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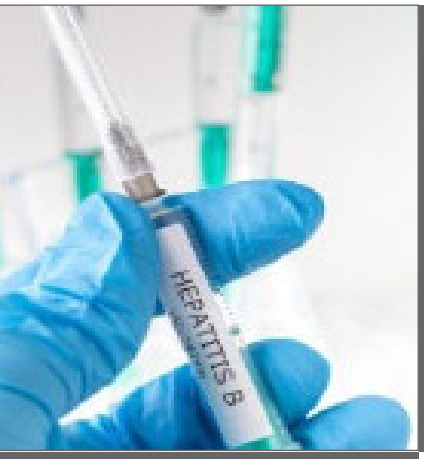

Third time's the charm

Heplisav gets thumbs-up; FDA Adcom recommends stringent postmarketing study to evaluate 'spurious' CV data

By Jennifer Boggs, Managing Editor

A cardiovascular signal that earned a second complete response letter (CRL) for Dynavax Technologies Corp.'s hepatitis B vaccine, Heplisav, was determined by members of the FDA's Vaccines and Related Biological Products Advisory Committee (VRBPAC) largely to be a "spurious" finding that should be

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No abate of Checkmate debate

Astrazeneca says Merck instigated Lynparza; MYSTIC fizzle not conclusive factor

By Randy Osborne, Staff Writer

The fog began to dissipate at least somewhat late last week regarding the reasons behind – and the potential immuno-oncology (IO) fallout from – Astrazeneca plc's phase III blowup with the MYSTIC trial in non-small-cell lung cancer (NSCLC), news of which came just as the pharma giant made public its $8.5 billion deal with Merck & Co. Inc. around the oral poly ADP ribose polymerase (PARP) inhibitor Lynparza (olaparib).

Officials from London-based Astrazeneca hosted a breakfast Friday with analysts at which "they confirmed that Merck went to Astrazeneca, not the other way around, and that they would have concluded this deal with Merck irrespective of the results of MYSTIC," said Jo Walton, who covers large-cap pharma in the EU for Credit Suisse. "It was important for Merck to get this deal signed and out before the Merck [second-quarter earnings]

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Nantcell bets up to $365M on Cytrx's aldoxorubicin

By Michael Fitzhugh, Staff Writer

Nantcell Inc., the Patrick Soon-Shiong-backed company built in part with funds from the blockbuster albumin-bound chemotherapy Abraxane (nab-paclitaxel), has exclusively licensed Cytrx Corp.'s aldoxorubicin, another albumin-bound therapy, to incorporate into the treatment of multiple tumor types in combination with other

See Cytrx, page 5

Lawmakers creating some answers to high drug prices

By Mari Serebrov, Regulatory Editor

While recognizing that the bipartisan Creating and Restoring Equal Access to Equivalent Samples (CREATES) Act is not a silver bullet that will bring down all drug prices, U.S. officials and several experts gave the bill high marks last week during a House Judiciary subcommittee on antitrust concerns and the FDA drug approval process.

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Australian patients get help via amended access plan for unapproved drugs, devices

By Tamra Sami, Staff Writer

PERTH, Australia – Patients in Australia will now be able to get unapproved drugs through their doctors more quickly since Australia amended its drug and device regulations earlier this year.

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K-sunshine act aims to clean up corruption in S. Korean pharma sector

By Haky Moon, Staff Writer

HONG KONG – After the kickback scandal involving Novartis AG, South Korean authorities are determined to root out corruption from the country's pharmaceutical sector. (See *BioWorld Today,* Sept. 6, 2016.)

A new regulation, dubbed as the K-sunshine Act, was introduced in South Korea to tackle corruption and increase transparency by making it a legal requirement for companies to keep records of financial transactions in the medical industry.

According to the regulation, the Ministry of Health and Welfare (MOHW) of Korea may request the

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The BioWorld Biome

Study finds potential new treatment for Zika virus

By John Fox, Staff Writer

A potent new anti-Zika virus peptide that appears to be safe and reduces viral levels in pregnant mice and their fetuses, has been identified in a Chinese study published in the July 25, 2017, edition of *Nature Communications*.

See Zika, page 9

Bench Press

BioWorld Bench Press was not published this week and will return on Monday, Aug. 7.

Other news to note

Agile Therapeutics Inc., of Princeton, N.J., said the FDA accepted its NDA resubmission for Twirla (AG200-15), an investigational low-dose combined hormonal contraceptive patch, responding to the complete response letter issued in February 2013 that recommended Agile conduct a new clinical trial and provide additional information on the manufacturing process for Twirla. The FDA's PDFUA goal for making a ruling on the NDA is Dec. 26.

Amgen Inc., of Thousand Oaks, Calif., said the FDA granted priority review to its supplemental BLA for Repatha (evolocumab) to include risk reduction of major cardiovascular events based on data from the 27,564-patient FOURIER (Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk) cardiovascular outcomes study. Amgen also said that a second application to expand the lipid-lowering indication to include additional patient populations was also accepted by the FDA. The PDUFA goal for a decision on the sBLA is Dec. 2. (See *BioWorld Today*, March 20, 2017.)

Elite Pharmaceuticals Inc., of Northvale, N.J., said Sungen Pharma LLC, of Princeton, N.J., will co-develop four additional generic products, bringing the total number of drugs developed under the companies' 2016 partnership to eight. The four new undisclosed drugs are in the categories of antidepressants, antibiotics and antispasmodics and have total U.S. sales of more than $1.4 billion in 2016, according to IMS Health Data cited by Elite.

Enanta Pharmaceuticals Inc., of Watertown, Mass., said the European Commission has granted **Abbvie Inc.**, of North Chicago, marketing authorization for Maviret (glecaprevir/pibrentasvir), a once-daily, ribavirin-free treatment for adults with chronic hepatitis C virus (HCV) infection across all major genotypes (GT1-6). Maviret is an eight-week treatment for patients without cirrhosis and new to treatment, who comprise the majority of the estimated 71 million people worldwide living with HCV, the company said. The drug is also indicated for patients with specific treatment challenges, including those with compensated cirrhosis across all major HCV genotypes, and those who previously had limited treatment options, such as patients with severe chronic kidney disease or those with genotype 3 chronic HCV infection.

