] and to make sure what we get out of this investment is scaled systems that can be rolled out across the U.K.," said Thompson.

> *"The timing could not have been better: We've been pushing for this for a long time and now it is happening as approvals are coming through.*
>
> Keith Thompson
> CEO, Cell and Gene Therapy Catapult

One element it is important to centralize is the collection of real-world evidence showing how products perform when on the market. That will make it possible to do long-term follow-up of patients treated with therapies that in some cases are expected to provide cures for diseases where currently there are only palliatives, and provide data for cost-effectiveness analyses of expensive products.

Getting government funding to develop dedicated systems for cell and gene therapies is a recognition of the intrinsically different nature of those products and the challenges of adoption, Thompson said.

"For new chemical entities or large molecules, no one has to think about how to get them into a hospital; you just send them to the hospital pharmacy," he said. "However, for advanced therapies you need new supply chains, IT systems for patient registries and product tracing, near-patient thawing, and so on. The idea of the project is [to] systematize all of this."

The work will help companies to commercialize cell and gene therapy products, regardless of their size and budgets.

"Even big pharma can't do it without systems being in place," said Thompson. "They are all welcoming this initiative." ♦

In the clinic

Acesion Pharma ApS, of Copenhagen, started a phase I trial testing the safety and tolerability of AP-30663 in 48 healthy subjects. The trial is expected to be complete in June with data available by the end of August. AP-30663, which inhibits SK channels, is being developed as a treatment for atrial fibrillation.

Aptevo Therapeutics Inc., of Seattle, reported outcomes data from a study of Ixinity (coagulation factor IX) at the Thrombosis and Hemostasis 2018 Summit of North America San Diego. The median annualized bleed rate for hemophilia B patients using Ixinity as a prophylaxis was 1.6. In the study, 89 percent of patients were very satisfied or somewhat satisfied with the drug while 22 percent of patients reported they were very active and 56 percent reported they were somewhat active.

Arrowhead Pharmaceuticals Inc., of Pasadena, Calif., treated the first patient in the phase I AROAAT1001 trial testing ARO-AAT in five cohorts of eight healthy volunteers who will receive placebo or different doses ARO-AAT, an RNAi drug designed to reduce the liver production of Z-AAT protein in patients with alpha-1 antitrypsin deficiency.

India

Continued from page 1

The Central Drugs Standard Control Organisation (CDSCO) plans to set up a cell to support innovation in the pharmaceutical sector by facilitating the flow of information on regulatory procedures at all stages of drug development. The proposed Innovation Support Regulatory Cell will address the regulation information needs of different types of innovators, from those working on small-molecule generic drugs to complex, large molecules or biologics such as vaccines and peptides; as well as medical devices and startup companies, India's Drugs Controller General S. Eswara Reddy told reporters on the sidelines of the recent BioAsia India 2018 conference.

The cell will also provide detailed information online on procedures to be followed and regulatory standards required to be met at all stages of drug development, from preclinical animal studies to clinical phase I, phase II and phase III studies. That could help drug and medical devices innovators understand the regulatory requirements that are needed to get marketing approval for a new product.

Reddy announced the launch of the cell during a CEO conclave at India's annual biotechnology industry conference, BioAsia 2018. Innovators are considered scientists who have specific domain expertise but may genuinely lack information about regulatory requirements, Reddy said. Scientifically sound regulation would, in turn, promote ease of doing business for drug companies.

"We will have dedicated manpower under this cell to design standard operating procedures and also put up an FAQ on our website," he added.

India has seen a gradual increase in innovation investments by biotech and pharma companies and the last decade has been "transformational" with respect to improving the overall ecosystem for innovation in life sciences.

"Suddenly, there is real hunger for innovation in newer areas in India. Lots of younger companies are willing to innovate," Taslimarif Saiyed, CEO and director of Centre for Cellular and Molecular Platforms (C-CAMP), Bangalore, told the conference attendees. C-CAMP is an initiative of India's Department of Biotechnology to foster cutting-edge life science research and innovation.

