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Despite skeptics, Celltrion aims to build Incheon bio-valley via $33.5B investment

By Jihyun Kim, Staff Writer

HONG KONG – Celltrion Inc., a South Korean biopharma known for Remsima (infliximab), the first biosimilar monoclonal antibody to gain EMA approval, plans to invest more than $33 billion over the next decade to build itself into a top global player and develop Korea as a biomedical hub.

Jungjin Seo, the founder and chairman of the company, said the firm had set up plans to invest KRW40 trillion (US$33.5 billion) by 2030. Those investments would carry through even after his retirement in the late 2020s.

See Celltrion, page 3

AMF analysis notes improvement by industry, calls for more effort on global access to medicine

By Nuala Moran, Staff Writer

LONDON – A 10-year analysis of how pharma is working to improve access to medicines in the developing world shows the industry has moved beyond paying lip service and is implementing policies that provide more and better drugs in poorer countries.

The analysis, by the Access to Medicines Foundation (AMF), finds the issue is now widely seen as being of strategic importance, with 17 out of 20 leading pharma companies having targets for addressing access in low- and middle-income countries. That compares to eight companies that set access-related goals in 2010. The 20 companies account for 70% of global pharma revenues.

"Compared with 10 years ago, pharmaceutical companies are taking seriously the problems people face in low- and middle-income countries when accessing health care," said Jayasree Iyer, executive

See AMF, page 4

Huons collaboration offers global network for biobetter, rare disease drug pipeline

By Jihyun Kim, Staff Writer

HONG KONG – Pharmaceutical manufacturer Huons Co. Ltd. and biopharmaceutical research and development venture Genexine Inc. inked a memorandum of understanding for a deal, under which they will combine Genexine's biobetters and rare disease pipeline with Huons' existing global commercial network.

According to the South Korean firms, both based in Seongnam, Gyeonggi-do, Huons will lead the planning and Genexine will focus on R&D. Specific financial terms and target candidates

See Huons, page 5

Takeda and Frazier establish Phathom for acid-related diseases

By Brian Orelli, Staff Writer

Rather than develop vonoprazan in the U.S., Europe and Canada on its own, Takeda Pharmaceutical Co. Ltd. decided to spin the drug out into a new company, Phathom Pharmaceuticals Inc., with the help of venture capitalists at Frazier Healthcare Partners.

"Granting Phathom rights to develop and commercialize vonoprazan in the United States, Canada and Europe enables Takeda R&D to focus on advancing its diverse pipeline developing specialty GI treatments in inflammatory bowel disease, celiac disease, liver diseases and

See Takeda, page 7

Korea to collaborate with Italy and Japan on cancer biomarker

By Jihyun Kim, Staff Writer

HONG KONG – The Korea Cancer Biomarker Consortium (KCBC), a research group of 13 university hospitals in South Korea, and South Korean biotech Cbsbioscience Inc. inked a deal with medical research institutes in Italy and Japan to develop biomarkers aimed at improving the efficiency of cancer drugs.

The three academic groups, which will include the Istituto Nazionale Tumori IRCCS Fondazione G. Pascale, a national institute of tumor studies in Naples, Italy, and Wakayama Medical University, Japan, signed a five-year agreement. Under the terms, they will proceed by expanding clinical

See Korea, page 6

MIXiii Biomed 2019

'Greatest emerging market'? Cannabis-based drug R&D finally going mainstream

By Alfred Romann, Staff Writer

TEL AVIV, Israel – An awakening is underway in the biotech field to develop new products from cannabis, with efforts based on strong science and supported by clinical trials and rigorous research, particularly into the many potential uses of cannabinoids.

"We have no doubt that cannabis is helpful to patients," said Hinanit Koltai, of the Volcani Center, a lab in Israel that works with biotech companies to identify compounds that originate in cannabis plants and develop products. "There

See Cannabis, page 8

Other news to note

Batavia Biosciences BV, of Leiden, the Netherlands, said it will work together in a consortium including the European Vaccine Initiative and Stanford University and headed by the University of Tokyo to develop an epidemic preparedness vaccine against Nipah virus. The University of Tokyo received a $31 million grant from the Coalition of Epidemic Preparedness to use its measles vector technology to develop and stockpile a Nipah vaccine. As a partner in the consortium, Batavia will receive $9.6 million to deliver a low-cost manufacturing process that can be easily applied for stockpiling of the vaccine. The Nipah virus, which is prevalent in southeast Asia and the Indian subcontinent, causes illness ranging from fever and headache, to acute respiratory illness, and even fatal encephalitis.

Scientists from the **Beijing Institute of Biotechnology** have discovered an interaction between telomerase and the protein Pescadillo (PES1) that facilitated telomerase activity. Telomerase lengthens the telomeres, or chromosome tips. Because those tips are not replicated during cell division, telomere shortening is a cellular clock that keeps track of how many generations removed from its parent stem cell a cell is. Telomerase activity is important for stem cells to retain their degenerative potential, but it is also present in many cancer cells, which is one mechanism enabling their uncontrolled proliferation. The authors showed that PES1 facilitated telomerase assembly, and that its expression correlated "positively with telomerase activity and negatively with senescence in patients with breast cancer. Thus, we identify a previously unknown telomerase complex, and targeting PES1 may open a new avenue for cancer therapy." The team published its results in the May 15, 2019, issue of *Science Advances*.