Gilead Sciences Inc., of Foster City, Calif., said the European Commission granted marketing authorization for Vosevi (sofosbuvir/velpatasvir/voxilaprevir), as a once-daily single tablet regimen for the treatment of adults with genotype 1-6 chronic hepatitis C virus infection. The approval was supported by four phase III trials, POLARIS 1-4.

Haemalogix Pty. Ltd., of Eveleigh, Australia, inked an agreement with Westmead Institute for Medical Research, Western Sydney Local Health District, Children's Medical Research Institute and the University of Sydney for commercialization rights to an immuno-oncology agent designed to target malignant cancer cells present in the bone marrow of individuals with multiple myeloma. Researchers at Haemalogix and Westmead expect to test the CAR T-cell therapy in myeloma patients beginning next year. Financial terms were not disclosed.

Iteos Therapeutics SA, of Gosselies, Belgium, was granted €7.5 million (US$8.8 million) in non-dilutive funding by the Walloon Region to support the clinical development of its lead anti-cancer drug. The funding needs to be reimbursed over the economic life of the project with 30 percent payable based on a fixed reimbursement schedule and the balance refunded through royalties. Iteos plans to use the proceeds to fund a clinical trial of its adenosine receptor A2A antagonist in 2018.

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

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

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

Business office

Donald R. Johnston (Senior Director, Current Awareness), Penney Holland (Web Production Manager)

Contact us

Jennifer Boggs, (770) 810-3120 | Anette Breindl, (770) 810-3134 | Michael Fitzhugh, (770) 810-3064 | Penney Holland, (770) 810-3047 | Donald R. Johnston, (770) 810-3118 | Nuala Moran, 44-7778-868-579 | Randy Osborne, (770) 810-3139 | Marie Powers, (770) 810-3136 | Mari Serebrov, (770) 810-3141 | Cormac Sheridan, 353-87-6864323 | Peter Winter, (770) 810-3142 | Lynn Yoffee, (770) 810-3123

Heplisav

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investigated more fully in a required postmarketing study.

In a 12-1 vote, with three abstentions, VRBPAC voted Friday that available data provide sufficient safety evidence for use of Heplisav in adults. The FDA is not bound by the adcom's recommendation, but generally follows its advice. The PDUFA date is Aug. 10.

Should the FDA grant approval, it will mark a hard-fought win for Dynavax, which first submitted a BLA in 2012 for Heplisav, a vaccine that combines hepatitis B surface antigen with a Toll-like receptor 9 (TLR9) agonist.

The vaccine's efficacy has never been in question, with Heplisav having clearly met pre-specified noninferiority criteria to active comparator Engerix-B (Glaxosmithkline plc) in pivotal trials DV2-HBV-10 and DV2-HBV-16. Heplisav consistently has shown higher and earlier protection with fewer doses than the licensed hepatitis vaccine, with one of the biggest advantages cited among physicians as its two-dose administration over the course of one month. Engerix requires administration of three doses over a six-month schedule, resulting in many patients not receiving the full dosing.

A 2012 VRBPAC meeting yielded a positive vote 13-1 in favor of Heplisav's efficacy, but the committee voted 8-5, with one abstention, against approval, citing inadequate safety data. The FDA followed with a CRL in February 2013, after which Berkeley, Calif.-based Dynavax conducted a third pivotal study, DV2-HBV-23, aiming to provide a more robust safety database. Instead, the study raised further concerns when findings indicated a numerical imbalance in a small number of cardiac events – specifically acute myocardial infarction (AMI) – in the Heplisav group vs. the Engerix group, prompting the agency to issue a second CRL in late 2016 after nixing plans for an adcom. The second CRL asked for further clarification of the safety data recorded in DV2-HBV-23, and results of those analyses were the primary focus of Friday's meeting. (See *BioWorld Today*, Nov. 16, 2012, Feb. 26, 2013, and Nov. 15, 2016.)

Committee members were tasked with deciding whether the available data support the safety of the vaccine in patients 18 and older. However, panel members seeking conclusive data on which to base their votes were largely disappointed. In its safety review, the FDA noted 14 reports of AMI in the Heplisav group vs. one in the Engerix group – the DV2-HBV-23 study was randomized 2-to-1 – for rates of 0.25 and 0.04, respectively. A major adverse cardiac events, or MACE, analysis performed by Dynavax indicated three deaths adjudicated to cardiovascular causes in the Heplisav group vs. one death in the Engerix group, though reviewers noted that no cause could be determined for seven deaths in the Heplisav group.

In the briefing documents released by the FDA ahead of the meeting, reviewers said the numbers appear too small to draw any conclusions. Speaking on behalf of the sponsor during Friday's meeting, cardiologist Darren McGuire, professor of medicine at the University of Texas Southwestern Medical Center, attributed the imbalance "most likely due to random variation," with no apparent causality to Heplisav's mechanism of action.

For most committee members, the efficacy combined with the need for a more reliable and convenient hepatitis B vaccine outweighed the risks.

"I think there is a reasonable chance this myocardial infarction signal is spurious," said Mark Sawyer, professor of clinical pediatrics at the University of California, San Diego, who voted in favor. "I do think the benefit outweighs the current assessment of the risk," he added, recommending that a postmarketing study be designed to quickly determine whether Heplisav is linked to an increased risk for AMI.

Jay Portnoy, of the Children's Mercy Hospital, who attended the meeting by phone and also voted yes, called Heplisav "extremely effective" and pointed out that getting the vaccine was much safer than contracting hepatitis B. "I don't think it would be right to withhold this vaccine from the millions of people who could benefit from it."

Postmarketing surveillance

The sole negative vote came from Pamela McInnes, deputy director for the National Center for Advancing Translational Sciences at the NIH. Though she referred to Heplisav as a "very exciting vaccine," with an "impressive" immunogenicity profile, the available data simply don't provide sufficient reassurance. "We mined them for what we could get out of them," she said of the data, "and they are what they are." The AMI signal, however, "could be a real observation and I can't come up with a construct" to discount that.

"I am of the opinion this needs further study," McInnes said, adding that she was "not comforted" by the sponsor's proposal for a postmarketing study.