"There is an explosion of innovation happening in India," said Kiran Mazumdar Shaw, chairman and managing director of Bangalore-based Biocon Ltd. A major trigger is that Indian companies no longer have intellectual property rights concerns. "Lots of companies in India are beginning to focus on IP-driven innovation," she said.

Telengana state, whose capital Hyderabad hosts BioAsia, is home to India's largest startup incubator, T-Hub. T-Hub's CEO, Jay Krishnan, said early data pointed to significant innovation happening in health technology startups, which includes life sciences, biotech and medical technology.

That said, Indian biopharma companies need to do a lot more. "India needs an open innovation model," Saiyed said.

And while India has "done great work on the development side, for example in chemical technology, generics and reverse engineering," it has not, "unfortunately, seen that kind of success" in the field of research and innovation, Sudhir Kumar Singh, president of discovery and development at GVK Biosciences, Hyderabad, cautioned.

Research and innovation require multidisciplinary talent for new drug discovery, and collaboration between academia and industry, Singh noted. "India is not quite there."

Risks and regulations

A major snag is Indian companies' averseness to risk.

"Indian companies need an appetite for risk-taking," Singh added.

"Risk aversion of Indian companies in drug discovery is huge," agreed Anil Koul, director of the Institute of Microbial Technology, Chandigarh, under India's public-funded Council of Scientific and Industrial Research.

"Indian companies are also lacking in innovations in manufacturing, be it active pharmaceutical ingredients [APIs], or vitamins or vaccines," added Dhileep Krishnamurthy, chief scientific officer at China-based Zhejang Nhu Co. Ltd. Indian companies continue to use old technologies for manufacturing, and should tap opportunities for using new technologies in making new enzymes and biologics, as well as opportunities for public-private partnerships, Krishnamurthy said.

Companies are also focusing on improving regulatory compliance.

"Companies need to upgrade their standards of compliance," Shaw said. They are also focusing on training their personnel to plug the gap of good training, she said.

The BioAsia conference itself saw new innovation initiatives take off. For example, Bangalore-based Biocon announced it would set up an R&D lab of subsidiary Syngene in Genome Valley, Hyderabad. Biocon's Shaw also announced plans for expansion of the company's current API /intermediates facility.

And the Telangana State Industrial Infrastructure Corp. and Malaysia's Central Spectrum (M) Sdn Bhd, which is the master developer of Selangor Bio Bay mixed development project in Malaysia, signed a memorandum of understanding at the conference, to collaborate in research in life sciences, biotechnology, health care and medical devices.

Under the agreement, the two sides would jointly market and promote the Telangana and Selangor Bio Bay as possible hubs in the Asian region for companies and investors in the field of life sciences, medical devices, health care and biotechnology, especially in the areas of preclinical and clinical research, pharmaceutical regulations, medical device development, good manufacturing practices and commercialization.

In addition to India's efforts to foster applied research in institutions and nurture innovation-driven entrepreneurship, in a parallel track, Indian companies are addressing regulation issues by setting up pharmacovigilance units. ♦

Brexit

Continued from page 5

investment relative to health care spending," Thomas said.

Cancer and rare diseases, by their nature, are particularly amenable to analysis and therapeutic intervention with the tools and technologies of molecular biology. Addiction, in its myriad, multidimensional complexity, is a tougher problem – the notion that a single druggable molecular target exists still seems fanciful, even as researchers continue to probe the genetic underpinnings of the problem.

Progress in pain and depression hasn't been much better. Clinical trial starts for new drugs in depression dropped 50 percent over the 2011–2016 period vs. 2006–2010. Over the same period, trial starts for new pain drugs fell by 25 percent, Thomas said, citing recently published BIO reports, which are part of its effort to encourage a response from both industry and policy makers.

But much of industry these days is a taker rather than a maker of innovation. The ideas and insights that could eventually help to make a difference will come from academic research not from industry discovery labs.

"The science hasn't really advanced. There isn't anything we can do about it," Ji Li, head of global business development at Beijing-based Beigene Ltd. said. "The brain is a very complicated organ – the last frontier."