Bioarctic AB, of Stockholm, said it will receive a €15 million (US$16.8 million) milestone payment from partner **Eisai Co. Ltd.**, of Tokyo, for achievement of the first patient dosed in a confirmatory phase III study with BAN-2401 in Alzheimer's disease.

Biocure Pharm Corp., a subsidiary of Biocure Technology Inc., of Vancouver, British Columbia, entered an agreement with **Pharos Vaccine Inc.**, of Seongnam, South Korea, for the development of anti-CD19 CAR T-cell therapy products. Biocure will have rights to the products in all countries except China for 15 years from the starting date of sales in the markets. Financial terms of the agreement weren't disclosed.

Cue Biopharma Inc., of Cambridge, Mass., said it will earn a $2.5 million milestone payment from **LG Chem Life Sciences**, the life sciences division of LG Chem Ltd., of South Korea, on the FDA acceptance for a IND to start phase I testing of Immuno-STAT candidate CUE-101 in head and neck squamous cell carcinoma. The companies entered the oncology-focused deal last year. (See *BioWorld*, Nov. 9, 2018.)

Cumberland Pharmaceuticals Inc., of Nashville, Tenn., said it entered an exclusive agreement granting China's **Winhealth Pharma Group** licensing rights to commercialize two products in China: Acetadote (acetylcysteine), used to prevent or reduce liver damage resulting from acetaminophen overdose, and Caldolor (ibuprofen), used to treat pain and fever in the hospital setting. Terms of the deal were not disclosed.

Kazia Therapeutics Ltd., of Sydney, entered a collaboration with the Alliance for Clinical Trials in Oncology Foundation, a U.S.-based cancer research network sponsored by the National Cancer Institute. Alliance will launch a multicenter phase II study to investigate the potential use of Kazia's GDC-0084, alongside several other targeted cancer therapies, in the treatment of brain metastases. The trial is expected to recruit up to 150 patients in multiple centers. The trial will be led by Alliance, with Kazia providing support including study drug and a financial grant.

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Celltrion

Continued from page 1

Celltrion plans to pour the money into three sectors.

The first is a biomedical business centered in Songdo, Incheon, in which the company plans to invest KRW25 trillion to develop more than 20 second-generation biosimilars to treat cancer and expand its biomedicine efforts. Funds also will be used to expand its production facilities and build a network of direct sales in Europe, South America, Canada and the U.S.

The company is already negotiating with the government of Incheon city and Samsung Biologics Co. Ltd., another top biosimilar company in Korea, to expand factories and R&D facilities based in Songdo. Celltrion also expects to expand its manufacturing capacity by as much as 330,000 square meters so that its three factories can produce as much as 360,000 liters per year.

The second sector for expansion is chemical medicines out of the company's facilities in Ochang, Chungbuk Province. That project will operate about 50 pipelines and develop new drugs through in-licensing based on R&D and manufacturing.

The third sector will tap into big data and artificial intelligence to expand the company's medical services and devices platform.

The ambitious plan, however, has attracted some criticism, with observers questioning whether the company can afford to invest that much money.

Celltrion has only KRW1 trillion in resources available immediately, after issuing bonds worth around KRW400 billion and cash in hand worth KRW1.4 trillion. It also has KRW700 billion in debt as of May 20.

The company has said the massive investment budget is based on future earnings. Celltrion expects its operating profit by 2030 will be a cumulative KRW32 trillion, about 40% of sales. From the operating profit, the company is going to pull KRW30 trillion for the investment.

"Most of the investment fund will come from our operating profits," a Celltrion spokesman told *BioWorld Asia*.

The company is also expecting to benefit from a number of commercial launches of about 15 biosimilar products, including biosimilars of Avastin (bevacizumab), Lucentis (ranibizumab), Stelara (ustekinumab). The patents for those drugs expire between 2020 and 2030. Currently, Celltrion's annual sales are about KRW1 trillion.

In addition, the firm has said it would fund KRW10 trillion from external investment.

Chairman Seo said the aim is to build a virtual ecosystem of pharmaceutical businesses and make Songdo a bio-valley of Korea.

"If we combine the biosimilar production bases of Celltrion and Samsung Biologics in Songdo, it will be bigger than Genentech Inc., which has the world's largest production facilities. We will attract foreign companies to Korea as the country will become the largest buyer," said Seo.

> *"If we combine the biosimilar production bases of Celltrion and Samsung Biologics in Songdo, it will be bigger than Genentech Inc.*
>
> Jungjin Seo
> Founder and Chairman, Celltrion

Doubts remain

But, beyond the doubts of Celltrion's own ability to invest that much money, there are doubts that Samsung Biologics will be able to invest in the facilities.

Samsung Biologics has also been hit by a fraud scandal linked to inflated values from its subsidiary Samsung Bioepis Co. Ltd. Taehan Kim, CEO of Samsung Biologics, was summoned by prosecutors on May 20. (See *BioWorld*, May 6, 2019.)