The study, outlined by Robert Janssen, Dynavax's chief medical officer, would enroll 40,000 vaccine recipients – 20,000 to receive Heplisav and 20,000 to receive another hepatitis B vaccine. Patient accrual is expected to take about a year, and the study will include 13 months of follow-up, with analysis focusing on MACE and immune-related events, as well as rates of herpes zoster.

The trial will be 99 percent powered to rule out a twofold increase in the incidence of MACE if the background incidence rate is six per 1,000 person years. Depending upon the rate of uptake, Dynavax estimates the first interim analysis will be conducted 12 months following initiation of the study.

For their part, VRBPAC members had several specific recommendations for the postmarketing study, starting with interim analyses as early as possible that could identify an AMI signal if there truly is one. Many members also voiced opposition to the company's proposed use of one health center, Kaiser Permanente, as the host of the postmarketing trial, requesting that more sites and health centers be incorporated into the trial, the better for assuring that Heplisav would be administered in an unbiased fashion to a greater diversity of patients.

A "reliance on one area of the country and one health entity could be risky," noted Arnold Monto, professor of epidemiology at the University of Michigan School of Public Health. Regarding timeliness, he added, "you just want to set this to rest as

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Astrazeneca

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results, hence the reason it was done when it was done. It just happened to coincide with MYSTIC. [Astrazeneca] would never have had the resources, even if with a positive MYSTIC [outcome], to capitalize on Lynparza in the way they wanted," she said during a conference-call briefing with investors.

Results from MYSTIC on progression-free survival (PFS) from the study with checkpoint inhibitor Imfinzi (durvalumab) when paired with the company's CTLA-4 inhibitor, tremelimumab, vs. platinum-based standard-of-care (SOC) chemotherapy in previously untreated patients with metastatic first-line NSCLC showed the combo missed the primary endpoint of improving PFS compared to SOC in patients whose tumors express PD-L1 on 25 percent or more of their cancer cells. As a secondary endpoint, although not formally tested, Imfinzi monotherapy also would not have met the pre-specified threshold of PFS benefit over SOC, the company said. The MYSTIC trial will keep going in order to measure two more primary endpoints: overall survival (OS) for Imfinzi monotherapy and OS for the Imfinzi plus tremelimumab combo. Final OS data from both are expected during the first half of next year.

"The negative results of MYSTIC were absolutely not to do with their statistical plan," Walton said. "They have told us in the past that they put more of the statistical power behind the OS element rather than the PFS element. This did not disadvantage them – they still had it adequately powered, such that if there were any clinically meaningful benefit, they would have seen it. They haven't penalized themselves unduly. It just did not work." Astrazeneca's brass "admitted they would lower slightly" their general probability possibility of success, given the PFS findings, even though "they don't think there's a great correlation" between PFS and OS. A link between the two has been noted in other trials, but patient entry criteria vary widely. The company pointed to the Keynote 24 trial, a phase III experiment testing Kenilworth, N.J.-based Merck's Keytruda (pembrolizumab, Merck & Co. Inc.) compared to platinum-based chemotherapies in NSCLC. There, 85 percent of patients put forward were rejected for various reasons, including PD-1 levels. Astrazeneca "emphasized that theirs was a true all-comers study, although they wouldn't tell us what the effective screening failure rate of their study was," she said.

The tricky, still-young IO space

As a result of MYSTIC, "a little bit of the shine of the product has come off," Walton said. "We took our peak for the MYSTIC indications down from $4 billion to $3 billion and we delayed it for a couple of years." Her firm has maintained its generally bright viewpoint "because we don't think that [Imfinzi] is just a rubbish drug." In May, Astrazeneca disclosed positive results from the phase III PACIFIC trial, a randomized, double-blinded, placebo-controlled multi-center study with Imfinzi as sequential treatment in patients with locally advanced, unresectable (stage III) NSCLC who had not progressed following standard platinum-based chemo concurrent with radiation therapy. A planned interim analysis by an independent data monitoring committee found that the trial has already met a primary endpoint by showing statistically significant and clinically meaningful PFS, with a favorable risk-benefit profile. Details will be offered in September at the European Society for Medical Oncology meeting in Madrid, Spain. For now, she said, "we're assuming that there isn't that much read-across to other companies, but some investors who might have thought that this was going to be a PD-1 that gets to the market without any failed studies, and therefore it was going to be a superior product, will just have to accept that it's like all the other drugs which have a mix of positive and negative data," especially in the tricky, still-young IO space.

> *"The negative results of MYSTIC were absolutely not to do with their statistical plan," Walton said. "They have told us in the past that they put more of the statistical power behind the OS element rather than the PFS element. This did not disadvantage them – they still had it adequately powered, such that if there were any clinically meaningful benefit, they would have seen it. They haven't penalized themselves unduly. It just did not work.*
>
> Jo Walton, Credit Suisse

Astrazeneca CEO Pascal Soriot, in his opening remarks at the breakfast, assured investors that their dividend is not going away. "There is a huge focus on the dividend here," Walton said. "You're getting a 5 percent yield on both [Glaxosmithkline plc] and Astrazeneca in the U.K.," where backers of the company represent "a dominant force and they are holding the feet to the fire of management to continue paying out dividends. I think that part of the reason that the reaction [to the MYSTIC data] is not more severe is that the dividend is definitely going to be paid. Astrazeneca of course can pay this by getting slugs of money in for partially selling their assets. Clearly, they will be using some of the proceeds from the Merck upfront to pay this year's dividend, but they are going to continue with their externalization and therefore the dividends should not be at risk." The future will depend to some extent on the MYSTIC combo "working eventually in the OS setting," she added.

The pact with Merck brings $1.6 billion up front, $750 million for certain license options and up to $6.15 billion more if regulatory and sales milestones are met. Development and commercialization costs will be shared for Astrazeneca's oral poly ADP ribose polymerase (PARP) inhibitor Lynparza as well as experimental MEK inhibitor selumetinib as a monotherapy plus various non-PD-L1/PD-1 combo therapy opportunities. Gross profits from Lynparza and selumetinib product sales will be split, too. Merck has agreed to fund all development and commercialization costs of Keytruda when combined with

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Cytrx

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immuno-oncology and cell-based therapies.

