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Biopharma execs to Senate Finance Committee: Current rebate system no longer 'fit for purpose'

By Mari Serebrov, Regulatory Editor

Following the Senate Finance Committee's second hearing on prescription drug prices Tuesday, U.S. lawmakers, at least some of them, may change their tune on the rebate reforms the administration has proposed.

Each of the seven biopharma executives called to testify before the committee said the system in which drug companies pay large rebates to pharmacy benefit managers (PBMs) for a preferred place

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FDA adcom counsels delaying review decision for Karyopharm's selinexor

By Michael Fitzhugh, News Editor

Karyopharm Therapeutics Inc.'s lead agent, selinexor, endured a tough hearing before the FDA's Oncologic Drugs Advisory Committee Tuesday, leading agency advisors to ultimately vote 8-5 in favor of delaying approval until the results of the randomized phase III trial, BOSTON, are available. The outcome could delay selinexor's potential approval by about two years.

Karyopharm is seeking accelerated approval for the medicine, in combination with dexamethasone, for the treatment of patients with relapsed refractory multiple myeloma (MM) who have received at least three prior therapies and whose disease is refractory to at least one proteasome inhibitor, at least one immunomodulatory agent and an anti-CD38 monoclonal antibody.

The Newton, Mass.-based company's request for

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Keep an ion Tetragenetics: Purdue subsidiary's $273M deal targeting non-opioids

By Randy Osborne, Staff Writer

Douglas Kahn, CEO of Tetragenetics Inc., told *BioWorld* that his firm "in pretty short order went from introducing the technology to discussing the terms of a potential relationship" for the purpose of developing non-opioid pain drugs with Imbrium Therapeutics LP, a subsidiary of Purdue Pharma LP, the embattled maker of Oxycontin (oxycodone).

Arlington, Mass.-based Tetragenetics is collecting as much as $25 million up front and contingent payments as high as $248 million in a deal with Imbrium centered on pain biologics. Imbrium will

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Henlius wins approval for China's first homegrown biosimilar

By Elise Mak, Staff Writer

HONG KONG – Chinese drug regulators have approved the first homegrown biosimilar, Shanghai Henlius Biotech Inc.'s HLX-01, a biosimilar referencing Roche Holding AG's Mabthera (rituximab), to treat non-Hodgkin lymphoma (NHL). It will be marketed as Hanlikang.

"The approval for Hanlikang broke up the monopoly by foreign drugmakers in China's monoclonal antibody market," Henlius said.

It took the company a little more than a year to score this approval. The National Medical Products Administration (NMPA, formerly the

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The BioWorld Biome

Researchers plan phase III GDNF trial in Parkinson's; delivery device is key

By Nuala Moran, Staff Writer

LONDON – Researchers in the U.K. are moving ahead with plans for a phase III study of glial-derived neurotrophic factor (GDNF) in Parkinson's disease, after overcoming the obstacles to repeated delivery of the drug directly into the brain that confounded previous studies.

The automated delivery device, developed by neurosurgeon Steven Gill, was successfully implanted in 41 patients who took part in the phase II trial. They received a combined total

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Newco News

Anaveon closes $35M series A for selective IL-2 receptor agonists

By Cormac Sheridan, Staff Writer

DUBLIN – The concept of harnessing interleukin-2 (IL-2) signaling to boost immune responses to cancer is almost as old as the biotechnology industry. Up until now, however, the idea has only been imperfectly realized because of the limitations of using recombinant IL-2.

The flagship IL-2 product, Proleukin (aldesleukin), gained approval in metastatic renal cell carcinoma (RCC) in 1992 and in metastatic melanoma in 1998 on the strength of its complete response rates of 7 percent and 6 percent, respectively. But

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Financings

Briacell Therapeutics Corp., of Berkeley, Calif., disclosed a nonbrokered private placement financing of 5 million shares priced at CA10 cents (US7.5 cents) per share for gross proceeds of CA$5 million. Recently appointed director Jamieson Bondarenko will purchase the shares and, upon closing, will have beneficial ownership of an aggregate of 23 million shares, representing about 13.7 percent of issued and outstanding shares. Briacell will use proceeds to finance its phase IIa combination study of immunotherapy candidate Bria-IMT with Keytruda (pembrolizumab, Merck & Co. Inc.) in advanced breast cancer, as well as to support other research opportunities and for working capital and general corporate purposes.

Cyclerion Therapeutics Inc., of Cambridge, Mass., entered an agreement for a private placement of up to $175 million. The offering commitments come from existing shareholders of **Ironwood Pharmaceuticals Inc.**, also of Cambridge, which is spinning off Cyclerion, as well as new investors and certain members of future Cyclerion management. Final proceeds are expected to support Cyclerion's sGC stimulator portfolio for at least two years, including four clinical data readouts expected in the second half of 2019. The financing transaction is anticipated to close in early April, immediately following the completion of Ironwood's planned tax-free spin-off of Cyclerion to Ironwood shareholders. (See *BioWorld*, Jan. 25, 2019.)

Hookipa Pharma Inc., of New York and Vienna, said it completed a $37.4 million series D financing led by Redmile Group with participation from new investors Invus and Samsara Biocapital as well as current investors. Funding will be used primarily to progress clinical development of lead development programs, including HB-101, a prophylactic cytomegalovirus vaccine candidate currently in a phase II trial in patients awaiting kidney transplantation, as well as HB-201 and HB-202, the company's lead oncology product candidates, in development for the treatment of human papillomavirus-positive cancers. In addition, Hookipa plans to apply its arenavirus platform to develop additional immuno-oncology product candidates.

Oyster Point Pharma Inc., of Princeton, N.J., disclosed a $93 million series B financing co-led by Invus Opportunities and Flying L Partners in collaboration with Falcon Vision. Existing investors New Enterprise Associates and Versant Ventures, as well as new investor Vida Ventures, participated in the round. Funds will support phase III development of its ocular surface-sparing nasal spray for treating signs and symptoms of dry eye disease. The company closed a $22 million series A in 2017. (See *BioWorld*, Nov. 8, 2017.)

PTC Therapeutics Inc., of South Plainfield, N.J., said the sole underwriter of its January public offering of 6.72 million shares partially exercised its option to purchase additional shares, increasing the total offering to about 7.6 million shares. PTC's aggregate net proceeds are expected to total about $224.1 million. RBC Capital Markets acted as the sole book-running manager.

Sage Therapeutics Inc., of Cambridge, Mass., priced a public offering of about 3.3 million shares at $150 per share for gross proceeds of about $500 million. Goldman Sachs & Co. LLC and J.P. Morgan Securities LLC are acting as joint book-running managers for the offering, set to close on or about Feb. 27. Sage granted underwriters a 30-day option to purchase up to an additional 500,000 shares of common stock. Sage is awaiting a March 19 FDA PDUFA date for Zulresso (brexanolone) injection, under review for treatment of postpartum depression. The drug got a thumbs-up from an FDA advisory committee in November. Shares of Sage (NASDAQ:SAGE) closed Tuesday at $152.76, down $6.61. (See *BioWorld*, Nov. 5, 2018.)

BioWorld

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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

Senate

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on the formulary is hurting competition and creating perverse incentives for higher and higher prices.

The CEOs were careful not to point fingers as they discussed the misalignment of the drug pricing chain. At one point, the system worked, Astrazeneca plc CEO Pascal Soriot told the committee, but today, it is no longer "fit for purpose." No one player in the system can fix it, he said, adding that the U.S. government will have to do that.