Of course, in gaps lie opportunities. Genentech is routinely collecting genetic information from the patients it enrolls in clinical trials. It also recently signed up to the Finngen consortium, a €59 million (US$73 million) initiative to sequence the genomes of some 500,000 people, or about 10 percent of the Finnish population.

"The Finnish population is a so-called founder population," Tom Zioncheck, global head of neuroscience, ophthalmology and research tools and technologies business development, told *BioWorld*. The data emanating from the project will be shared with other industry partners – other participants include Abbvie Inc., Astrazeneca plc, Biogen Inc., Celgene Corp., Merck & Co. Inc. and Pfizer Inc. But each will be able to analyze the data in a proprietary fashion and to conduct their own individual analyses.

The meeting continues Tuesday. ♦

In the clinic

Asit Biotech SA, of Brussels, said results of a phase III trial testing gp-ASIT+ as a treatment of grass pollen-induced rhinitis were published in *Allergy*. The treatment produced a reduction in the combined score of symptoms and medication intake during natural exposure to grass pollens.

Biogen Inc., of Cambridge, Mass., reported interim data from the ongoing phase II NURTURE trial testing Spinraza (nusinersen) in 25 pre-symptomatic infants with spinal muscular atrophy at the Muscular Dystrophy Association Clinical Conference in Arlington, Va. The patients had a mean CHOP INTEND score of 58.4 out of 64 at last visit, with all the infants achieving the age-expected World Health Organization motor milestone of sitting without support. Biogen also reported data from Study CS2, a case study of five teens who received Spinraza over 2.5 years who had improvement in the Hammersmith Functional Motor Scale–Expanded, stabilization on the Upper Limb Module, improvement in the six-minute walk test, and stable or improved scores on the Assessment of Caregiver Experience with Neuromuscular Disease.

Bristol-Myers Squibb Co., of New York, and **Pfizer Inc.**, of New York, presented findings at the American College of Cardiology meeting in Orlando, Fla., from a real-world data analysis reporting outcomes among different direct oral anticoagulants, including Eliquis (apixaban), rivaroxaban and dabigatran, to date. In that analysis, apixaban use was associated with significantly lower rates of both stroke/systemic embolism (S/SE) (p=0.004) and major bleeding (MB) (p=<0.001) when compared to rivaroxaban; and significantly lower rates of both S/SE (p=<0.001) and MB (p=<0.001) when compared to dabigatran.

Cadent Therapeutics, of Cambridge, Mass., started a phase I trial testing CAD-1883, a positive allosteric modulator of the small conductance calcium-activated potassium (SK) channel. Further details of the trial weren't disclosed; however, Cadent noted that changing the calcium sensitivity of SK channels could help patients with spinocerebellar ataxia and essential tremor.

Other news to note

Biohaven Pharmaceutical Holding Co. Ltd., of New Haven, Conn., announced a restructuring of its global license agreement with **Bristol-Myers Squibb Co.**, of New York, for Biohaven's small-molecule calcitonin gene-related peptide (CGRP) receptor antagonist platform, which includes rimegepant, a CGRP receptor antagonist for the acute treatment of migraine, and BHV-3500, a CGRP receptor antagonist for the acute treatment and prevention of migraine. As part of the restructuring, Biohaven will make an up-front payment of $50 million to BMS in return for a low single-digit reduction in the royalties payable on net sales of rimegepant and a mid-single-digit reduction in the royalties payable on net sales of BHV-3500. Under the original license agreement with BMS, Biohaven was obligated to make tiered royalty payments based on annual worldwide net sales of licensed products upon their approval and commercialization, with percentages in the low- to midteens. The change also removes BMS's right of first negotiation to regain its IP rights or enter into a license agreement with Biohaven following the company's receipt of top-line data from its phase III trials with rimegepant. It also permits Biohaven to potentially license rimegepant or BHV-3500 to a company with a CGRP antibody program, it said. Biohaven's obligations to make development and commercial milestone payments to BMS remain unchanged. The restructuring was financed through a $55 million private placement of 2 million Biohaven common shares at a price of $27.50 per share.