"While Celltrion has grown its resources for the huge investment step by step, Samsung Biologics has little shown the business structure for the funding," Jaecheon Yeo, executive director of the Korea Drug Research Association, told *BioWorld Asia*. "We need to see how the company will plan to re-invest in its production system as Samsung Biologics is currently in a very tough situation."

Meanwhile, operating profit of Celltrion dropped 32.9% in the first quarter this year from the fiscal quarter. The company's operating income from January to March this year recorded KRW77.4 billion, and sales declined 9.5% year over year to KRW221.7 billion. Net profit fell 28.4% to KRW63 billion. The company attributed the results to a partial shutdown of the first plan last year to expand the production facility.

Celltrion's stock price (068270.KS) fell 3.72% from KRW188,000 to KRW181,000 on May 21, affected by the rapid drop in stock price of Celltrion Healthcare Co., a distributing company of Celltrion. Stock price of Celltrion Healthcare plummeted 9.19% from KRW65,300 to KRW59,300.

JP Morgan Chase & Co., an early investor in Celltrion Healthcare, announced on May 20 that the investment bank's affiliate PEF management firm One Equity Partners LLC would sell 6.5 million shares (a 4.5% stake) of Celltrion Healthcare for KRW390.6 billion.

One Equity Partners is the second biggest shareholder of Celltrion Healthcare. The PEF management firm raised KRW400 billion by selling a 3% stake, or 4.4 million shares, last year. Despite selling stakes, One Equity Partners will maintain the second largest shareholder of Celltrion Healthcare with more than a 10% stake. ♦

AMF

Continued from page 1

director of AMF. But she added, "The situation is still fragile. A retreat by one company, or a drop in health care investments will jeopardize progress made so far."

It remains the case that 2 billion people lack access to medicines.

Companies are using three main ways to improve access, through "equitable" pricing, the licensing of intellectual property to let local manufacturers produce drugs at lower cost, and through direct donations of products.

AMF has been tracking the industry's progress on improving access since 2008; the data in the 10-year analysis cover 83% of the world's population, living in 106 countries.

One of the key motivating factors for pharma's increasing commitment to improving access pinpointed in the analysis is that those countries will account for 25% of global spending on pharmaceuticals by 2020.

Astrazeneca plc and Sanofi SA, among other companies, now generate approximately 30% of their revenues from those emerging markets, giving them an incentive to be good corporate citizens. AMF refers to that as "social license to operate," saying acceptance of a company's way of doing business and the ability to attract, retain and motivate employees, increasingly rests on addressing access to drugs for people that need them, regardless of their income

AMF said companies also have come to recognize that actively addressing access is a way to manage risks associated with adverse public opinion over issues such as drug pricing, the potential for increased regulatory scrutiny, and demands for compulsory licensing of branded products.

The most striking progress over the past 10 years has been made in the expansion of R&D in diseases that cause the greatest disease burden and suffering in developing countries, including HIV/AIDS, malaria and tuberculosis. The number of drugs in the pipeline for 47 high-burden and priority diseases has doubled since 2014, and there are now 285 products in clinical development.

However, the data on approved drugs for the 47 diseases hint the increase in R&D may be more driven by commercial opportunity than corporate social responsibility. Of the 103 new drugs approved for the 47 diseases from 2008 to 2018, most are for noncommunicable diseases and sell at a profit.

And the increased commitment to R&D is not seen across the board. In 2018, five companies – Glaxosmithkline plc, Johnson & Johnson Inc., Merck KGaA, Novartis AG and Sanofi SA – were among them carrying out 63% of R&D projects.

As one measure of how pharma's attitude to access is changing things on the ground, more than half of all the people infected with HIV in the 106 countries are now being treated with antiretroviral drugs.

The level of coverage is attributed to voluntary granting of licenses to local manufacturers. In 2010, 12 compounds were licensed; by 2018, the number was 22. The number of licensed compounds for treating hepatitis C has risen from two in 2014 to seven in 2018.

At the same time, more products are covered by equitable pricing. Of 589 drugs tracked by the index, the prices of 447 are controlled by that mechanism.

There has been less of an improvement in the volume of free drug donations for neglected tropical diseases, with half of the companies making donations in 2018, compared to eight in 2008.

In the face of progress over the past decade, the poorest countries continue to do worst. In 2018, 13 of the sub-Saharan countries in Africa had no registration filings for new products for diseases that are access priorities. Those 13 countries are home to 150 million people.

Even in countries like Brazil, India and China, equitable pricing policies still leave drugs beyond the means of the poorest people.

AMF, based in Amsterdam, is funded by the Dutch and U.K. governments and the Bill & Melinda Gates Foundation. The foundation relies on the goodwill of pharma companies in giving access to their data.

While reporting progress, AMF said that "the uptake of good practice is uneven, with the current pharmaceutical model offering limited incentives to engage in countries with only a weak, or no commercial market, but a high disease burden."

The most effective recipe for encouraging pharma companies to engage is that priorities are set by international experts in global health; that publicly funded derisking or market shaping mechanisms are put in place to reduce uncertainty; and that there is long-term coordinated support from donors and sustained investment in health care by national governments.