Abbvie Inc. CEO Richard Gonzalez agreed, saying that legislative action will be needed to create a final fix to realign the pricing structure.

Several of the CEOs explained that even though their list prices have continued to increase because of the rebates, their net price is decreasing – and patients are continuing to see price hikes at the pharmacy.

For instance, Jennifer Taubert, executive vice president and worldwide chairman at Janssen Pharmaceuticals, a Johnson & Johnson (J&J) company, said J&J's 2018 aggregate list price increased 6.3 percent; yet for the second year in a row, the discounts and rebates the company had to pay outweighed that increase. As a result, the aggregate net price dropped 6.8 percent.

"Across the industry, net prices for branded medicines have increased well below the rate of medical inflation in recent years," Taubert testified. But that trend hasn't been reflected in patients' out-of-pocket (OOP) costs, which increased 54 percent from 2006 to 2016.

Taubert attributed the OOP increase to changes in how health insurance is designed and how pharmaceutical benefits are managed. She noted that while patients are required to pay 13 percent of overall pharmaceutical costs, they're expected to pay only 3 percent of hospital costs.

That design hasn't kept up with advances in medicines and technologies that today treat diseases that previously had been treated with surgeries, hospitalizations and other complex interventions, Taubert said.

Until Tuesday's hearing, it seemed as if Congress had pretty much dismissed the administration's proposed rule to remove the anti-kickback safe harbor for rebates. Some lawmakers saw it as a nonstarter, saying it would increase premiums. The Pharmaceutical Care Management Association, the PBM industry group, has been pushing that perception. Last week, it urged congressional leaders to keep HHS from finalizing the rule. (See *BioWorld*, Feb. 22, 2019.)

Search for solutions

During the hearing, the biopharma execs also supported other solutions, including increased transparency on pricing, advancing biosimilar competition and removing legislative and regulatory barriers to value-based pricing. Several of the solutions they included in their written testimony – such as 340B reforms and changes to Medicare Parts B and D – were similar to the suggestions policy experts discussed at the committee's first hearing on prescription drug prices. (See *BioWorld*, Jan. 30, 2019.)

> *"You pharma executives are here because the way you do business is unacceptable and unsustainable.*
>
> Sen. Ron Wyden (D-Ore.)
> Ranking Member, Senate Finance Committee

One solution they didn't promote was using an international price index to set prices for brand drugs with no competition, noting that most new drugs are available in the U.S. first. And it can take years for some countries to approve them.

Although a few senators used their five minutes at the hearing to chastise the CEOs personally or the industry as a whole, committee Chair Chuck Grassley (R-Iowa) made it clear in his opening remarks that the purpose of every hearing in the series on drug prices is to discuss solutions for a complex problem. He also cautioned the biopharma CEOs against merely pointing fingers at other players.

"Most members of Congress are sick and tired of the blame game," he said. "It's time then for solutions. One way or another, we're going to get some clarity." Grassley also noted the need to maintain the balance between incentivizing innovation and keeping drugs affordable. "Like all systems, things can get out of balance," he acknowledged.

Senatorial scolding

Ranking Member Ron Wyden (D-Ore.) was one of the senators who chose to use his time to upbraid the executives sitting at the witness table. "It is morally repugnant when ailing patients are forced to choose between filling that next prescription or putting food on the table, because they can't afford both. It is morally repugnant when patients are forced to skip doses," he told them in his opening remarks. "You pharma executives are here because the way you do business is unacceptable and unsustainable."

He then went down the line, calling each of the witnesses out individually for something they or their company reportedly had done. He started with Abbvie, noting that the annual bonuses of Gonzalez and other top executives were tied, in part, to Humira (adalimumab) sales. Meanwhile, the company had doubled the list price of a 12-month supply of the drug from $19,000 to $38,000 over a six-year period, he said.

Wyden gave Pfizer Inc. first prize for the "emptiest gesture on pricing in 2018," citing the New York company's temporary freeze on prices last year following a phone call with President Donald Trump. "But once the president got his splashy headlines, his gaze turned elsewhere, and Pfizer's former CEO told investors it was back to 'business as normal,'" the senator said. (See *BioWorld*, July 13, 2018.)

Merck & Co. Inc. "gets second prize for emptiest gesture on pricing in 2018," Wyden continued. "It made sweet sounding promises after coming under criticism, but it cut prices for

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Karyopharm

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accelerated approval of the selective inhibitor of nuclear export compound was primarily based on part two of the phase IIb trial, KCP-330-012, also known as STORM, a single-arm trial of selinexor and dexamethasone. That trial enrolled 123 patients with relapsed refractory multiple myeloma (RRMM) who had received at least three prior therapies, including an alkylating agent, bortezomib, carfilzomib, lenalidomide, pomalidomide, daratumumab and a glucocorticoid, and whose disease was considered triple-class refractory.

The overall response rate observed in STORM was 26.2 percent, with a duration of response of 4.4 months. But the treatment was also associated with significant toxicity, the FDA said in briefing documents released ahead of the meeting. "In Part 2 of STORM, all patients experienced at least one TEAE," it said, using the initialism for treatment-emergent adverse events. Nearly two-thirds of patients experienced a serious adverse event, and most patients (88.6 percent) required a dose modification due to a TEAE, the agency pointed out. More than a quarter (28.5 percent) of patients discontinued treatment with selinexor-dexamethasone due to a TEAE.

In voting to recommend delaying review of Karyopharm's application, panelists appear to have been swayed by the toxicity, one of a trio of concerns raised by agency reviewers. STORM's status as a single-arm trial of combination therapy was another top concern, making it "difficult to isolate the treatment effect of selinexor," the agency said. Finally, "the safety profile and high rate of dose modifications suggest that the optimal dose may not have been identified," reviewers noted.

Tanya Lewis, head of global regulatory affairs at Karyopharm, framed her company's view by noting that the "rate and depth of response" to selinexor and dexamethasone in STORM was comparable to that of other recent myeloma therapies receiving accelerated approvals in patients with "markedly" less refractory disease. Patients with triple-class refractory myeloma, she said, "cannot wait and need urgent access to selinexor."

Karyopharm's head of clinical strategy, Jatin Shah, also argued the similarity angle, concluding that the drug offered "clear efficacy" in STORM for patients with triple-class refractory MM who've exhausted all other options. "For patients who entered a study with rapidly progressive disease and expected overall survival of three to five months, these responses are clinically meaningful," he said.

The BOSTON phase III randomized controlled trial that Karyopharm will now need to complete for potential approval is already fully enrolled, Lewis said. But potential approval of selinexor based on data from the study would not occur for at least two years from now, based on an NDA submission in the fourth quarter of 2020.

Even as they acknowledged significant need among the patients Karyopharm wants to treat and potential precedent for accelerated approval of other medicines for the same indication, panelists had mixed views on the company's overall presentation.

Natalie Compagni Portis, a patient representative on the advisory committee, voted in favor of delaying approval until the results of BOSTON are in. "I think the data that we have doesn't meet the FDA standard for evidence on safety and effectiveness," she said. "We absolutely need more treatments that help patients live longer and/or improve quality of life, and not just treatments that aren't worse than those available. I feel like the trial leaves us with a lot of incomplete information on both of these issues," she said.

"Given the fact that there is expanded access for those willing to take on the risk in concert with support and education from their physician and given the serious side effects and even fatal adverse events and the real lack of clarity on dosing," she added, "it seems vital and responsible to wait for more data."