The albumin of Abraxane was designed to activate a specific receptor in blood vessel walls called gp60, driving paclitaxel into the tumor microenvironment via transcytosis and is the only molecule that transcends beyond the blood vessel wall to the tumor microenvironment, Nantcell CEO and chairman Patrick Soon-Shiong told *BioWorld*. "Aldoxorubicin follows that path, and that's what's so exciting about it." he said.

Aldoxorubicin leverages an acid-sensitive linker that selectively binds to albumin, which may allow its cytotoxic payload to preferentially accumulate in the tumor and potentially spare the surrounding healthy tissue. It is also the first anthracycline to allow for continuous dosing without increasing cardiac toxicity, something that Soon-Shiong highlighted as being beneficial for the 17 indications for which doxorubicin is currently approved.

Aldoxorubicin, which has already been tested in soft tissue sarcomas, glioblastoma, HIV-related Kaposi's sarcoma and solid tumors, will now be tested alongside Nantcell's NANT Cancer Vaccine. The vaccine, a regimen of low-dose radiation and chemotherapy with tumor-associated antigen vaccines and natural killer cells, was green-lighted by the FDA for testing in May and is now slated for testing in more than 10 types of cancer, including sarcoma, the indication in which Cytrx expects to file a rolling 505(b)(2) application with the agency during the fourth quarter of this year. It has been granted orphan status by both the FDA and EMA.

At the close of its deal with Cytrx, Nantcell will take on all future development, manufacturing and commercialization costs for the drug. It's also buying $13 million of Cytrx stock and could pay Cytrx $343 million more for meeting approval and commercial milestones. Cytrx also issued Nantcell warrants to purchase up to 3 million shares of common stock at $1.10 over the next 18 months.

But potentially more significant for Cytrx, CEO and chairman Steve Kriegsman told *BioWorld*, is that the deal also includes increasing double-digit royalties for sales of aldoxorubicin for soft tissue sarcomas and mid-to-high single-digit royalties for what could turn out to be many eventual combinations with the NANT Cancer Vaccine.

"The sky's the limit here," Kriegsman said. "He's the best partner we could ever have."

With its first-generation albumin-mediated chemotherapy "now in the best hands," Kriegsman said, the company can begin to focus on its low-profile but biggest operation, the company's Freiburg, Germany-based lab, where aldoxorubicin was originally developed.

"What we're doing is not only going to the next generation, but doing one better: developing ultra-high potency chemotherapeutics" which employ the company's linker activated drug release, or LADR technology. While the technology is already incorporated into DK-049, a derivative of gemcitabine combined with a dual-releasing linker, Kriegsman suggested the company, he said the company is still deciding how to proceed with that program. News about new molecules from the LADR program is expected late this year or early next year.

That said, Kriegsman also sees the deal with Nantcell as an opportunity to raise the visibility of its home base, Los Angeles, as a home for breakthrough drug development. Nantcell, based in nearby Culver City, Calif., "are really going to put L.A. on the map an an epicenter of excellence going forward," he said.

Nantcell has had a busy summer. In June, it moved to purchase Miramar, Fla.-based Altor Bioscience Corp., a company developing cytokine-based immunotherapies for cancer and infectious diseases. ♦

Other news to note

Jaguar Animal Health Inc. and **Napo Pharmaceuticals Inc**., both of San Francisco, said stockholders of the respective companies approved proposals to merge the companies in separate stockholder meetings. The merger is on track to close on July 31, at which point Jaguar will change its name to Jaguar Health Inc. and Napo will operate as a wholly owned subsidiary of Jaguar that will focus on human health and the commercialization of Mytesi, which is approved for the treatment of diarrhea in adult patients with HIV/AIDS on antiretroviral therapy.

Kalobios Pharmaceuticals Inc., of Brisbane, Calif., said it plans to change its name to Humanigen Inc. effective Aug. 7, 2018, now that the company has shifted focus to neglected and rare disease. Shares of the company will begin trading under a new ticker symbol HGEN on the OTCQB market at the same time.

Otsuka Pharmaceutical Co. Ltd., of Tokyo, and **H. Lundbeck A/S**, of Valby, Denmark, said Abilify Maintena (aripiprazole) for extended-release injectable suspension was approved by the FDA for the maintenance monotherapy treatment of bipolar I disorder in adults. The drug, which won its first approval in 2013 for schizophrenia, is a once-monthly injectable formulation for intramuscular use created by Otsuka and has been co-developed and co-commercialized with Lundbeck. Based on phase III study data, it delayed the time to recurrence of any mood episode in adult patients experiencing a manic episode at screening compared to placebo.

Regeneron Pharmaceuticals Inc., of Tarrytown, N.Y., and **Sanofi SA**, of Paris, said the FDA approved a label update for Praluent (alirocumab) for injection, extending the time the PCSK9 inhibitor can be stored at room temperature, up to 77 degrees Fahrenheit, from 24 hours to up to 30 days. The approval provides greater flexibility for patients to help them manage the storage of their Praluent treatment, the companies said. Praluent is the only PCSK9 inhibitor antibody with two biweekly doses (75 mg and 150 mg). It's also approved as a monthly 300-mg dosing option in the U.S.

Prices

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Reintroduced in April in both the House and Senate, CREATES doesn't take aim at all the complexities of the U.S. market that have led to the highest drug prices in the world. Instead, it is an "elegant, narrowly tailored" bill, as described by David Olson, an associate professor at the Boston College School of Law, that targets delays in competition caused by brand abuse of risk evaluation and mitigation strategies (REMS) and restricted distribution systems.

The narrow focus has garnered support from lawmakers all along the political spectrum, as well as from a range of industry and health care organizations. Because of that support, CREATES has a higher likelihood of becoming law than some of the more controversial proposals out there.

The bill does two things. First, it would enable would-be competitors to turn to the courts to seek injunctive relief if an innovator denies them access to samples of a reference product needed to develop a generic or biosimilar. As a deterrent, the court also could award damages. The second part of the bill would give the FDA more discretion to approve an alternative REMS instead of trying to get the innovator to share its REMS, which it may have patented, with competitors.