However, at present, that recipe is only successfully being applied to a few diseases, such as neglected tropical diseases and HIV/AIDS, and to child and maternal mortality.

At the same time, the bulk of private sector engagement is being carried by a few companies. "A retreat by just one of these companies could have a catastrophic effect on the progress made to date," the report says. A more diverse group of companies must be brought to the table. ♦

Other news to note

Kerastem, a subsidiary of Bimini Technologies LLC, of Solana Beach, Calif., and Seoul, South Korea-based **Myungmoon Bio Co. Ltd.**, said they expanded their existing commercial partnership to bring Kerastem's hair growth cell therapy to China and ASEAN member states. Kerastem will receive more than $5 million up front in cash and initial product purchase commitments in a deal, which has a potential value of $140 million when development milestones, product purchases and royalties are factored in. Kerastem reported top-line data from its clinical trial (STYLE), a 70-patient, phase II study investigating its therapy in patients with early hair loss that demonstrated a statistically significant increase in the number of mature hairs in men treated with a targeted low dose of cells compared to placebo control.

Huons

Continued from page 1

have not been confirmed.

Huons is known mostly for generics, producing about 300 generic medicines for circulatory system, metabolic and musculoskeletal diseases. The company also manufactures medical devices such as continuous glucose monitoring, and cosmetics and health-functioning foods. Based on contract manufacturing operations, Huons exports eyedrop medicine to Japan.

In 2018, Huons won ANDA approval from the U.S. FDA for the company's lidocaine ampule, a local anesthetic, and started exporting the medicine with a 20-year supply contract worth KRW$89.3 billion. Three more Huons products are awaiting ANDA approval.

"Huons has a wide distribution network in Korea and has much experience in marketing overseas," Seungtaek Eddie Oh, an equity analyst at Leading Investment & Securities Co. Ltd., told *BioWorld Asia*. "In particular, they have had good performance in exporting generic medicine to the U.S. and eyedrop products to Japan. Based on this experience, the company seems to be able to support Genexine's global promotion."

According to Huons' quarterly financial report released on May 15, the company's sales and operating profit increased 11.6% and 5.8%, respectively, compared with last fiscal quarter, to KRW82.6 billion (US$69.5 million) and KRW12 billion.

"Even though we have primarily focused on generic medicine, we currently plan to expand our biopharmaceutical business in the long term," a spokesman at Huons told *BioWorld Asia*. "This is the reason why we have decided to collaborate with Genexine. Genexine has great capabilities for R&D of new drugs, and we aim to commercialize new drugs we would develop together."

Genexine focuses on developing biobetters and new drugs. Its growth hormones, short bowel syndrome treatments and immune cancer drugs have been designated as rare disease drugs by the FDA.

In addition to drugs, Genexine has developed technologies, including the hybrid Fc fusion protein and therapeutic DNA vaccines. The biotech also conducts research that maximizes efficient gene expression in the body and has in the clinic a vaccine for the treatment of cervical cancer-causing human papillomavirus.

In April, Genexine and Neoimmunetech Inc. started administering its combination treatment of Hyleukin-7 and Merck & Co. Inc.'s PD-1 inhibitor, Keytruda (pembrolizumab), for phase Ib and II trials in triple-negative breast cancer (TNBC) patients.

Hyleukin-7 is a T-cell amplifier that stabilizes interleukin-7, an essential growth factor for the development and proliferation of T cells in the body. It increases the half-life and efficacy of the body by applying hyFc technology, a technology developed by Genexine.

The company also has received FDA approval for phase Ib and IIa trials for joint administration with Tecentriq (atezolizumab),

See Huons, page 10

Korea

Continued from page 1

trials of a European liver cancer vaccine to Korea. The vaccine has been developed by Hepavac, a consortium of nine medical research institutes across Europe and coordinated by Pascale, and clinical trials are ongoing in Europe.

Other work will focus on verifying results of liver cancer prediction tests as well as for companion diagnostics for Nexavar (sorafenib, Bayer AG) through clinical trials in Europe and Japan. Nexavar is an FDA-approved drug primarily used for liver and kidney cancers. Around 1,000 liver patients in South Korea use the drug every year, according to KCBC.

The new partners also will co-develop liver cancer vaccines based on biomarkers and analyze big data from clinical trials and experiments that have been done in Korea and Italy.

KCBC has researched biomarkers of liver, colon, head and neck, breast and stomach cancers for 10 years. The organization verifies new technology for developing cancer biomarkers, conducts clinical research, uses statistical analysis technologies and trains medical professionals.

Under the new agreement, Pascale of Italy and Wakayama Medical University have become members of the South Korean consortium.

"Korea has data on more than 2,000 cancer patients and advanced technologies of gene analysis," said Heejung Wang, head of KCBC and a professor of Ajou University School of Medicine told *BioWorld Asia*. "Pascale of Italy has a strong research network in Europe and a vast amount of data on clinical trials of European cancer patients," while Wakayama has held pancreatic surgery symposiums with Ajou University Hospital and has used a liver cancer prognosis diagnostic test developed by Cbsbioscience for Japanese patients.