David Harrington, a panelist from the Dana-Faber Cancer Institute who voted against delaying accelerated approval, saw a different dimension of the presentation, saying that while the data were not conclusive on benefits and risks of selinexor, "I think we provide patients some potential benefit here if this agent is used constructively and intelligently while we wait for additional data in a population that is not naive to side effects."

Trading in shares (NASDAQ:KPTI) of Karyopharm was halted by midday Tuesday, just ahead of the advisory committee's meeting. By that point, shares had fallen 3.6 percent to $4.88.

The FDA has granted selinexor orphan status in MM and a fast track designation for the patient population evaluated in the STORM study. The company's marketing authorization application submission to the EMA for its selinexor and dexamethasone combination has been granted accelerated assessment by the EMA's Committee for Medicinal Products for Human Use. It remains under review there. ♦

Financings

Samsara Therapeutics Inc., of New York, closed a seed financing round led by Apollo Ventures. James Peyer, managing director of Apollo, joined Samsara's board. Earlier this month, *Nature Communications* published a paper authored by the company's scientific team, demonstrating the capability of the firm's platform to identify MoA geroprotective small molecules that extend healthy life span across species and which are protective in mammalian models of disease.

Ultragenyx Pharmaceutical Inc., of Novato, Calif., said it commenced a public offering of up to $250 million of shares of common stock. The number of shares and share price have not yet been disclosed. The rare disease company also is expected to grant underwriters an option for a period of 30 days to purchase up to an additional $37.5 million. J.P. Morgan Securities LLC, Goldman Sachs & Co. LLC, BofA Merrill Lynch and Cowen are acting as joint book-running managers.

Vistagen Therapeutics Inc., of South San Francisco, priced a public offering of 10 million shares of common stock at $1 each for gross proceeds of about $10 million. Vistagen also granted underwriters a 30-day option to purchase up to an additional 1.5 million shares. The company intends to use the net proceeds for continued development of its CNS pipeline programs, and for general research and development, working capital and general corporate purposes. William Blair & Co. LLC is acting as sole book-running manager for the offering, set to close on or about Feb. 28. Shares of Vistagen (NASDAQ:VTGN) closed Tuesday at $1.12, down 24 cents.

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Tetragenetics

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take advantage of Tetragenetics' antibody discovery platform called Tetraexpress, which finds large molecule drugs targeting ion channel and other membrane proteins associated with diseases. Tetragenetics said that it expects to bring new antibody therapeutics to IND readiness so that Imbrium can advance them through trials.

"We produced some ion channels that we thought would be of interest to Purdue over a year ago," Kahn recalled. "These are channels that are implicated in pain. Scientists throughout the community are well aware of their connections to pain. We reached out to Purdue and said, 'We have a research program underway. We've had some good success to date but we do not have the resources to continue it ourselves. We need a partner if we're going to move it forward.' They took a look at the data and got quite excited about it. We have a program outlined, and the target time frame to get to [the IND stage] is 36 months." At the end of January, the state of Massachusetts sued Purdue for what it called in the complaint "a web of illegal deceit. First, Purdue deceived Massachusetts doctors and patients to get more and more people on its dangerous drugs. Second, Purdue misled them to use higher and more dangerous doses. Third, Purdue deceived them to stay on its drugs for longer and more harmful periods of time. All the while, Purdue peddled falsehoods to keep patients away from safer alternatives." Purdue characterized the complaint as "part of a continuing effort to single out Purdue, blame it for the entire opioid crisis, and try the case in the court of public opinion rather than the justice system. Such a serious allegation demands clear evidence linking the conduct alleged to the harm described, but Massachusetts fails to show such causation and offers little evidence to support its sweeping legal claims."

Tetragenetics uses the protozoa *Tetrahymena thermophila* to produce recombinant proteins for use in antibody discovery. "We're producing human ion channels created in Tetrahymena," Kahn said. Tetrahymena "turns out to be just a model organism for producing high quality and large quantities of membrane proteins, including ion channels," he said. "To the best of my knowledge, we have the only system that can produce large quantities of properly folded functional ion channels. That's the basis for all of our drug discovery."

In the Imbrium deal, Tetragenetics expects to garner the full $25 million, Kahn said. Services that the company will deliver as part of the program have "all been laid out, and they basically add up to that amount of money. Unless for some reason we stop the program, it's virtually all going to get paid," he said. The rest depends on the usual uncertainties, though he has cause for optimism. "We're like everybody else; there are numerous milestones along the way to the marketplace. Antibodies to ion channels are not easy to develop. They're among the hardest classes of drugs out there," and his firm is pioneering the effort. "There just hasn't been the technology available until now to do it," he said. "We've had some great success."

> *"To the best of my knowledge, we have the only system that can produce large quantities of properly folded functional ion channels. That's the basis for all of our drug discovery.*
>
> Douglas Kahn
> CEO, Tetragenetics

Internal effort targets type 1 diabetes

Tetragenetics "in-licensed some technology from several universities [14 years ago], but we've gone a long way from that," Kahn said, so the approach was "mostly created in-house. Our founder is an immunologist at Cornell University and has been working with this technology throughout his professional life." The techniques deployed by the firm "have been around for a long time, but the materials to generate an immune response in the animals have not been available," he said.

Among Tetragenetics' disclosed partnerships are those with Kenilworth, N.J.-based Merck & Co. Inc. and Medimmune, the unit of Astrazeneca plc, of London. "Our larger bio partners are really eager to discover biologics for the ion channels and other membrane proteins, but I'm not aware of any programs underway that we're not part of," he said.

Tetragenetics' most advanced internal program involves Kv1.3, a voltage-gated potassium channel implicated in autoimmune diseases. The company is taking aim at type 1 diabetes, with funding from the Juvenile Diabetes Research Foundation (JDRF). "We've been in a hit-to-lead program, we've just this month selected our lead, and we have a collaborator in the U.K. called Lifearc doing the humanization right now." Formerly known as MRC Technology, the London-based medical charity partnered with Tetragenetics in late 2017. IND-enabling studies are expected by the middle of this year. "We shared our data with JDRF [and] they had already identified Kv1.3 as a potential therapeutic to arrest the progression of the disease," he said. "We essentially eliminate the T cells that are attacking the beta cells. Once a patient is down to about 20-25 percent of their beta cells, that's when the symptoms of type 1 diabetes usually appear, but they still have functioning beta cells.

"We think that in time [the Tetragenetics candidate] will be a combination therapy" to be used with treatments (now in development) to regenerate the beta cells.

According to Cortellis, last year companies working on pain indications received grants and signed deals worth just under $1 billion – $997.49 million – although not all are focused on non-opioid therapies. A total of 16 included financial terms with up-front payments amounting to $374.23 million and milestone payments reaching $513.95 million. The highest money deals for the year were between Kineta Chronic Pain LLC, a subsidiary of Kineta Inc., of Seattle, and Basel, Switzerland-based Roche Holding AG's Genentech in April for non-opioid therapies, with all of the $359 million coming on the back end, and the $215 million merger of Avenue

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Parkinson's

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of 347 of 350 scheduled monthly infusions over the 40-week blinded stage of the trial, with no serious safety concerns.

The convection enhanced delivery device administered GDNF in a controlled way, with PET scans showing the drug diffused throughout the putamen.

"This trial has shown we can safely and repeatedly infuse drugs directly into a patient's brain over months or years, through a small implanted port that emerges through the skin behind the ear," Gill said. "This is a significant breakthrough in our ability to treat neurological conditions such as Parkinson's."