In the clinic

Eleven Biotherapeutics Inc., of Cambridge, Mass., completed enrollment in the phase III VISTA trial testing Vicinium, an antibody-drug conjugate targeting epithelial cell adhesion molecule antigens, in patients with non-muscle invasive bladder cancer who have been previously treated with bacillus Calmette-Guérin. Top-line data measuring responses and durability of responses after three months of treatment are expected in mid-2018, while 12-month data from the trial are expected in mid-2019.

Immune Design Corp., of Seattle, reported data from a trial testing CMB-305, a prime-boost immunotherapy targeting NY-ESO-1+ cancers, in 25 NY-ESO-1+ soft tissue sarcoma (STS) patients, including 14 synovial sarcoma patients. The median overall survival across all STS patients was 23.7 months, while the median for the subset of synovial sarcoma patients has not been met. Patients who developed anti-NY-ESO-1 immune responses had better survival. The company plans to start a phase III trial for CMB-305 as a maintenance therapy in synovial sarcoma patients in the middle of this year. Immune Design also reported data from a phase II trial testing G-100, a TLR4 agonist, in combination with fractionated, low-dose radiation (XRT) with and without Keytruda (pembrolizumab, Merck & Co. Inc.) in 26 follicular lymphoma patients. G-100 plus XRT produced an objective response rate (ORR) of 15 percent while G-100 plus XRT with Keytruda had an ORR of 45 percent. The eight patients with high TLR4 expression had an ORR of 75 percent after treatment with the G-100 plus XRT and Keytruda combination.

Immutep Ltd., of Sydney, said it entered a clinical trial collaboration and supply agreement with **Merck & Co. Inc.**, of Kenilworth, N.J., to evaluate the combination of its lead immunotherapy product candidate, eftilagimod alpha, with Merck's anti-PD-1 therapy, Keytruda (pembrolizumab), in a planned phase II trial, referred to as TACTI-002 (Two ACTive Immunotherapies), which will evaluate the safety and efficacy of the immunotherapy combination in patients with non-small-cell lung cancer, head and neck cancer or ovarian cancer. Up to 120 patients across the three indications are planned to be treated, starting in the second half of this year.

IO Biotech AsP, of Copenhagen, entered a collaborative agreement with Kenilworth, N.J.-based **Merck & Co. Inc.** to test its IO-102, an IDO-derived immune modulating therapy, with Merck's Keytruda (pembrolizumab) in patients with metastatic non-small-cell lung cancer (NSCLC). IO will run the phase I/II trial testing the combination with or without chemotherapy as a first-line treatment for metastatic NSCLC, with Merck providing Keytruda for the study.

Janssen Pharmaceuticals Cos., part of New Brunswick, N.J.,-based **Johnson & Johnson**, reported results of a new analysis showing that Invokana (canagliflozin) significantly reduced the risk of cardiovascular (CV) death or hospitalization for heart failure (HHF) in patients with type 2 diabetes (T2D) at high CV risk. The exploratory analysis from the CANVAS Program was presented at the American College of Cardiology meeting in Orlando, Fla., and simultaneously published in *Circulation*. Results showed canagliflozin was associated with a significant reduction in risk of CV death or HHF by 22 percent, fatal or hospitalized heart failure by 30 percent, and HHF alone by 33 percent. The benefit of reduced risk of CV death or HHF was 39 percent greater in patients with a prior history of heart failure, compared to the 13 percent without heart failure, at baseline.

Merrimack Pharmaceuticals Inc., of Cambridge, Mass., will expand enrollment in its ongoing phase II SHERLOC trial testing MM-121 in combination with docetaxel, compared with docetaxel alone, in patients with heregulin-positive non-small-cell lung cancer who have progressed after a platinum-containing regimen. The trial, which will measure progression-free survival, will now enroll 100 patients, up from a previous target of 80 patients. Top-line data from the trial are expected in the second half of 2018.

Myr Pharma GmbH, of Burgwedel, Germany, said it completed its MYR 202 phase IIb trial testing Myrcludex B in chronic hepatitis delta virus (HDV). A total of 120 subjects were enrolled and results of the study will be presented at the upcoming International Liver Congress in Paris. Myrcludex B, an entry inhibitor, has orphan designation for HDV from the EMA and FDA, plus PRIME eligibility from the EMA.