"Based on the collaboration of the three countries, we expect to facilitate developing anticancer biomarkers," Wang said.

To find a biomarker, the organization focuses on an analysis of cell tissue from liver cancer patients by using Encounter, a device for genome data analysis.

The tool analyzes more than 1,000 genes from each patient and, based on those gene data, KCBC builds a genome atlas of liver cancer and finds certain patterns of genes in patients resulting from some cancer treatments.

According to Cbsbioscience, the overall response rate (ORR) to Nexavar for liver cancer is only 2% to 3%. However, using the biomarker the company has developed, the response rate increases up to 15% to 16%.

Cbsbioscience and KCBC have conducted clinical trials of Nexavar biomarker since 2014. The company is preparing to commercialize it in South Korea.

Specializing in developing programs for biomarker analysis tests, Cbsbioscience develops 3D models that visualize gene expression maps of cancer patients based on patient responses to drugs. Also, the company builds 3D cancer multi-omics atlases based on clinical trial data of patients from Korea, Japan and Europe.

"Using our own 3D cancer multi-omics atlas and analysis platform CBSJukebox, we do machine learning and analyze big data to develop biomarkers of anticancer drugs," a spokesman of Cbsbioscience told *BioWorld Asia*. "Based on the co-research with international partners, we plan to actualize precision medicine high-throughput experimental and real-world cancer patients' data from various countries."

The company is preparing to list on Kosdaq this year and to move forward with the commercialization of the Nexavar biomarker as well as other cancer biomarkers. ♦

Appointments & advancements

Avita Medical Ltd., of Melbourne, Australia, appointed Tim Rooney, Avita's chief administrative officer, interim chief financial officer. Rooney joined the company as CFO and chief operating officer in 2012, leading in various key executive roles, including interim CEO from 2013 to 2015. Prior to Avita, he was an executive at PDI Enterprises Inc., a pharmaceutical wholesale distributor, where he served as CFO/COO.

Botanix Pharmaceuticals Ltd., of Sydney, appointed Vince Ippolito president to lead global commercial operations. Ippolito has more than 30 years of experience in the pharmaceutical industry, including more than 20 years in dermatology. He most recently served as president and chief operating officer of Dermavant Sciences Inc.

Eisai Inc., of Woodcliff Lake, N.J., the U.S. pharmaceutical subsidiary of Tokyo-based Eisai Co. Ltd., appointed Luca Dezzani vice president, U.S. Medical Affairs, Oncology Business Group. He will be responsible for creating the Medical Affair's strategy for the company's oncology portfolio of both commercialized and investigational products in the U.S. He will also oversee Eisai's Health Economics & Outcomes Research (HEOR), Medical Science Liaisons (MSL) and Medical Information & Education teams. Dezzani joins Eisai from Novartis Oncology, where he held senior medical roles in Europe and the U.S.

Imugene Ltd., of Sydney, appointed Jens Eckstein to its board as a non-executive director. A biotechnology executive and entrepreneur, Eckstein recently joined Apollo Ventures as managing partner. Prior to that he served as president of SR One Ltd., the corporate venture capital arm of Glaxosmithkline plc.

Sanbio Group, of Tokyo, appointed Bijan Nejadnik chief medical officer in charge of development and regulatory affairs. Nejadnik held key roles at Johnson & Johnson, as well as pioneering clinical programs at Jazz Pharmaceuticals plc, Galena Biopharma Inc. and Eureka Therapeutics Inc. ♦

Takeda

Continued from page 1

microbiome therapies," Takeda spokesperson Chris Stamm told *BioWorld Asia*, explaining the decision to out-license vonoprazan so Takeda can put its resources elsewhere.

The formation of Phathom stemmed from a relationship between Tachi Yamada, a venture partner at Frazier, and Takeda, where Yamada was previously chief medical officer and chief scientific officer.

"This was always a compound that he was very interested in," David Socks, interim CEO of Phathom and venture partner at Frazier, said of Yamada, who has experience with acid-related diseases, having been the chief of the division of gastroenterology at the University of Michigan. Yamada will serve as Phathom's chairman.

Takeda and its partner, Otsuka Pharmaceutical Co. Ltd., both of Tokyo, have sold vonoprazan, a potassium competitive acid blocker (P-CAB), in Japan since 2015 where the drug goes by the brand name Takecab. Takeda also markets the drug in Malaysia, Philippines, Singapore, South Korea, Taiwan and Thailand. During the fiscal year that ended in March, Takeda racked up ¥58.2 billion (US$530 million) in sales of Takecab.

Through the licensing deal, Takeda will get an undisclosed up-front cash payment and equity in Phathom and is eligible for milestones payments and royalties on net sales of the drug.

Phathom plans to start phase III development of vonoprazan in the U.S. and Europe later this year in patients with gastroesophageal reflux disease (GERD) and in combination with antibiotics for the irradiation of Helicobacter pylori, a bacterial pathogen associated with gastritis, peptic ulcer and gastric cancer.