It is unfortunate then, that the phase II trial, results of which are published in two journal papers Wednesday, just failed to reach the primary endpoint, of a statistically significant improvement in the unified Parkinson's disease rating score (UPDRS), compared to placebo.

Patients receiving GDNF in the first nine months of the trial saw a 17 percent improvement in symptoms, compared to 12 percent in the placebo arm. There was a large variance in response, with some patients improving much more than others. Nine of the GDNF group improved by more than 35 percent in the double-blind part of the trial.

In the second part of the trial, in which all patients received GDNF, there were again improvements in both groups of patients, with no statistical significance between the two.

However, there was a significant difference between the group which received GDNF for the full 18 months of the trial and the patients in the blinded placebo group at nine months.

"Between nine and 18 months, the GDNF group continued to get better; by the end they were 30 percent better, but all had improved," said Gill, professor of neurosurgery at Bristol University.

Gill told *BioWorld* a number of factors played into the failure to reach the primary endpoint. Those included the need for caution in dosing, evidence that neurotransmitter release was initiated by administration of the infusate in the placebo arm and the fact that UPDRS gives a low weighting to reductions in the amount of "off" time patients experience when levodopa starts to lose its effect.

All 41 patients had been experiencing motor symptoms for five years at the start of the trial. Thirty-seven of them showed clinically meaningful improvements in their symptoms at the end of the study.

After nine months, there was no change in the PET scans of those who received placebo, whereas scans showed regrowth of dopaminergic neurons in all treated patients.

Alan Whone, principal investigator, said the improvement in brain scans is beyond anything seen previously in trials of surgically delivered growth factor treatments for Parkinson's disease.

The failure to produce the same effect on symptoms could be for a number of reasons. "It may be that the effects on symptoms lag behind the improvement in the brain scans, so a longer double-blind trial may have produced a clearer effect. It's also possible that a higher dose of GDNF would have been more effective, or that participants at an earlier stage of the condition would have responded better," said Whone.

Despite not reaching the endpoint, Gill said, taken as a whole, the EMA and FDA agree the data indicate GDNF is "neurorestorative." The regulators have given approval to the phase III trial design, which will use four times the dose of the phase II.

The delivery challenge

Gill has been pursuing delivery of GDNF for the past two decades. He conducted the first open-label trial, in which the growth factor was administered to five patients daily for 18 months, through an indwelling catheter.

All five showed improvements, with "off" periods of severe immobility that occupied 20 percent of their waking day before surgery completely eliminated after six months. (See *BioWorld Today*, April 2, 2003.)

GDNF owner Amgen Inc. picked up the baton, but in late 2004 halted a 48-patient phase II study, citing limited efficacy and the presence of neutralizing antibodies in some patients. None of the patients in the phase II Bristol trial had any neutralizing serum antibodies. (See *BioWorld Today*, Feb 14, 2005.)

The license to recombinant GDNF subsequently was acquired by Medgenesis Therapeutix Inc., of Victoria, British Columbia, which supported the phase II trial in Bristol.

Gill attributes the failure of the Amgen study to poor drug delivery, saying most GDNF accumulated at the tip, or refluxed up, the catheter. "You need a high flow rate to fill the volume of the putamen," he said. "That's the problem we faced after the failure of the Amgen trial."

The system Gill devised in collaboration with U.K. engineering company Renishaw plc is being used by the Finnish company Herantis Pharma plc to deliver another growth factor, cerebral dopamine neurotrophic factor (CDNF), in a phase I safety trial. The study received a €6 million (US$6.8 million) grant from the EU's Horizon 2020 research funding program. (See *BioWorld*, Sept. 26, 2018.)

Pekka Simula, CEO of Herantis, told *BioWorld* the Bristol GDNF study has paved the way for the CDNF trial. "CDNF and GDNF are structurally and mechanistically completely different. They are very distinct as neurotrophic factors, but share the same challenge that they need to be delivered intracerebrally," he said.

Gill also has been using the delivery system in the treatment of children with the lethal brain cancer diffuse intrinsic pontine glioma. Although not a formal trial, he said overall survival has doubled.

The results of the phase II trial in Parkinson's disease are not as clear-cut as would have been desirable, but there are signs of promise, said Erich Mohr, chair and CEO of Medgenesis. "In particular, when the scores on three of the key assessments are combined – motor response, activities of daily living and good quality on time – it reveals a highly significant difference

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Henlius

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CFDA) accepted the NDA for HLX-01 in October 2017 and put it under priority review in January 2018. Henlius is also conducting a phase III trial for treating rheumatoid arthritis with HLX-01.

The company, a joint venture of Shanghai Fosun Pharmaceutical Group Co. Ltd. and Henlius Biopharmaceuticals Co. Ltd., is seeking to list on the Hong Kong Stock Exchange with plans to use proceeds from an IPO to fund the ongoing clinical trials.

"We have been working diligently on the HLX-01 launch plan to ensure HLX-01 will be covered by the public health insurance as soon as possible," a spokeswoman for Henlius told *BioWorld*. "The NMPA approval is based on a comprehensive submission data package of extensive analytical characterization, nonclinical data and three clinical trials (phase Ia, Ib and III) evaluating clinical pharmacology, immunogenicity, clinical safety and efficacy data, which demonstrated a high degree of similarity for HLX-01 and the originator product," she said.

Bin Li, CEO at Ally Bridge LB Healthcare Fund, told *BioWorld* that with the first biosimilar approval in China, the regulators have paved the regulatory pathway for future biosimilars.

Hua Su, managing director of EY-Parthenon at Ernst & Young (China) Advisory Ltd., agreed with Li. Su told *BioWorld* that "more homegrown biosimilars will be approved from now on."

Since 2001, the originator Mabthera has been approved in China for the treatment of three types of NHL: diffuse large B-cell lymphoma, relapsed or refractory follicular central lymphoma and previously untreated CD20-positive stage III-IV follicular lymphoma. Henlius' NDA for HLX-01 seeks approval for all three indications.

Mabthera is also included in the National Reimbursement Drug List and the National Essential Drugs List after price negotiations with the Chinese government. Henlius said it believes that adding it to the lists had increased market awareness and boosted its penetration in China.

"The market is expecting Henlius' biosimilar rituximab to be included in national reimbursement drug list in the future. If that happens, we expect the price will be much lower than the branded drug price and therefore the volume of biosimilars will rise rapidly," said Ally Bridge's Li. That advantage could help Henlius secure greater market share, especially versus higher-priced imports, he said.

Li's view is supported by a Frost and Sullivan report, in which the consultant estimated that rituximab biosimilars will eventually gain a bigger market share than the originator in China from 2026 onward.

According to the report, sales revenue of China's Mabthera biosimilar market are expected to grow at a compound annual growth rate (CAGR) of 62 percent from 2018 to around ¥2 billion (US$298 million) in 2022, and further grow at a CAGR of 14.3 percent to reach ¥5.8 billion in 2030.

In 2017, global sales of the originator drug amounted to $7.5 billion while sales in China reached $298 million.

Currently, Mabthera's price has been slashed significantly to ¥2,418 per 10 mL/100 mg/vial and ¥8,298 per 50 mL/500 mg/vial in China under the national reimbursement drug list.

It is not immediately known how Henlius will price its biosimilar to compete with Mabthera. The company said there will be further details soon on Hanlikang's pricing.