NGM Bio Inc., of South San Francisco, confirmed results from an exploratory 12-week phase II trial of NGM-282 in nonalcoholic steatohepatitis (NASH) patients, which revealed improvements in histological measures of disease. Treatment improved fibrosis and NASH-related histology in patients with biopsy-confirmed NASH, which is preceded by significant decreases in hepatic steatosis, liver transaminases and fibrosis markers at six weeks. Data were published in *The Lancet*.

Portola Pharmaceuticals Inc., of South San Francisco, reported interim results from ANNEXA-4, its ongoing phase IIIb/IV trial of universal factor Xa inhibitor antidote Andexxa (andexanet alfa) among patients experiencing acute major bleeding while taking a factor Xa inhibitor. Data from 228 patients (of which 132 were adjudicated for efficacy) showed that Andexxa rapidly and significantly reversed anti-factor Xa activity when administered as a bolus, and sustained that reversal when followed by a 120-minute infusion. In addition, 83 percent of those patients achieved excellent or good hemostasis (stoppage of bleeding) over a 12-hour period following treatment with Andexxa. Thrombotic events (11 percent) and death rates (12 percent) were consistent with previous ANNEXA-4 trial results and with the high background thrombotic risk of the enrolled patient population. Results were presented at the American College of Cardiology meeting in Orlando, Fla.

Other news to note

Cocrystal Pharma Inc., of Atlanta, a company discovering and developing potential antiviral therapeutics that target the replication machinery of hepatitis viruses, influenza viruses and noroviruses, has completed an uplisting to the Nasdaq Capital Market, where its shares now trade under the symbol COCP.

Other news to note

Emmaus Life Sciences Inc., of Torrance, Calif., said its marketing authorization application for Xyndari (L-glutamine oral powder) was validated and is under assessment by the EMA for sickle cell disease. The FDA approved the product, branded Endari in the U.S., last year for use in adult and pediatric patients, age 5 and older, for reducing the acute complications of sickle cell disease. (See *BioWorld*, July 10, 2017.)

Hikma Pharmaceuticals plc, of London, said it received a response from the FDA in connection with its abbreviated new drug application for the generic version of London-based **Glaxosmithkline plc**'s Advair Disku (fluticasone propionate and salmeterol inhalation powder). Stemming from a complete response letter from the agency in May, the company was able to address and clarify the majority of the questions raised. However, in regards to an outstanding issue on a clinical endpoint study, the company engaged in the FDA's dispute resolution process. The FDA has now concluded that process, upholding its original determination and requesting the completion of an additional clinical endpoint study. The company said, in anticipation of that as one of the potential outcomes, it has already finalized the planning for a new study and expects to start patient enrollment in the coming weeks, with the potential of submitting a response with new clinical data by early 2019.

Mannkind Corp., of Westlake Village, Calif., said it is restructuring certain of its outstanding debt obligations, reducing outstanding principal by an aggregate of $14.5 million along with the corresponding interest expense. That will be effected by: canceling approximately $8.2 million in principal under a promissory note with the Mann Group through the purchase of 3 million shares at $2.72 each; extending the maturity date of the remaining principal of approximately $71.5 million under the amended and restated promissory note with the Mann Group by 18 months to July 1, 2021, with principal and any accrued and unpaid interest permitted to be converted into common stock, at the option of the Mann Group, at a conversion price of $4 per share; exchanging $5 million in principal due May 2018 under a Deerfield facility for 1.83 million shares at $2.72 per share; and exchanging approximately $1.3 million in principal due May 2018 under the Deerfield facility for 441,618 shares of common stock. Following those transactions, the company's current amount of principal owed to Deerfield is $45 million.

