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Gilead To File Filgotinib For RA in 2019, Earlier Than Forecast

KEVIN GROGAN kevin.grogan@informa.com

The US filing for rheumatoid arthritis (RA) of Gilead Sciences Inc. and Galapagos NV's closely watched filgotinib is now expected by the end of this year, allaying fears that the drug would be at a competitive disadvantage to AbbVie Inc.'s already-submitted rival JAK inhibitor upadacitinib.

Gilead has announced that it has held a pre-submission meeting with the US Food and Drug Administration to provide an update about filgotinib, an oral, selective JAK1 inhibitor, and discussed the positive Phase III FINCH program. Significantly, the talks with the FDA also focused on the ongoing Phase II MANTA safety study assessing semen parameters with filgotinib treatment in men with moderately to severely active ulcerative colitis or Crohn's disease, and whether the agency wanted to see the full MANTA data set before accepting a submission. *(Also see "Galapagos Flies As Filgotinib Soars In FINCH Studies" - Scrip, 31 Mar, 2019.)*

If that were to have been the case, the filgotinib filing would have been pushed back to 2021 when MANTA is due to be completed. However it seems that the FDA talks went well, as Gilead said in a statement that "as a result of this discussion, a path forward has been established to submit the new drug application (NDA) for filgotinib as a treatment for RA in 2019."

The FDA wanted the MANTA trial to be conducted after animal studies found a link between the high doses of filgotinib (over 200mg) and a lowering of sperm counts. Following the discussions, the 52-week data from the trial, expected later this year, will be sufficient for Gilead to file the NDA.

In an interview with *Scrip* at the European League Against Rheumatism congress in Madrid last month, where the full results from FINCH 1 and 3 were presented, chief medical officer Walid Abi-Saab spoke about the MANTA study. He noted that "in Europe and Japan, and Japan usually tends to be very conservative, they're OK with this. Of course they're interested to see the results of MANTA in humans but they're not putting a lot of emphasis on it. The FDA took a little bit more of a more conservative position."

Abi-Saab said, "At the end of the day, it's a risk/benefit discussion. Now that we have the full data set from FINCH, we can say, 'Guys, this is the efficacy of this compound, this is the safety of the compound and we're very pleased with our safety profile.'" He stressed that "we don't want to get into an acrimonious relationship with the FDA and we need to demonstrate to them that we genuinely want to do that study as fast as possible," although he admitted enrolment has been slow.

Abi-Saab added, "We are very keen to figure this out and put it behind us because if you ask me honestly, I think the likelihood that we're going to be demonstrating that filgotinib has any issues is extremely low." He went on to say that he understood the agency's stance as "they worry that once they give you approval, then the cat is out of the bag and then they don't have much more power to impose post-approval studies other than public shaming."

The response to the news from analysts was positive. Credit Suisse issued an

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from the editor

eleanor.malone@informa.com

The effectiveness of the UK government might be in freefall these days, but it hasn't always been that way. In one area in particular, it has been a world leader. The efforts of the outgoing chief medical officer Dame Sally Davies and others, including Lord (Jim) O'Neill, helped galvanize global efforts to tackle the crisis of antimicrobial resistance in recent years. It is therefore especially bleak to read O'Neill's assessment of the treatment of the issue at last month's G20 summit in Japan (see p21).

O'Neill was commissioned by former UK Prime Minister David Cameron to conduct a review on antimicrobial resistance in July 2014. The work was completed in May 2016, just a month before the country voted in favor of Brexit, prompting Cameron's departure and effectively launching a long-lasting political and social tidal wave that has seen so many other issues swept out of the public eye.

One of the major contributions to progress in the field was the O'Neill Review's itemization of specific measures that could be adopted to correct the unfavorable economics of antibacterial drug development and commercialization, which have strangled R&D in the field and left us to rely on old drugs to which infections are becoming increasingly resistant. The fact is that the G20 statement in 2019 failed to reflect advances over the past few years and made no hard commitment despite work already undertaken by the O'Neill Review and others in the field. What a shame if Brexit has reduced the UK's policy heft where it could really be of benefit.