REMS tend to be attached to specialty drugs to ensure their safe use. Since those drugs are often pricey, a delay in competition can have a significant financial impact. The Congressional Budget Office has estimated that the CREATES Act would save the government $3.3 billion, while generating even greater savings for patients and private insurers.

Earlier this year, Bruce Leicher, senior vice president and general counsel for Momenta Pharmaceuticals Inc. and chair of the Biosimilars Council, told a different House subcommittee that the biggest barrier to biopharma competition is innovators' abuse of REMS and self-imposed restricted distribution systems. (See *BioWorld Today*, March 24, 2017.)

Access to samples is a big factor in determining which generics or biosimilars Momenta develops, Leicher said, as its only recourse when denied a reference drug is to go to court or move on to a different generic or biosimilar. "We can't afford to litigate for three years to purchase samples at a fair market value and then start development three years from now," he testified.

Remedies not pursued

Under current law, the FDA has no authority to intervene when an innovator denies a competitor access to drug samples through a restricted distribution system. But the agency has some recourse if a REMS is used as an excuse to block samples. When the FDA receives a complaint from a potential competitor, it reviews the development protocol and informs the innovator that the intended use will not violate the REMS. As of March, the FDA had received more than 150 complaints from companies that had been denied samples because of REMS.

If the innovator still refuses to supply the drug, the FDA refers the case to the FTC. But to date, the FTC has not charged any drug company with antitrust violations for refusing to provide the samples needed to develop a generic or biosimilar. Instead, it has filed amicus briefs in private litigation involving REMS, the FTC's Markus Meier told the Subcommittee on Regulatory Reform, Commercial and Antitrust Law Thursday.

Refusing to provide a sample is not enough for an antitrust violation, Meier said. The FTC must be able to show that the refusal is a monopolistic strategy. He warned that if companies know they can get by with "running out the clock" on competition, getting access to reference drugs will be a bigger problem for generic and biosimilar sponsors in the future.

Rep. Tom Marino (R-Pa.), chairman of the subcommittee and the sponsor of the House bill, reminded FDA Commissioner Scott Gottlieb that his agency has the authority to hit innovators with civil penalties for refusing to provide their drugs to competitors.

The FDA hasn't used that authority, because it's a time-consuming, complex process, Gottlieb said, adding that the penalties are too low to be much of a deterrent. And the lengthy process still allows innovators to delay competition.

The sharing of REMS is another problem delaying competition, Olson said, noting that some innovators are patenting their REMS and then refusing to license them to competitors. Since the REMS adhere closely to the FDA standards, it's hard to design around the patents. Olson added that some innovators, after patenting their REMS, have filed citizen petitions to prevent generic companies from using a different REMS.

While CREATES could address these problems, it would not end other delaying tactics, such as the use of pay-for-delay settlements that allow innovators to fend off competition. Rep. Bob Goodlatte (R-Va.), chairman of the Judiciary Committee, said it also wouldn't respond to concerns about escalating prices for old drugs under the FDA's Unapproved Drugs Initiative.

Incentives, balance

Gottlieb explained that the initiative is intended to incentivize clinical testing of drugs that were already on the market when the current regulatory scheme was implemented in the 1960s. If a drug company goes through the steps to get an old drug approved, it receives three years of exclusivity, so all the other companies making unapproved versions of the drug have to remove their product from the market.

The result is that drugs once selling for a few dollars suddenly are priced at hundreds or thousands of dollars, Goodlatte said.

Gottlieb tried to provide some context for the initiative, noting that companies need an incentive to put an old drug through the regulatory process. He cited only 23 cases of an old drug being approved and its competitors being cleared from the market.

Goodlatte questioned whether monopolies could be avoided for those old drugs if someone else did the research.

In opening his testimony, Gottlieb reminded the subcommittee that the FDA doesn't oversee any aspect of pricing, but he acknowledged that the agency's policies do impact the cost of drugs. And while a handful of companies game the rules, Gottlieb said the U.S.' market-based system for drug development has unlocked significant discoveries and improvements. ♦

TGA

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The amended regulations passed by the Senate in June streamline the application processes for the country's Special Access Scheme and Authorized Prescriber programs. (See *BioWorld Today*, June 19, 2017.)

Previously, access to unapproved drugs required pre-approval, and doctors needed to submit clinical justification for authorization. Now, however, patients in Australia can get access to certain drugs that have an established history of use in similar overseas markets via a simple notification process known as the Special Access Scheme (SAS) category C.

Category C is a notification pathway that allows access to a single patient on a case-by-case basis for certain therapeutic products that are deemed to have an established history of use. These products are specified in a list along with the type of health practitioner that can supply the products.

Under the rules, the practitioner must inform the patient that the product is not approved in Australia. Adverse events must be reported to the Therapeutic Goods Administration (TGA) and the drug sponsor.

The process remains the same for SAS Category A and Category B pathways. Category A is a notification pathway, which allows access to seriously ill patients who would likely die without treatment. Category B requires TGA approval to access an unapproved drug that is not deemed to have an established history of use and can't be accessed through Category C.

Ausbiotech said in its comments on the proposal that the changes would help reduce administrative burden at the TGA. The association also supported the TGA engaging directly with the doctors that would be the primary users of the system.

Dials back notification for category B

In the draft guidance, category B was to be a notification process, but the agency dialed that back in the final regulation so that doctors must submit an application to the agency for approval before prescribing the unapproved drug.

The TGA said once a category B SAS application is received, the approval takes two to five working days. Urgent requests could be turned around more quickly.

The Medical Technology Association of Australia had also expected category B to be a notification process, and it praised the move in its comments on the earlier guidance.

"The low rate of SAS B rejections by the TGA [0.3 percent from around 20,000 applications per year[is evidence that a significant number of therapeutic goods currently used under the SAS B do not appear to pose an issue for public health and safety," MTAA said in its comments.

The list of medicines that would qualify under category C of the SAS pathway includes 27 drugs to treat conditions ranging from sleep disorders to resistant *H. pylori* infection. Many of the drugs on the list are antibiotics.

The list of biologics under category C includes numerous human tissues for skin grafts and bovine material as a calcium source for bone grafts.