Oncosec Medical Inc., of San Diego, said research by company scientists aimed at improving the therapeutic efficacy of IL-12 intratumoral gene electrotransfer through novel plasmid design and modified parameters using the firm's current clinical electroporation (EP) platform has been published in *Nature Gene Therapy*. Researchers sought to improve the efficacy and systemic antitumor response of the company's clinical IT-pIL12-EP platform by modifying in vivo electroporation conditions and enhancing plasmid-derived IL-12p70 expression. The improved IL-12 therapeutic platform was evaluated in vitro and in vivo using murine syngeneic tumor models. Findings showed that modifications to the EP parameters, including lowering the electric field strength (low voltage) combined with a longer pulse length, significantly increased the transfection efficiency of intratumoral electroporation.

In the clinic

Realm Therapeutics plc, of Malvern, Pa., said its phase II study of PR-013, a topical ophthalmic solution for the treatment of allergic conjunctivitis, did not demonstrate efficacy, and the company decided to discontinue further development of that program. Further details were not disclosed. Enrollment of a phase II atopic dermatitis study testing PR-022 topical gel is on track, with top-line results expected in the third quarter.

Regeneron Pharmaceuticals Inc., of Tarrytown, N.Y., and **Sanofi SA**, of Paris, reported data at the American College of Cardiology meeting in Orlando, Fla., showing that the ODYSSEY OUTCOMES trial met its primary endpoint, demonstrating that high-risk patients who added PCSK9 inhibitor Praluent (alirocumab) to maximally tolerated statins experienced significantly fewer major adverse cardiovascular events compared to those on maximally tolerated statins alone. Adding a lipid-lowering therapy to maximally tolerated statins was associated with reduced death from any cause. A more pronounced effect was observed in patients with baseline LDL-C levels at or above 100 mg/dL despite maximally tolerated statins, who are at high risk of suffering a future event; in that group, Praluent reduced risk of major adverse cardiovascular events by 24 percent and was associated with a 29 percent lower risk of death overall. The safety profile of Praluent in the 18,924-patient, long-term trial was consistent with previous trials, and no new safety issues were observed.

Ritter Pharmaceuticals Inc., of Los Angeles, reported microbiome data from a phase IIb study of RP-G28 in 377 lactose intolerance patients, showing the drug modified the relative abundance of 28 bacterial species. Specifically, a dramatic increase in species of *Bifidobacterium* was observed, including some known to metabolize lactose. The understood mechanism of action of RP-G28 for mitigating lactose intolerance symptoms is by increasing lactose-metabolizing bacteria in the colon that compensate for the deficit of endogenous lactase activity. Ritter is moving toward phase III testing in the second quarter.

Selecta Biosciences Inc., of Watertown, Mass., said the first patient was dosed in a phase I trial of SEL-403, its candidate consisting of SVP-Rapamycin in combination with LMB-100, a recombinant immunotoxin. The study will enroll patients with malignant pleural or peritoneal mesothelioma who have undergone at least one regimen of chemotherapy and is being conducted under a Cooperative Research and Development Agreement with the National Cancer Institute. The open-label, dose-escalation trial will enroll up to 18 patients and will evaluate the safety and tolerability and provide data on pharmacokinetics, anti-drug antibody levels and an objective response rate assessment.

In the clinic

Sienna Biopharmaceuticals Inc., of Westlake Village, Calif., said the first patient was dosed in its phase I/II proof-of-concept trial of topical candidate SNA-125, a dual JAK3/TrkA inhibitor, in atopic dermatitis and associated pruritis. The randomized, double-blind, placebo- and comparator-controlled, intra-individual trial will evaluate the safety, tolerability and efficacy of SNA-125 compared to vehicle and other reference formulations in about 30 patients with atopic dermatitis. Results are expected in the fourth quarter.