In a phase III study in Japanese patients with erosive esophagitis caused by GERD run by Takeda, vonoprazan was deemed noninferior to lansoprazole, with 99% of patients taking vonoprazan healed at week 8, compared to 95.5% of patients taking lansoprazole ($p<0.0001$). In a post-hoc analysis, the difference was enough to conclude vonoprazan was superior ($p=0.0337$).

Unlike proton pump inhibitors (PPIs), vonoprazan isn't primarily metabolized by CYP2C19, which can result in interpatient variability. Consequently, the difference in the proportion of healed patients with the extensive metabolizer genotype of CYP2C19 was greater (98.9% for vonoprazan vs. 94.5% for lansoprazole). Vonoprazan also worked substantially better than lansoprazole in patients with the more-severe LA Grade C and D erosive esophagitis (98.7% vs. 87.5%).

In a longer, 24-week phase III study in patients with healed erosive esophagitis, 16.8% of patients taking lansoprazole had recurrence of their disease compared to 5.1% of patients taking the 10-mg dose and 2% of patients taking the 20-mg dose ($p=0.0002$ and $p<0.0001$, respectively).

In a separate phase III study of patients with H. pylori infections, vonoprazan plus amoxicillin and clarithromycin was superior to lansoprazole plus amoxicillin and clarithromycin, with an eradication rate of 92.6% for patients taking the vonoprazan combination compared to 75.9% for patients taking the lansoprazole combination ($p<0.0001$).

If it makes it to the market in the U.S., vonoprazan will have to compete with PPIs, such as Prilosec (omeprazole), Prevacid (lansoprazole) and Nexium (esomeprazole), many of which are available as generics in the U.S. But Socks said he sees an opportunity to treat the 30% to 40% of patients with GERD taking a PPI who continue to experience symptoms. And PPIs combined with clarithromycin and amoxicillin or metronidazole only eradicate H. pylori infections in 70% to 80% of patients, leaving room for improvement, as seen in Takeda's phase III study.

"We think that there is also potential opportunity for the drug to be used as a first-line as well, given its much more rapid onset of action and superior acid suppression compared to PPIs," Socks told *BioWorld Asia*.

Socks said there are other P-CABs in early stage development, but vonoprazan is the only late-stage program that he's aware of for the Western markets. Astrazeneca plc, of Cambridge, U.K., developed AZD-0865 through phase II, but development seems to have stalled. Revanex (revaprazan, Yuhan Corp.) is approved for the treatment of gastritis in Korea.

Building a GI company

Phathom was established with a $90 million private financing led by Frazier with additional investments from Medicxi, RA Capital Management, Abingworth, certain accounts managed by Janus Henderson Investors, BVF Partners LP, Greenspring Associates, Richard King Mellon Foundation, Sahsen Ventures and undisclosed institutional investors. The company also took out a $50 million term loan facility with Silicon Valley Bank.

The initial capital was characterized as a crossover financing, but Socks left options open as to whether the next step would be an IPO or some other form of financing.

Whatever the next financing step, Socks said he envisions building "a major company in the GI space. There's a significant opportunity to treat GI disorders. We're building a team with expertise, who we think we can leverage to not only commercialize vonoprazan but also to, over time, bring in assets to leverage the infrastructure we're building."

That would be accomplished by in-licensing additional compounds. "We don't have any near-term plans to do drug discovery," Socks noted.

Phathom's home base is in a bit of flux until a permanent CEO is established, but Socks noted that the company is likely to have a presence in the Chicago area where its chief operating officer, Azmi Nabulsi, is based. Until last fall, Nabulsi also worked at Takeda for 14 years where he was the deputy chief medical officer, chief scientific officer and head of global development. ♦

Cannabis

Continued from page 1

are clinical trials and anecdotal evidence that it can address multiple symptoms."

Volcani takes a systematic approach to develop products from cannabis plants by extracting products from different cannabis lines, examining medical activity, undertaking trials and then working to develop products in combination with commercial companies. As part of that process, the lab separates compounds into fractions and analyzes their chemical qualities. Using that approach, Volcani has been able to identify and produce active pharmaceutical ingredients (APIs) from cannabis and has been working to identify targets for those APIs.

"We are talking about the actual molecules that are being synthesized by the plants," said Koltai. "And then, we build our API formulation."

Volcani is working with a couple of pharmaceutical companies. One is Medc Biopharma Ltd., a Canadian company developing cannabis-based pharmaceutical products to treat cutaneous T-cell lymphoma (CTCL), actinic keratosis and diseases of the nervous system. In December, Volcani prepared patents for its CTCL treatment.

The lab is also working with Israeli company Plantext Ltd. to develop drugs for inflammatory bowel disease (IBD), pain and psoriasis.

"We know now that cannabis is definitely helpful. However, we are talking about hundreds of different compounds," said Koltai.

As of today, the FDA has not approved any new drug application for a cannabis plant, but there are products that use CBD on the way and there is strong pipeline of cannabinoid receptor products.

"This could be one of the greatest emerging markets… that we have seen in our careers," said Dorman Followwill, a partner and director for Europe, Israel and Africa at Frost & Sullivan.