Only one device is listed under category C: a synovasure lateral flow test IFU for detecting periprosthetic joint infection in the synovial fluid of patients experiencing pain following joint replacement.

Authorized prescriber program streamlined

The TGA also operates an authorized prescriber program which allows practitioners to prescribe unapproved drugs to their patients directly. The program allows doctors to supply the product to a specific class of patients without seeking approval or notification on an individual patient, as is the case with the SAS.

Under the amended regulation, authorized prescribers don't need to notify the TGA when they prescribe the unapproved product, but they do need to report the number of patients being treated with the product twice annually.

A medical practitioner seeking to become an authorized prescriber needs to get clearance from a human research ethics committee (HREC) or a specialist college. Ausbiotech said it supported relying on the expertise of a HREC or specialist medical college to approve the clinical justification for these products.

Ausbiotech also said it supported the longer time frames under which an authorized prescriber would be able to continue prescribing an unapproved drug for up to three years. The association also suggested that the agency be in close contact with medical device sponsors for the AP scheme since they would have more reliable information about the latest iterations of products as well as any adverse events or recalls.

MTAA also lauded the changes to the AP scheme, particularly extending the time frame for AP approval from one year to three years for medical devices.

The agency released a guidance tool to help doctors figure out which pathway makes the most sense. ♦

Heplisav

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quickly as possible."

Assuming the FDA follows VRBPAC's guidance, Dynavax will have some other questions to answer, namely whether the firm pursues commercialization of Heplisav on its own. Company execs have suggested they might seek a partnership, and early this year suspended manufacturing activities and commercial preparations for Heplisav in a restructuring effort.

Since then, it has focused much of its attention on a burgeoning immuno-oncology business, including SD-101, an intratumoral TLR9 agonist, which demonstrated encouraging early data at the American Society of Clinical Oncology meeting in Chicago in combination with PD-1 inhibitor Keytruda (pembrolizumab, Merck & Co. Inc.) in metastatic melanoma patients.

The company has not yet reported second-quarter earnings. As of March 31, it had about $84.5 million on its balance sheet.

Trading in Dynavax (NASDAQ:DVAX) was suspended for the Friday adcom, but shares surged $6.75, or 73 percent, in after-hours trading on Friday. ♦

Sunshine

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submission of the expenditure report and related books and supporting data against relevant drug providers, if necessary.

The new regulation closely resembles the Physician Payments Sunshine Act in the U.S. It comes at a time when corruption is still pervasive in the South Korean pharmaceutical market despite stringent anti-rebate regulations such as the dual punishment system was in place since 2010.

"Given the demand from society for information transparency and openness, as well as the importance of transactions of medicine and medical supplies, we believe the new policy, despite possible inconvenience that might follow, is worth going forward with," said Yun Byung-cheol, director at the MOHW.

"South Korean prosecutors and the South Korean Fair Trade Commission [FTC] have been strengthening anti-drug rebate regulations for a while now. With the new legislation in place, it reflects the government's will to eradicate drug rebates. We believe this would also increase related health care sectors to self-regulate. In the beginning we believe there will be some confusion on what is legal and illegal," Kim Yoon-hee, partner at law firm Shin and Kim, told *BioWorld*.

Starting Jan. 1, 2018, when requested by the MOHW, South Korean providers of pharmaceutical products must prepare an expenditure report that records any form of interaction between pharmaceutical providers and medical professionals. This must be prepared within three months after the completion of each fiscal year and expenditure reports must be kept for five years. Failure to comply will result in a fine of KRW2 million (US$1,796).

The requirements include six parts:

- When providing drug samples, pharmaceutical providers must disclose information about the medical institution, information about the drug including the name of the drug and the quantity of it, as well as the date of provision.
- The report should also show information about any symposiums that were held by pharmaceutical companies. Details on the host organization, name, place, and date of symposium must be shown and the expenditure on these symposiums should be disclosed, too.
- Information about clinical trials must be included.
- Information about health care professionals or medical institutions during product presentations must be disclosed. The supported amount, transportation, souvenirs, accommodations and even food and beverage covered by pharmaceuticals must be reported.
- Details on the post-marketing survey must be disclosed.
- When drugs are discounted, information about the medical institution and the contract must be revealed, including date of transaction, payment and the discount rate.

Although some have criticized the extra work required, many industry professionals including those from pharmaceutical companies supported the regulation. The MOHW also argued that its new policy would benefit doctors and pharmacists, since requiring them to keep records of financial transactions could protect medical personnel from false charges of corruption.

Going forward, South Korea remains one of the key international markets for innovative medicine launches, making it integral to the commercial prospects for multinational drugmakers.

South Korea has already become the fourth largest pharmaceutical market in the Asia Pacific region, and it is forecasted to grow from $15 billion in 2016 to $25 billion by 2026, according to BMI research. ♦

Other news to note

Servier SAS, of Suresnes Cedex, France, exercised its option to develop osteoarthritis drug GLPG1972/S201086 from **Galapagos NV,** of Mechelen, Belgium. Galapagos will receive a €6 million (US$7 million) license fee from Servier and is eligible for a total of €290 million (US$341 million) in success-based milestones. Servier and Galapagos will jointly make decision about the development of the drug, which targets a cartilage degrading enzyme called ADAMTS-5. Galapagos retains full commercialization rights to the drug in the U.S. and is entitled to receive royalties on commercial sales by Servier outside the U.S.

Teva Pharmaceutical Industries Ltd., of Jerusalem, said the company launched a generic version of Epiduo (adapalene and benzoyl peroxide, Galderma Laboratories L.P.). Being the first to file a generic drug application, Teva expects to have a 180-day genetic product exclusivity. Epiduo had annual sales of approximately $251 million in the U.S. according to IMS data as of March 2017 cited by Teva.

Tiziana Life Sciences plc, of London, said preclinical data for foralumab (NI-0401), an oral anti-CD3 monoclonal antibody, was published in *Clinical Immunology*. Foralumab modulated the immune system in a mouse model leading to indefinite graft acceptance without depletion of peripheral T cells. Tiziana is preparing clinical trial plans to test foralumab in patients with non-alcoholic steatohepatitis and type 2 diabetes.