China first, then the world

Henlius has vowed to put China first in its commercialization plan for Hanlikang before exploring oversea opportunities.

Marketing efforts will have an initial focus on grade A class III hospitals followed by efforts to increase product and brand awareness among doctors and other medical practitioners in small to medium-sized hospitals in second and third tier cities.

In China, other competitors of Hanlikang include Sinocelltech Ltd.'s SCT0400, Innovent Biologics Inc.'s IBI-301, Zhejiang Hisun Pharmaceutical Co. Ltd. and Beijing Mabworks Biotech Co. Ltd.'s chimeric anti-CD20 monoclonal antibody. They are all in phase III studies.

Meanwhile, Henlius also intends to gain market access into Southeast Asia, South America and other emerging markets via licensing and commercialization agreements with local partners.

In fact, the first step has already been made. Henlius' spokeswoman told *BioWorld* in a previous interview that the company has inked a licensing agreement with Argentina-based Biosidus SA to commercialize the biosimilar in Argentina, Paraguay, Uruguay and Bolivia. (See *BioWorld*, Dec. 19, 2018.)

The era of biologics

Hanlikang's approval is another landmark in China's biopharma space after the approval of the first homemade PD-1 monoclonal antibody, JS-001, developed by Shanghai Junshi Biosciences Co. Ltd. It marks Chinese drugmakers' ability to develop biologics that are usually imported.

"Currently, China has the most biosimilar drugs in research and development. NMPA has approved 200-plus clinical trials of biosimilar drugs so far; some of them have already completed phase III trials and are waiting for a marketing approval," the NMPA said.

David Li, head of China and Hong Kong Healthcare at CLSA, has said that China is switching to biologics with the first biosimilar entering the market. "The industry is undergoing upgrading, so we expect to see the best-selling drugs in China will be biologics in the near term," Li said at CLSA's annual investors' forum in Hong Kong last year. (See *BioWorld*, Oct. 10, 2018.)

Su from EY-Parthenon said the Chinese regulators are favoring local players over the foreign entrants when reviewing the NDAs.

"Pfizer is trying to get biosimilar approvals in China, and as a compromise, the company invested in a local biosimilar manufacturing site in Hangzhou to accelerate its biosimilar approval, but it is still not going as fast as those filed by local players," he said.

Su also noted that it may take more commercial effort for the China market to switch from originator drugs to biosimilars.

"We need to wait and see whether China will move fast like the EU, or slower like the U.S.," he said. ♦

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Anaveon

Continued from page 1

its commercial and clinical potential have been limited by its narrow therapeutic window and by the necessity of having access to intensive care facilities.

Although Proleukin is a potent T-cell activator, it is burdened with numerous drawbacks. It has a short half-life, which necessitates intravenous infusion three times daily; it causes neutrophil impairment, which increases the risk of bacterial endocarditis and sepsis; and it can induce capillary (also called vascular) leak syndrome, a potentially catastrophic loss of fluid and proteins from the vasculature into the surrounding tissues. An additional complication of IL-2 therapy is its stimulatory effect on regulatory T cells (Treg cell) as well as on cytotoxic T cells.

Swiss startup Anaveon is one of a clutch of companies to revisit IL-2-based immunotherapy, armed with new biological insights, which, it hopes, will enable it to capture the benefits of IL-2 signaling while minimizing the harmful consequences. It has secured significant backing for its strategy and its science. The Zurich-based company has just raised CHF35 million (US$35 million) in a series A round to develop selective IL-2 receptor agonists to act as immune adjuvants.

Co-founder Onur Boyman, who chairs the department of immunology at the University of Zurich in Switzerland, has played a prominent role in unpicking important aspects of IL-2 signaling over much of the past decade and a half. Back in 2006, Boyman and colleagues reported that IL-2-antibody complexes could, depending on their composition, selectively boost either CD8 T-cell or Treg cell populations. That initial insight enabled them – and others – to unlock further details of how IL-2 mediates its multiple effects.

The IL-2 receptor (IL-2R) comprises three polypeptide chains, alpha (CD25), beta (CD122) and gamma (CD132), different forms of which bind IL-2 with differing affinities. The high-affinity receptor comprises all three chains associating in a heterotrimeric configuration; the intermediate-affinity receptor consists of the beta and gamma chains; and the low-affinity receptor comprises the alpha chain only. Selective targeting of different receptors can have significantly different downstream consequences.

For example, Boyman's lab reported in 2010 that IL-2-induced pulmonary edema – caused by vascular leak syndrome – was due to direct binding of IL-2 to the high-affinity IL-2R expressed on lung endothelial cells. The antitumor effects of IL-2, in contrast, were mediated by the cytokine activating the intermediate-affinity IL-2R, which is highly expressed on CD8 cytotoxic T cells and natural killer cells. Additional work has identified the IL-2R alpha chain – or CD25 – as the main culprit for inducing vascular leak syndrome, as well for inducing a Treg cell response to IL-2 activation. Although it does not actively signal, CD25 greatly increases the binding affinity of IL-2 to the heterotrimeric form of IL-2R.

Aiming for best in class

Anaveon was established in late 2017 by Boyman and CEO Andreas Katopodis, former director of autoimmunity, transplantation and inflammation at the Basel lab of the Novartis Institutes of Biomedical Research, to translate the research tools and insights Boyman developed into drug candidates. The most advanced was described in a 2017 paper in the Nov. 30, 2016, issue of *Science Translational Medicine*. It consists of a complex comprising IL-2 and a CD25-directed antibody, NARA1, which was difficult to obtain. "People have tried before. It was only Boyman's lab in the end that succeeded," Katopodis told *BioWorld*.

The combination selectively triggers a CD8-positive T-cell response, while damping down the Treg cell response. As well as eliciting the desired form of immune activation, the complex has an antibody-like half-life due to the presence of the antibody. "These are very tight complexes that behave like a single molecule," Katopodis said. The absence of CD25 binding also cuts its toxicity – by five- to 10-fold in animal models, he said.

The company now has enough cash to conduct a high-quality phase I/IIa study, although it has not yet decided on the precise design. "We are about a year and a half from the clinic," Katopodis said. Although it will need to demonstrate activity as a monotherapy, the complex's future lies in combination settings. "I see it more as an incredibly useful adjuvant, which will dial up just about any immuno-oncology approach," he said. "We firmly believe we have a best-in-class [molecule]. We need to show we have a best in class."

Several other novel approaches to IL-2 stimulation are at varying stages of development. Bempegaldesleukin (NKTR-214), a pegylated form of IL-2, which San Francisco-based Nektar Therapeutics Inc. is developing, is in phase III combination trials in RCC and melanoma with the PD-1 inhibitor Opdivo (nivolumab, Bristol-Myers Squibb Co.). La Jolla, Calif.-based Synthorx Inc. grossed $131 million in an IPO in December to take forward its IL-2 variant, THOR-707, for which it plans to file an IND in the second half of this year. That molecule incorporates an unnatural amino acid residue at a specific location, which allows for site-specific attachment of polyethylene glycol. As with bempegaldesleukin, the modification not only increases the molecule's half-life, it also blocks its interaction with the CD25 receptor.