Regulation "is going to be a slow process and it should be a slow process," said Followwill. "If you are a pharma company and you look at this as a potential channel… you are going to want to look at potential economic channels."

For instance, the U.K.'s GW Pharmaceuticals plc has developed Epidiolex (cannabidiol, or CBD) oral solution, the first plant-derived cannabinoid approved by the FDA and launched in November in the U.S. for the treatment of Dravet syndrome, previously known as severe myoclonic epilepsy of infancy.

Other discovery activity is ongoing. Sunrise Genetics Inc. in Colorado, for instance, is using genomics to identify gene combinations that could lead to useful medicines.

For the most part, big pharma firms have been reluctant to dive into the space, but they are starting to research CBD-based drugs and those efforts could take the sector to the next level.

"Once the big pharma guys decide to get behind and spend their billions," said Followwill, "then you have not hope, but hope realized… and that is what I'm seeing in this space."

What took so long?

The possibilities inherent in cannabinoids is not a surprise for Raphael Mechoulam. He has been working in this field for half a century and is generally considered to be one of the pioneers in the space. He is revered in Israel as the godfather of cannabinoid research and has published more than 450 papers on the topic.

"When I started working on cannabinoids more than 50 years ago, I was surprised that nobody was interested," said Mechoulam speaking during the recent MIXiii Biomed conference.

As far back as the 1960s, Mechoulam managed to pull out a large number of compounds from cannabinoids. The potential of cannabinoids to treat myriad indications has been known for a long time but research has been scant.

"There is essentially no work [being done] on the more advanced stages of cannabinoid research," said Mechoulam.

The vast majority of the work is being done on tetrahydrocannabinol (THC) and CBD but more advanced endocannabinoid-like compounds have never been used on humans despite being widely known. Endocannabinoids are lipid-based retrograde neurotransmitters that bind to cannabinoid receptors. Further research may lead to finding ways to use the endocannabinoid system to deal with autism, for example.

"These are not the compounds that the plant produces," he said.

Something similar may happen in the use of cannabinoids to treat type 1 diabetes. But while there are indications that cannabinoids might have potential, no clinical trials have been done in diabetes. Similarly, there have been no trials related to the use of CBD in cancers, inflammations, brain injuries, cerebral ischemia or autoimmune disease.

Over the past few years, however, the research is slowly making its way into the mainstream. CBD has already been approved for epilepsy, a capability that Mechoulam and collaborators in Brazil identified decades ago.

"And yet, it took 30 years before public pressure led the U.S. to approve a clinical trial… today it is an excellent drug," he said. "Why did we have to wait for so long? We could have helped thousands of children." ♦

Other news to note

Mannkind Corp., of Westlake Village, Calif., signed an exclusive marketing and distribution agreement with the AMSL Diabetes division of **Australasian Medical & Scientific Ltd.**, of Chatswood, Australia, for the commercialization of Afrezza (insulin human) inhalation powder in Australia. The international partnership is Mannkind's third. Terms were not disclosed.

Clinical data for May 14 – 20, 2019

Company	Product	Description	Indication	Status	Date
Phase I					
Immutep Ltd., of Sydney	Eftilagimod alpha	Immune checkpoint molecule LAG3	Melanoma	More mature data relating to Part B of ongoing TACTI-mel study in combination with Keytruda (pembrolizumab) in 24 patients with unresectable or metastatic disease were consistent with previous data reported at 6 months; patients in Part B continued to report positive results in terms of tumor reductions after 9 months of treatment; 4 patients are continuing to receive treatment	5/17/19
Neuclone Pharmaceuticals Ltd., of Sydney	Neulara (Stelara, or ustekinumab, biosimilar)	Dual IL-12/ IL-23 receptor antagonist	Psoriasis	Randomized, double-blind, 3-arm, single-dose study will be initiated in second half of year, enrolling healthy volunteers at multiple sites in Australia to compare pharmacokinetics and safety of biosimilar candidate to Stelara	5/15/19
Noxopharm Ltd., of Sydney	Veyonda (NOX-66)	Formulation of idronoxil	Late-stage metastatic castration-resistant prostate cancer	Interim results from phase I/II Lupin trial in combination with 177Lu-PSMA-617 published in the Journal of Nuclear Medicine show PSA response rates for 400-mg and 800-mg doses were 62.5% and 75%, respectively, producing overall PSA response rate of 69% across 16 patients; results compare favorably to 177Lu-PSMA-617 alone, which ranges between 31% and 61% in 10 published trials	5/20/19
Phase II					
Cocrystal Pharma Inc., of Bothell, Wash.	CC-31244	Non-nucleoside inhibitor	Hepatitis C virus infection	Started 16-patient study in Hong Kong in combination with Sovaldi (sofosbuvir, Gilead Sciences Inc.) and Daklinza (daclatasvir, Bristol-Myers Squibb Co.) with or without a protease inhibitor	5/20/19
Opthea Ltd., of Melbourne, Australia	OPT-302	Dual VEGF-C/ VEGF-D ligand inhibitor	Wet age-related macular degeneration	Last participant completed final visit in double-blind phase IIb trial that randomized 366 participants to compare OPT-302, in combination with ranibizumab (Lucentis, Genentech Inc.), to ranibizumab alone	5/15/19
Phase III					
Takeda Pharmaceutical Co. Ltd., of Osaka, Japan	Vedolizumab (Entyvio)	Integrin alpha-4/beta-7 antagonist and MAdCAM inhibitor	Ulcerative colitis	Exploratory data from phase IIIb Varsity study showed greater proportion of intravenously treated patients achieved clinical response at week 14 vs. those treated with Humira (adalimumab, Abbvie Inc.) subcutaneously (67.1% vs. 45.9%, respectively); separation between treatment groups, favoring vedolizumab, was seen as early as week 6; absence of active histologic disease was achieved in 33.4% and 42.3% of patients treated with vedolizumab, measured across Geboes Score (<3.2) and Robarts Histopathology Index (<5), respectively, compared with 13.7% and 25.6% treated with adalimumab, respectively	5/20/19