Vilacto Bio Inc., of Copenhagen, said it plans to expand its exposure in Asia, meeting with partners, distributors and investors. The company also expects to start fundraising efforts in the fourth quarter of this year, targeting $5 million. Vilacto has developed the fully patented Lactoactive, which consists of highly refined colostrum and has demonstrated above-average effect treating conditions such as inflammatory diseases, diabetes, psoriasis, skin aging, and skin issues, the company said.

Zika

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Led by Shibo Jiang, a professor at Shanghai Medical College and director of the Institute of Medical Microbiology at Fudan University, the study's finding that the new inhibitor was safe for use in pregnant mice, suggests it could be considered for further preclinical and clinical development in humans.

A flavivirus related to the dengue and yellow fever viruses, Zika virus is transmitted to humans by Aedes mosquitoes such as *A. aegypti* and *A. aldopictus*. Zika virus infections are predominantly mild and transient, but have recently been linked with development of neurological disease such as Guillain-Barré syndrome.

The Zika virus can also be passed from an infected woman to her fetus during pregnancy, potentially leading to serious birth defects such as microcephaly. This prompted the World Health Organization to declare Zika an international emergency last year. However, no approved vaccines or drugs are currently available to prevent or treat Zika virus infection.

Now Jiang and his team have identified a new peptide, the intra-peritoneal administration of which in mice was shown to inactivate Zika virus particles and prevent the virus from entering cells.

The new peptide, designated Z2, was designed and developed based on Jiang's group's previous experience in the discovery of peptides effective against the human immunodeficiency virus (HIV), and the severe acute respiratory syndrome (SARS) and middle-East respiratory syndrome (MERS) coronaviruses.

In their new study, they also demonstrated that intra-peritoneal injection of the Z2 peptide could reduce transmission of the Zika virus to the fetuses of pregnant mice.

"We used types I and II interferon receptor-deficient mice for testing the in vivo efficacy of the Z2 peptide, since these two mouse strains are particularly susceptible to Zika virus infection," Jiang told *BioWorld*.

"Using viral inhibition and inactivation assays, we have demonstrated that the Z2 peptide interacts with Zika virus surface protein and disrupts the integrity of the viral membrane, resulting in inactivation of the virions, such that they cannot enter the host cells," he explained.

"This is a different mode of action to the mechanisms of most of the antiviral drugs used in clinical practice, which must enter host cells in order to inhibit viral replication. Conversely, the Z2 peptide can inactivate virions outside the host cells, thus being more effective and less toxic," noted Jiang

"Such inactivation of viral particles by a peptide is a novel approach to treating Zika virus infections, with this approach not having been used previously for other antiviral treatments."

Importantly, the Z2 peptide exhibited no apparent adverse effects in pregnant mice or their offspring when administered during pregnancy, so it may also be safe for use in humans.

"By using the Z2 peptide to treat Zika virus-infected pregnant mice, we showed that the Z2 peptide can penetrate into the placenta and enter the fetus' head to block Zika virus infection in maternal placentas and fetal heads," said Jiang.

Jiang noted that further studies are necessary to evaluate the safety and efficacy of the Z2 peptide in preclinical studies in animals and in clinical trials in humans. "If sufficient funding becomes available, it should take less than one year to complete preclinical studies, before applying for clinical trials."

In future, the approach of inactivating the virus particles could be used to develop novel treatments for Zika virus infection in high-risk populations, particularly pregnant women, he said.

Use of peptides as drugs has some drawbacks, notably immunogenicity and short half-lives. However, in the present study, Z2 did not induce anti-Z2 antibodies and, while it's half-life was only 2.7 hours, various techniques are now available to prolong peptides' half-lives.

"We are currently looking for partners who can license our patent or jointly fund the further development of the Z2 peptide," said Jiang. "We aim to develop this peptide in clinical trials and make it available as soon as possible to high-risk populations for the treatment and/or prevention of Zika virus infection." ♦

In the clinic

Evofem Biosciences Inc., of San Diego, started a phase III trial evaluating Amphora for the prevention of pregnancy. The compound, which consists of L-lactic acid, citric acid, and potassium bitartrate, is being studied as a vaginal contraceptive and for the prevention of certain vaginal infections. The study is designed to be supportive of the first phase III study that showed non-inferiority of Amphora compared to another marketed form of contraception over seven cycles of use, the company said.

Astrazeneca

Continued from page 4

Lynparza or selumetinib, while Astrazeneca will pay those costs with regard to combos that involve its urothelial carcinoma drug, Imfinzi, and Lynparza. (See *BioWorld Today*, July 28, 2017.)

Merck president Roger Perlmutter, speaking on Merck's earnings conference call Friday, told investors that "with respect to the failure of the MYSTIC trial, we learned about it at the same time that you did, and we have access to the same material that you have, which is just what has been presented in terms of study design and clinicaltrials.gov. I really don't know what the nature of the patient population was in detail. I don't really know what the data look like, and hence, it's not fair for me to comment. Suffice it to say it was not what they had hoped for in terms of a PFS result."

For Merck, anyway, Lynparza was the main focus. Cowen and Co. analyst Stephen Scala wanted to know if a similar deal might be done eventually with tremelimumab. "The Lynparza situation and our partnership with Astrazeneca was a very special transaction that reflects the genuine alignment of the two companies," Perlmutter said, adding that the company has "an interest in CTLA-4. We do believe quite strongly that there will be opportunities for a range of different combinations with Keytruda that we hope will improve outcomes in individual patients, and it will become very personalized. But we do have our own CTLA-4 antibody, MK-1308, and we've put a lot of work into developing that molecule."

Meanwhile, opinions continued to vary over what MYSTIC's outcome may augur for the phase III study known as Checkmate 227, testing PD-1 inhibitor Opdivo (nivolumab), from New York-based Bristol-Myers Squibb Co. (BMS), or Opdivo plus the same company's CTLA-4 checkpoint inhibitor Yervoy (ipilimumab), or Opdivo plus platinum-doublet chemo compared to chemo alone in stage IV NSCLC. The study is set to enroll about 2,220 patients, with an estimated primary completion date of next January. (See *BioWorld Today*, Aug. 8, 2016.)