A newer venture, Neoleukin Therapeutics Inc., has been formed around a computational approach for recapitulating the binding sites of IL-2 and other cytokines in unrelated protein structures. The group, based at the Institute for Protein Design, at the University of Washington in Seattle, described the development of an IL-2 mimic that selectively binds the IL-2R-alpha-beta-c heterodimer in a paper published in the Jan. 9, 2019, issue of *Nature*. ♦

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Senate

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drugs that provide essentially no revenue to the company. Left untouched were the cash cows, Keytruda and Januvia, which account for more than a quarter of Merck's revenue. It's like promising car shoppers a great deal, except the only discounted model on the lot is an Edsel."

He had a similar complaint about J&J, accusing it of a "record-setting flip-flop" last month after CEO Alex Gorsky said the biopharma industry needed to police itself on pricing. "Sounds good, but it didn't last long," Wyden said. "Three days later, his company hiked the prices of hundreds of its drugs, including drugs that account for billions in Medicare spending."

Sanofi SA came under Wyden's fire for raising insulin prices, and he called out Bristol-Myers Squibb Co. for spending roughly $11.5 billion in 2017 on dividends, stock buybacks, marketing, sales and administrative costs. "That's roughly triple the amount it spent on R&D," he said.

Wyden's most personal attack was aimed at Astrazeneca's Soriot. He noted that the CEO had complained that his $12 million salary made him "'the lowest-paid CEO in the whole industry.'" At the same time, Astrazeneca continued to raise the price of Symbicort (formoterol and budesonide), its $3 billion asthma drug.

As the hearing came to a close, Wyden said, "I've heard a lot of happy talk here this morning," but no firm commitments to lower drug prices. He asked each of the companies represented to submit a written commitment that, if the rebates go away, it would support a law requiring drug firms to reduce their list price by the amount of the rebates they had been paying. ♦

Tetragenetics

Continued from page 5

Therapeutics Inc., of New York, and Invagen Pharmaceuticals, a subsidiary of Mumbai-based Cipla Ltd., in November. (See *BioWorld*, Dec. 5, 2018.)

Since the start of 2019, Stamford, Conn.-based Purdue has signed two other deals, one with Alivio Therapeutics Inc., a Boston-based affiliate of Puretech Health plc, worth $274.75 million for ALV-107 to treat interstitial cystitis/bladder pain syndrome, and the other with Ocular Therapeutix Inc., of Bedford, Mass., for an undisclosed amount to pursue pain treatments using Purdue's non-opioid new chemical entities with Ocular's bioresorbable hydrogel-based technology. ♦

Earnings

Clovis Oncology Inc., of Boulder, Colo., reported 2018 U.S. sales of PARP inhibitor Rubraca (rucaparib) totaling $95.4 million, including $30.4 million for the fourth quarter. The company reported a net loss of $99.3 million, or $1.88 per share, for the fourth quarter, and a net loss of $368 million, or $7.07 per share, for the full year. As of Dec. 31, Clovis had cash, equivalents and available-for-sale securities of $520.1 million. Shares of Clovis (NASDAQ:CLVS) closed Tuesday at $26.05, up 58 cents.

Parkinson's

Continued from page 6

between the treatment and placebo groups," he said.

This Parkinson's disease composite response is being championed by the patients' group European Parkinson's Disease Association, as a means to combine motor symptoms, non-motor symptoms and treatment-related complications, in a single disease rating score.

Mohr said he believes it may better capture the full effects of GDNF. "We're working to get it scientifically validated so that it can be used in future trials," he said.

Now Gill and Medgenesis need to raise £4 million (US$5.3 million) for the first stage of the phase III trial, treating 17 patients in each arm.

A year ago, Pfizer Inc. terminated an option it had with Medgenesis to license GDNF as a potential treatment for Parkinson's disease. "[The trial] was ready to roll, supported by Pfizer," Gill said. "Medgenesis was left stranded."

It is now a race against time to raise the money because existing supplies of GDNF expire in 2021. "The key thing is to get going before September," said Gill.

"Even at a low dose we have seen evidence of patient improvement, which is incredibly encouraging. Now we need to move towards a definitive clinical trial using higher doses, and this work urgently needs funding," he said. ♦

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Other news to note

Amgen Inc., of Thousand Oaks, Calif., said a Delaware jury delivered a verdict in its favor, upholding the validity of two Amgen patents related to PCSK9 antibodies, describing and claiming antibodies, including Repatha (evolocumab), that bind to a specific region on PCSK9 and reduce LDL-cholesterol levels. The verdict follows a previous trial in March 2016, in which Paris-based **Sanofi SA** and Tarrytown, N.Y.-based **Regeneron Pharmaceuticals Inc.** admitted infringement of Amgen's patents – the partners market anti-PCSK9 antibody Praluent (alirocumab) – and where a prior jury also upheld the validity of Amgen's patents. The prior jury decision was partially reversed on appeal and the case was remanded to the district court for a new trial on two validity issues. In the recent verdict, the jury found that the Amgen patents meet the legal requirements of written description and enablement. Regeneron and Sanofi responded that they "strongly disagree" with aspects of the jury verdict and said they will "continue to vigorously defend our positions against Amgen's overly broad patent claims." Jefferies analysts noted in a research report that a lawsuit for damages initiates immediately, with Amgen having until March 18 to file a motion for permanent injection against Praluent. "However, granting permanent injunction requires demonstrating the public good would not be negatively impacted by pulling Praluent from the market," analysts wrote, adding that Regeneron could alternatively be liable for royalties on Praluent sales. Regeneron also has disclosed plans to file post-trial motions seeking to overturn the latest verdict and is "also prepared to appeal to the Federal Circuit again, raising the possibility of a [third] jury trial." Interestingly, Jefferies analysts pointed out, Amgen's PCSK9 claims appear to exclude inclisiran, an anti-PCSK9 drug in development by **The Medicines Co.**, of Parsippany, N.J., because of its mechanism as an RNA-directed agent. (See *BioWorld Today*, March 17, 2016, and Oct. 6, 2017.)

Amicus Therapeutics Inc., of Cranbury, N.J., said it is establishing a global research and gene therapy center of excellence in Philadelphia. To be located in uCity Square, the 75,000-square-foot center is expected to be completed in the second half of 2019 and will serve as headquarters for the company's global science organization and gene therapy leadership team. Amicus expects up to 200 employees to eventually be based at the new facility.

Axim Biotechnologies Inc., of New York, said it successfully microencapsulated cannabinoids into its patented chewing gum delivery mechanism for use in its proposed clinical trials.

Biocorrx Inc., of Anaheim, Calif., said it engaged Irisys LLC, a contract pharmaceutical product development and manufacturing services company, for development and manufacturing of BICX-102, a multimonth sustained-release naltrexone implant. Terms were not disclosed. Biocorrx plans to conduct clinical trials and seek FDA approval for BICX-102 as a treatment for opioid and alcohol use disorders.

Cellectis SA, of Paris, published data in *The Journal of Biological Chemistry* showing that granulocyte macrophage-colony stimulating factor (GM-CSF) secreted by CAR T cells is a key factor promoting cytokine release syndrome. Using Talen-mediated gene inactivation, researchers knocked out GM-CSF in CAR T cells, which prevented secretion of pro-inflammatory cytokines by monocytes, but didn't compromise the antitumor activity of the CAR T cells.

Cell Medica Ltd., of London, said it was awarded an $8.7 million research grant from the Cancer Prevention and Research Institute of Texas to support preclinical and clinical development of the company's off-the-shelf chimeric antigen receptor-natural killer T-cell therapies to treat hematological and solid tumors. The grant will support development programs being conducted in collaboration with Baylor College of Medicine designed to address the limitations of the current first-generation autologous CAR T-cell therapies. The aim is to deliver an off-the-shelf approach, with simplified manufacturing, that can serve larger patient numbers, and which allows treatment closer to the time of patient presentation.