Notes

The date indicated refers to the *BioWorld* Clinical data table in which the news item can be found.

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

Regulatory actions for May 14 – 20, 2019

Company	Product	Description	Indication	Status	Date
Daiichi Sankyo Co. Ltd., of Tokyo	Pexidartinib	Oral, small-molecule CSF1R inhibitor	Tenosynovial giant cell tumor	FDA's Oncologic Drugs Advisory Committee voted 12-3 in favor of the drug for treating adults with symptomatic disease	5/15/19
Daiichi Sankyo Co. Ltd., of Tokyo	Quizartinib	FLT3 inhibitor	Relapsed/ refractory FLT3-ITD acute myeloid leukemia	FDA's Oncology Drugs Advisory Committee voted 8-3 that the results from the pivotal Quantum-R study failed to demonstrate that benefit outweighs the risk for patients	5/15/19
Takeda Pharmaceuticals Co. Ltd., of Osaka, Japan	Gattex (teduglutide)	Mimics naturally occurring glucagon-like peptide-2	Short bowel syndrome	FDA approved extending indication to pediatric patients, ages 1 and older, who need additional nutrition or fluids from intravenous feeding	5/17/19

Notes

The date indicated refers to the *BioWorld* Regulatory actions table in which the news item can be found.

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

Huons

Continued from page 5

a PD-L1 inhibitor developed by Swiss health care company Roche Holding AG, as a treatment for patients with high-risk progressive skin cancer.

Although it has had no sales abroad yet, Genexine has made foreign acquisitions. This year, Genexine and Handok Co. Ltd., a Korean pharmaceutical company, became the joint largest shareholder of Rezolute Co. Ltd., a U.S. biopharmaceutical firm. The pair jointly invested $25 million in Rezolute for a 54% stake. Also, Genexine and SCM Life Science took over Argos Therapeutics Inc., a U.S. biotech firm specializing in cancer therapies, for $11.1 million.

In 2018, Genexine incurred KRW38 billion in operating losses – KRW11.2 billion larger than in 2017 – and the company issued paid-in capital gains amounting to KRW200 billion and convertible bonds worth KRW50 billion to help finance its R&D costs.

In trading on South Korea's exchange on Thursday, Huons shares (KOSDAQ:243070) fell 3% to KRW61,000, while Genexine stock (KOSDAQ:095700) fell 1.7% to KRW69,400. ♦

Other news to note

Sosei Group Corp., of Tokyo, reported that the research phase of its multitarget drug discovery collaboration with **Pfizer Inc.**, of New York, delivered several milestones, leading to the advancement of potential candidate programs against G protein-coupled receptor (GPCR) targets nominated by Pfizer in multiple diseases. Sosei said the targets have clinical and biological validation for therapeutic interventions targeting metabolic and inflammatory diseases, but conventional discovery approaches were limited by technical challenges. Its Sosei Heptares unit delivered to Pfizer stabilized receptors – dubbed Star proteins – X-ray structures and biophysical data on certain programs to trigger the milestone payments, including a recent $3 million fee. The companies, which forged the potential $1.89 billion deal in 2015, expect to publish select findings from the ongoing collaboration, initially directed toward up to 10 GPCR targets. (See *BioWorld Today*, Dec. 1, 2015.)

Hemophilia A can be due to thousands of different genetic mutations in the blood coagulation factor VIII gene, which makes it challenging to develop an editing platform, despite the fact that as a monogenic disorder, hemophilia A is in principle amenable to gene correction approaches. Now, researchers at **Yonsei University College of Medicine** have developed a universal approach to hemophilia A gene correction. The team used CRISPR/Cas9 for the targeted insertion of the FVIII gene into a specific site, the human H11 site, of patient-derived induced pluripotent stem cells (iPSCs). "We derived corrected clones from two types of patient iPSCs with frequencies of up to 64% and 66%, respectively, without detectable unwanted off-target mutations," the authors wrote. "Moreover, we demonstrated that endothelial cells differentiated from the corrected iPSCs successfully secreted functional protein. This strategy may provide a universal therapeutic method for correcting all genetic variants found in [hemophilia A] patients." They reported their findings in the May 17, 2019, online issue of *Stem Cell Reports*. ♦