BMS hosted an earnings call last week, too. CEO Giovanni Caforio took pains to contrast Checkmate 227 with MYSTIC. "We all know that a competitor announced data this morning that is clearly important to the market, so let me make a few comments. First, our Checkmate 227 is a first-line NSCLC program, not just one trial, investigating several important scientific questions. We have at least three discrete opportunities for success. We will be able to evaluate the combination of Opdivo plus Yervoy, we will evaluate Opdivo plus chemo in PD-L1-negative patients, and we will be able to evaluate Opdivo plus chemo in all comers. Additionally, we are testing two cycles of chemo with the combination of Opdivo and Yervoy."

The dose schedules differ between Checkmate 227 and MYSTIC, as do the enrollment sizes: Checkmate 227 signed up more than 2,200 patients, with 1,200 in the PD-L1-positive portion. MYSTIC enrolled roughly 1,100 patients in all comers and its primary endpoint was evaluated in a subset of that population.

"While the MYSTIC results are important data, and we look forward to seeing more, it's very difficult to read across trials," he said.

That didn't stop people from trying.

Goldman Sachs analyst Jamilu Rubin asked BMS' to "comment generally about the role of CTLA-4 and your confidence in this asset. It's very hard to walk away from MYSTIC feeling warm and fuzzy about Checkmate 227." Thomas Lynch, chief scientific officer, said "lung cancer is an unbelievably difficult disease to treat. I've been at it for 30 years, and I continually am struck by how challenging it is to make progress in this disease." BMS is "not wedded to any one approach. We have optionality with monotherapy in first line." Regarding CTLA-4 as a mechanism, he said the results in OS have been encouraging. "I think as an oncologist, as a clinical researcher, when you see an agent that's associated with a survival advantage, I think it's important to find out what is the optimal way to use this drug and how can we improve outcome for our patients. One of the things that we become very aware of is that dosing schedules are important when you combine IO drugs, and I think that we feel certainly in [Checkmate 227] that we have a good dosing schedule for our patients."

Regarding the buzz on PARP inhibitors touched off by the Lynparza deal, Credit Suisse's Alethia Young said "Tesaro was the most debated name" as word of the pact spread. Some viewed the glass as half-full and the PARP space as further validated. Others grumbled that Merck's choosing Astrazeneca for a major tie-up "takes another potential buyer out of the market," she said. "[Reaction] was very tiered." Waltham, Mass.-based Tesaro Inc., for its part, last week disclosed a licensing deal with Takeda Pharmaceutical Co. Ltd., of Tokyo, for the commercialization and clinical development of PARP inhibitor Zejula (niraparib). The terms involve moving niraparib along for the treatment of all tumor types in Japan, and all tumor types excluding prostate cancer in South Korea, Taiwan, Russia and Australia. Tesaro gets $100 million up front and as much as $240 million in milestone payments. ♦

Earnings

Seattle Genetics Inc., of Bothell, Wash., reported second quarter revenues of $108.2 million, including $74.3 million in net sales of Adcetris (brentuximab vedotin) in the U.S. and Canada, compared to revenues of $95.4 million in the second quarter of 2016. Revenues for the first six months increased to $217.4 million on Adcetris sales of $144.7 million, compared to $206.6 million in revenues in the same period in 2016. Second quarter expenses were $167.5 million compared to $128.8 million in the same period in 2016, and six-month expenses were $336 million compared to $261 million in the first half of 2016. The company attributed the increase in 2017 expenses to investments in Adcetris and to its late stage and pipeline programs. The company's net loss for the quarter was $56.4 million, or 39 centers per share, compared to a net loss of $32.7 million, or 23 cents per share, for the second quarter of 2016. Seattle Genetics reported $473.0 million in cash, equivalents and investments as of June 30. On Friday, the company's shares (NASDAQ:SGEN) closed at $51.18 for a loss of $1.79.

In the clinic

Idorsia Ltd., of Allschwil, Switzerland, reported that the phase II program of its dual orexin receptor antagonist (DORA), known as ACT-541468, met its primary endpoint in insomnia, using zolpidem as an active comparator. The program comprised two placebo-controlled dose-response studies to evaluate the safety and efficacy of ACT-541468, collectively enrolling 418 adult and elderly patients with insomnia. The first, six-arm study enrolled 360 adults, ages 18 to 64 years, assigned to four doses of ACT-541468 or to zolpidem or placebo for four weeks, According to Cortellis Clinical Trials Intelligence. Findings showed a dose-dependent decrease in wake after sleep onset, or WASO, at day one and two, measured by polysomnography. In addition, ACT-541468 decreased latency to persistent sleep, or LPS, in a dose-dependent manner. Idorsia said treatment with ACT-541468 was generally well tolerated, with no reports of serious adverse events related to the study drug. The company said a second study, conducted in 58 patients, ages 65 to 85 years, confirmed the efficacy and safety profile of ACT-541468 in this population, also showing a decrease in WASO and LPS at day one and two in a dose-dependent manner. Idorsia said it will move forward with confirmatory efficacy and safety studies in both adults and older adults. The company plans to report detailed results at scientific meetings and in peer-reviewed publications. Idorsia was spun out of Actelion Ltd., also of Allschwil, and gained a public listing at the close of Actelion's acquisition by Johnson & Johnson, of New Brunswick, N.J. On Friday, Idorsia's shares (SIX:IDIA) rose 6.7 percent to close at CHF 17.50 (US$18.07) for a gain of CHF1.10. (See *BioWorld Today*, May 23, 2017.)

Oncolys Biopharma Inc., of Tokyo, enrolled the first patient in the phase II trial with Telomelysin (OBP-301) for the treatment of melanoma in the U.S. The drug will be administered locally on unresectable or metastatic melanoma patients in clinical centers, and the trial will enroll up to 50 patients in five sites across the country. After obtaining the results of the trial, Oncolys will also consider an additional clinical trial of Telomelysin in combination with immune checkpoint inhibitors. Telomelysin is an oncolytic adenovirus in which gene is modified to be able to selectively replicate in cancer cells by introducing human telomerase reverse transcriptase promoter.