Compugen Ltd., of Holon, Israel, is restructuring to reduce costs by consolidating and streamlining R&D operations. The restructuring, which includes eliminating approximately 35 positions – about 35 percent of its workforce – consolidating R&D activities and eliminating redundant activities in Israel and the U.S., is expected to save the company $10 million annually. One-time restructuring-related costs are expected to be in the range of $27 million to $29 million. With the restructuring, the company expects the $45.7 million in cash, cash-related accounts, short-term and long-term bank deposits that it had at the end of 2018 will last through mid-2020. Shares of Compugen (NASDAQ:CGEN) closed down 64 cents, or 17 percent, to $3.12 on Tuesday.

Gain Therapeutics SA, of Lugano, Switzerland, in conjunction with Marta Martinez Vicente from the Vall d'Hebron Research Institute, were awarded a grant from The Michael J. Fox Foundation for Parkinson's Research and The Silverstein Foundation to support development of Gain's non-competitive molecular chaperones for Parkinson's disease.

Immatics Biotechnologies GmbH, of Tuebingen, Germany, and **Roche Holding AG**, of Basel, Switzerland, are collaborating to test Immatics' autologous cell therapy, IMA-101, in combination with Roche's Tecentriq (atezolizumab) in patients with solid cancers. Starting later this year, the combination will be tested as part of an amendment to Immatics' ongoing phase I Actolog study.

Know Bio LLC, of Durham, N.C., launched a wholly owned operating subsidiary, Digestive Health Therapeutics Inc., to develop the company's nitric oxide technology for gastrointestinal disorders. The company will start with the development of compounds that provide tunable nitric oxide release for conditions associated with nitric oxide deficiency.

Nanoviricides Inc., of Shelton, Conn., and **Theracour Pharma Inc.**, of West Haven, Conn., have agreed, subject to a definitive agreement, on a license for Theracour's intellectual property on varicella-zoster virus (VZV), the virus that causes chickenpox and shingles. Theracour will receive 500,000 shares of Nanoviricides' series A preferred stock when the IND for the anti-VZV drug candidate becomes effective, $1.5 million after the completion of phase I studies and $2.5 million after completion of phase II studies. Theracour is also entitled to a 15 percent royalty on sales (net of costs) and 15 percent of sublicensing revenues.

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Other news to note

Nexion Biopharma Inc., of Denver, said it intends to file a pre-IND meeting request with the FDA following encouraging results of clinical observations of patients with nondystrophic myotonia and myotonic dystrophies type 1 and 2, indicating that specific cannabinoid formulations are supportive of relief of symptoms.

Pfizer Inc., of New York, warned patients and doctors, through the FDA, that a data safety monitoring committee for a study testing Xeljanz (tofacitinib) in rheumatoid arthritis patients at least 50 years old and with at least one cardiovascular risk factor found patients taking Xeljanz 10 mg twice daily had an increase in blood clots in the lungs and deaths compared to patients taking Xeljanz 5 mg twice daily or a TNF inhibitor.

Selexis SA, of Geneva, licensed its Suretechnolgy platform and Sure CHO-M Cell Line for the development of two biosimilar antibodies – a checkpoint inhibitor for the treatment of certain cancers and a monoclonal antibody for the treatment of metastatic HER2-positive breast cancer – to **Turgut Pharmaceuticals AS**, of Istanbul. Terms of the deal weren't disclosed. Through a 2017 deal, the companies are also developing biosimilars for paroxysmal nocturnal hemoglobinuria and atypical hemolytic uremic syndrome.

Sellas Life Sciences Group Inc., of New York, is conducting a review of its strategic options, including the potential sale of the company, strategic financing or a partnership. The company has engaged Cantor Fitzgerald & Co. to act as an advisor.

VBL Therapeutics Ltd., of Tel Aviv, Israel, reported preclinical data supporting the use of its VB-600 platform of antibodies targeting motile sperm domain-containing protein 2 (MOSPD2) at the Keystone Symposia on Myeloid Cells in Santa Fe, N.M. In an experimental autoimmune encephalomyelitis model for multiple sclerosis and the collagen antibody-induced arthritis model for rheumatoid arthritis, MOSPD2 knockout mice don't develop diseases. The knockout also reduced fibrosis in a high-fat-high-carbohydrate model for nonalcoholic steatohepatitis.

WARF Therapeutics, of Madison, Wis., was launched as a strategic initiative to develop and commercialize translational research at the University of Wisconsin, with the aim of taking select assets through preclinical development.

Wuxi Biologics, of Shanghai, and **Abl Bio Corp.**, of Seoul, South Korea, said they expanded their partnership for bispecific antibodies and immune-oncology programs. Under the terms, Abl has rights to use Wuxi's discovery platforms, including the Wuxibody and CD3 platform, to research, develop and commercialize bispecific antibodies, as well as rights to develop new bispecific antibodies targeting a novel immune checkpoint receptor. Wuxi will receive an up-front payment as well as development, regulatory and commercial milestone payments of about $220 million and will be entitled to royalties based on global sales of those programs.

Wondering what you missed in *BioWorld Insight*?

Science is there to make universal flu vaccine; money to follow?

WASHINGTON– The scientific capabilities exist to stop chasing ever-mutating epitopes, target a conserved region of the virus, and deliver a universal influenza vaccine, providing better and longer protection. "A lot of good science is getting us closer to this," Tony Fauci, director of the National Institute of Allergy and Infectious Diseases (NIAID), told attendees of the recent AAAS meeting. Fauci was speaking two days after U.S. Sen. Ed Markey (D-Mass) introduced an act calling for $1 billion to take that scientific promise and develop "a universal influenza vaccine that could be administered once or twice and provide a lifetime of protection."

Crypto tokens hit biotech Agenus launching BEST

Agenus Inc. is launching a Biotech Electronic Security Token (BEST), a blockchain-backed token that will be tied to its anti-PD-1 antibody, AGEN-2034. Holders of the token, which Agenus plans to sell for $1.67 per token, will get paid royalties on U.S. net sales of the drug, up to $7.50 per token. The tokens even offer some downside, allowing holders to trade them for Agenus shares (or cash at the company's discretion) if AGEN-2034 isn't approved by the FDA by the end of 2021.