Synlogic Inc., of Cambridge, Mass., presented expanded data from its phase I study of SYNB-1020, a synthetic biotic medicine in development for hyperammonemia associated with urea cycle disorders and cirrhosis, at the Society for Inherited Metabolic Disorders meeting in San Diego. In healthy volunteers, SYNB-1020, a probiotic engineered to convert ammonia into an essential amino acid arginine, was safe and well-tolerated in 52 subjects up to a maximum tolerated daily dose of 1.5x10^12 CFU for 14 days. As designed, the bacteria did not colonize and all subjects cleared SYNB-1020 from their systems within two weeks of the final dose. In the multiple ascending-dose component, a tracer study was undertaken using orally administered 15N ammonium chloride, a substrate for SYNB-1020, revealing a dose-dependent relationship between administration of SYNB-1020 and change in plasma and urinary nitrate. A dose-dependent relationship also was observed in total urinary nitrate. The firm recently initiated a phase Ib/IIa study in patients with cirrhosis and elevated blood ammonia.

XW Laboratories Inc., of Wuhan, China, said it started a phase I single, ascending-dose (SAD) study in healthy subjects in Australia for its XW-10172, its small-molecule treatment for narcolepsy, to assess safety, tolerability and pharmacokinetics. XW Labs intends to begin a multiple ascending-dose study pending satisfactory outcome of the initial doses from the SAD study.

Other news to note

Orbis Biosciences Inc., of Lenexa, Kan., said it granted **Daré Bioscience Inc.**, of San Diego, an exclusive option to license worldwide rights to its long-acting contraceptive products. The agreement leverages Orbis' Stratμm technology to create an etonogestrel contraceptive for six-month and 12-month durations. The agreement includes preclinical studies and the option to enter a license agreement for clinical development. Financial terms were not disclosed.

Orexigen Therapeutics Inc., of San Diego, said it elected to file a voluntary petition under Chapter 11 of the Bankruptcy Code in the U.S. Bankruptcy Court for the District of Delaware. It also intends to file a motion seeking authorization to pursue an auction and sale process under Section 363 of the U.S. Bankruptcy Code. The proposed bidding procedures, if approved by the court, would require interested parties to submit binding offers to acquire substantially all of Orexigen's assets, which would be purchased free and clear of the company's indebtedness and other liens and interests. The company said it has filed a series of motions with the court seeking to ensure the continuation of normal operations during that process and has the support of a controlling number of its senior secured noteholders for that process, who have made a $35 million financing commitment. Orexigen, which sells obesity drug Contrave (naltrexone HCl/bupropion HCl extended release), has struggled on the commercialization front. In its third-quarter 2017 earnings, Orexigen reported total revenue of $18.9 million, including $17.8 million in net sales of Contrave in the U.S. The company had $70.6 million on its balance sheet as of Sept. 31. Shares of Orexigen (NASDAQ:OREX) fell $1.07, or 76.4 percent, to close Monday at 33 cents.

Roche Holding AG, of Basel, Switzerland, joined the Biomed X Innovation Center in a collaboration in immunology. Under the terms, Biomed X will launch a global call for applications to establish a biomedical research group in Heidelberg, Germany, with the objective of developing approaches for treating immune-mediated diseases.

Sarepta Therapeutics Inc., of Cambridge, Mass., said the final minutes from a February type C meeting held with the FDA's Division of Neurology Products to solicit guidance on the development pathway for its therapeutic candidate, golodirsen, a phosphorodiamidate morpholino oligomer engineered to treat those patients with Duchenne muscular dystrophy (DMD) who have genetic mutations subject to skipping exon 53 of the DMD gene have been received. The company previously reported that a phase I/II study to assess the safety, tolerability, pharmacokinetics and efficacy of golodirsen in 25 boys with confirmed deletions of the DMD gene amenable to exon 53 skipping demonstrated statistically significant results in favor of golodirsen on all biological endpoints. Based on the results of that 4053-101 study and on the FDA's feedback, the company intends to complete a rolling submission of a golodirsen NDA by year-end, seeking accelerated approval based on an increase in dystrophin protein as a surrogate endpoint. It has proposed that its study 4045-301 (ESSENCE), a phase III ongoing placebo-controlled trial assessing the efficacy of golodirsen and casimersen, serve as the postmarketing confirmatory study. The division confirmed that ESSENCE could possibly serve as a confirmatory study if golodirsen is granted accelerated approval, with the understanding that it is incumbent upon Sarepta to describe how it will successfully enroll and complete the ESSENCE study in light of an accelerated approval.