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Clinical data for Feb. 26, 2019

Company	Product	Description	Indication	Status
Phase I				
Alkermes plc, of Dublin	ALKS-4230	IL-2 receptor agonist	Solid tumors	Initiated phase I/II ARTISTRY-2 to evaluate ALKS-4230 administered subcutaneously as monotherapy and in combination with Keytruda (pembrolizumab, Merck & Co. Inc.); dose-escalation stage designed to evaluate safety and tolerability; dose-expansion stage to evaluate overall response rate, duration of response, non-progression rate at specific time points and overall survival
Medigene AG, of Martinsried, Germany	MDG-1011	HLA class I antigen A-2 alpha modulator; tumor expressed melanoma antigen modulator	Acute myeloid leukemia, myelodysplastic syndrome, multiple myeloma	Dosed first patient in phase I/II trial investigating safety and feasibility; phase I portion will enroll 12 patients across the 3 indications, testing dose ranges from 100,000 to 10 million transduced T cells per kg of body weight; following positive DSMB assessment, 2 of 3 indications will be advanced into phase II, expected to enroll 80 participants across treatment and control groups with co-primary endpoints of safety and preliminary efficacy, measured as overall response rate at 3 months
Scholar Rock Holding Corp., of Cambridge, Mass.	SRK-015	GDF-8 antagonist	Spinal muscular atrophy	Interim results from single- and multiple-ascending dose trial in healthy adults showed SRK-015 was well-tolerated with no dose-limiting toxicities to highest evaluated dose of 30 mg/kg; pharmacodynamics evaluated using company's exploratory biomarker assay showed levels of latent myostatin increased from baseline, confirming target engagement, which was saturated after single dose at 3 mg/kg or greater; pharmacokinetic profile was consistent with that generally observed for monoclonal antibodies, supporting dosing regimen of once every 4 weeks
TG Therapeutics Inc., of New York	TG-1801	Anti-CD47/CD19 bispecific antibody	B-cell lymphoma	Initiated open-label, multicenter trial to assess safety, pharmacokinetics, efficacy and recommended phase II dose of TG-1801 in individuals with relapsed/refractory disease; primary objective is to determine maximum tolerated dose and characterize safety profile, with secondary objectives of characterizing pharmacokinetics and preliminary efficacy
Phase II				
Asana Biosciences LLC, of Lawrenceville, N.J.	ASN-002	JAK/SYK kinase inhibitor	Atopic dermatitis	Data safety monitoring board held second planned meeting and recommended continuation of phase IIb study in patients with moderate to severe disease
Beyondspring Inc., of New York	Plinabulin	Guanine nucleotide exchange factor stimulator; tubulin receptor antagonist	Chemotherapy-induced neutropenia	Phase II/III Study 106 data showed that combining plinabulin with Neulasta (pegfilgrastim) improved efficacy in CIN treatment and reversed Neulasta's potential immune-suppressive phenotype; percentage of patients with grade 4 neutropenia was lowered from 59% with Neulasta alone to 38% with the combination; percentage of those with absolute neutrophil count exceeding upper limit of normal was lowered from 50% with Neulasta to 31% with combo; immune-suppressive neutrophil-to-lymphocyte ratio levels were lower (<25% of patients) in combo vs. Neulasta alone (>50% of patients; p<0.0007 in the cycle)
Debiopharm International SA, of Lausanne, Switzerland	Afabicin (Debio-1450)	Enoyl ACP reductase FabI inhibitor	Staphylococcal bone and joint infections	Initiated randomized, open-label, active-controlled trial to assess safety, tolerability and efficacy of I.V./oral therapy vs. comparator in 60 patients at sites in Ukraine and U.S.; primary endpoints are safety and tolerability, with efficacy measures such as number of responders, resolution of disease-specific signs and symptoms, improvement of inflammation and microbiological eradication of baseline pathogen as secondary endpoints
Immunic AG, of Planegg-Martinsried, Germany	IMU-838 (vidofludimus)	Dihydroorotate dehydrogenase inhibitor	Relapsing-remitting multiple sclerosis	Enrolled first participant in global, double-blind, placebo-controlled, randomized, parallel-group trial expected to enroll about 200 patients for blinded 24-week treatment period with optional extended treatment period to evaluate long-term safety and tolerability of dose response to 30 mg/day and 45 mg/day of IMU-838, once daily; primary endpoint is cumulative number of combined unique active lesions, assessed by MRI, up to week 24

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Company	Product	Description	Indication	Status
Phase III				
ALK-Abello A/S, of Horsholm, Denmark	House dust mite (HDM) sublingual allergy immunotherapy (SLIT)-tablet	Allergy desensitization vaccine immunotherapy	Allergic rhinitis	Post-hoc analysis of MERIT trial using data from Rhinoconjunctivitis Quality of Life Questionnaire showed therapy can improve quality of sleep for individuals with allergic rhinitis; about 65% of participants had moderately or severely affected sleep at outset of trial compared with 7.3%-10.1% who remained in moderate/severe category at end of study
Astrazeneca plc, of Cambridge, U.K., and Merck & Co. Inc., of Kenilworth, N.J.	Lynparza (olaparib)	PARP inhibitor	Germline BRCA-mutated metastatic pancreatic cancer	Data from POLO trial showed statistically significant and clinically meaningful improvement in progression-free survival vs. placebo; safety and tolerability profile consistent with previous trials
Catalyst Pharmaceuticals Inc., of Coral Gables, Fla.	Firdapse (amifampridine phosphate)	Potassium channel inhibitor	Lambert-Eaton myasthenic syndrome	Additional data from confirmatory LMS-003 trial, published in *Journal of Clinical Neuromuscular Disease*, showed proportion of patients with ≥20% increase in average Triple Timed Up and Go walk test was statistically significantly higher (p=0.0112) in placebo group [8/13 (61.5%)] compared with study drug [1/13 (7.7%)], indicating improvement; scores from the Clinical Global Impression of Improvement showed statistically significant (p<0.0001) difference in favor of study drug
Recro Pharma Inc., of Malvern, Pa.	Meloxicam	COX-2 inhibitor	Pain	Data published online in *Clinical Pharmacology in Drug Development* reported that mean opioid consumption of 379 patients who underwent major elective surgical procedures was numerically lower in I.V. meloxicam (30 mg) group vs. placebo (3:1 randomization) at all time points (hours 0-24, 24-48, 48-72, 0-48 and 0-72) and reached statistical significance at hours 0-24, 0-48 and 0-72; over treatment period, I.V. meloxicam was associated with 23.6% reduction in opioid use vs. placebo; total I.V. morphine equivalent dose was 9.2 mg lower among I.V. meloxicam-treated patients vs. placebo-treated patients but difference was not statistically significant (29.8 mg vs. 39 mg; p=0.0531)
Notes For more information about individual companies and/or products, see Cortellis.				

Regulatory actions for Feb. 26, 2019

Company	Product	Description	Indication	Status
Celgene Corp., of Summit, N.J.	Revlimid (lenalidomide)	Immuno-modulatory drug	Previously treated follicular and marginal zone lymphoma	FDA granted priority review for supplemental NDA seeking approval in combination with rituximab; PDUFA date set for June 27, 2019
Inhibikase Therapeutics Inc., of Atlanta	IkT-148009	Cellular Abelson tyrosine kinase inhibitor	Parkinson's disease and related disorders	Submitted 2 INDs to the FDA; 1 is seeking to treat PD using standard measures such as the Unified Parkinson's Disease Rating Scale as primary readout of treatment benefit, while the second will use diagnostic tools and natural history patient data to evaluate treatment benefit using new primary endpoints in the gastrointestinal tracts; studies expected to begin in the second quarter of 2019
Romeg Therapeutics LLC, of Woburn, Mass.	Gloperba (colchicine) oral solution 0.6 mg/5mL	Anti-mitotic drug	Prophylaxis of gout flares	Approved by FDA as first liquid formulation of colchicine for prevention of gout flares in adults
Shanghai Henlius Biotech Inc., of Shanghai	Hanlikang (HLX-01)	Biosimilar to rituximab	Non-Hodgkin lymphoma	Approved by China's National Medical Products Administration
Spero Therapeutics Inc., of Cambridge, Mass.	SPR-720	Oral antimicrobial agent	Non-tuberculosis mycobacterial infections	FDA granted qualified infectious disease product designation for treating lung infections caused by NTM and lung infections caused by *Mycobacterium tuberculosis*
Notes For more information about individual companies and/or products, see Cortellis.				

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