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LEADERSHIP
Phil Jarvis, Mike Ward, Karen Coleman

SUBSCRIPTIONS
Dan Simmons, Shinbo Hidenaga

ADVERTISING
Christopher Keeling

DESIGN SUPERVISOR
Gayle Rembold Furbert

DESIGN
Paul Wilkinson

EDITORIAL OFFICE
Blue Fin Building
3rd Floor, 110 Southwark St
London, SE1 0TA

CUSTOMER SERVICES
US Toll-Free: +1 888 670 8900
US Toll: +1 908 547 2200
UK & Europe: +44 (20) 337 73737
Australia: +61 2 8705 6907
Japan: +81 3 6273 4260
Email: clientservices@pharma.informa.com

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christopher.keeling@informa.com

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UK Committee Attacks Pharma Over Lack Of Medicinal Cannabis Research

IAN SCHOFIELD ian.schofield@informa.com

A UK parliamentary committee has criticized the pharmaceutical industry for not putting medicinal cannabis products into clinical trials, saying that companies that fail to do so should be "named and shamed."

"It is concerning that that some pharmaceutical companies are still resistant to making their products available for research," says the House of Commons' health select committee. Without a robust evidence base allowing patients and clinicians to weigh up any risks and benefits of medicinal cannabis products, they "will remain unlicensed for the many areas where patients wish to know if they could be effective."

In a report published on 3 July, the committee urges the Department of Health and Social Care to investigate cases where companies are not providing their products, and to "set out a plan to incentivize industry to take a more active role in research itself."

It also says that even though medicinal cannabis products were reclassified as Schedule 2 controlled drugs last year, allowing them to be prescribed by specialist doctors under specific conditions, "very few prescriptions have been issued for such products," because most of them do not have a UK or EU marketing authorization, nor have they been OKd by the health technology assessment (HTA) body, NICE.

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To read the rest of this story go to: https://bit.ly/2JtVkPD

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investor note on 2 July that referred to comments by new Gilead CEO Daniel O'Day on the company's first quarter earnings call indicating that it would be able to file for approval without the full data from MANTA, so "we see this as a positive sign for O'Day's tenure in that he is able to execute against his word and is focused on pipeline execution."

The broker noted the market's fears that with the absence of clear timelines from MANTA trial, the launch of filgotinib could have been delayed to at least 2022, potentially placing the drug a long way behind AbbVie's JAK inhibitor upadacitinib. The FDA is expected to give its decision on the drug for RA in the third quarter after AbbVie used a priority review voucher to speed up evaluation.

"They worry that once they give you approval, then the cat is out of the bag..." – Walid Abi-Saab

Analysts at Morgan Stanley agreed that timing for a US launch had been a key investor focus given filgotinib is likely to get to market after upadacitinib and "we believe a 2019 filing plan is a bull case scenario and clearly indicates that the FDA is comfortable with interim safety data from the MANTA studies being included in a filing." However, in a 2 July note, the broker wrote that "one lingering concern" investors may have "is whether a more rapid path to filing may come at the expense of a more restrictive label [but] overall, we believe this news is a clear positive for Gilead and Galapagos, as a 2019 NDA filing sets up filgotinib for a US RA launch in 2021, one year ahead of consensus expectations."

Jefferies analysts described the announcement as "an incremental positive surprise" but claimed that "an outstanding question is whether Gilead has a priority review voucher handy and thus can keep the timing tight." If MANTA comes out clean, they said that "we would certainly argue everything would be very good and Gilead would be very competitive if not best-in-class compared to AbbVie."

If the data were negative and filgotinib did cause a reduction in sperm count, "this scenario wouldn't appear to block Gilead's ability to file. Rather, it would be an issue in the label, which isn't too commercially relevant in our opinion given that these indications comprise of mostly females," Jefferies concluded.

At SVB Leerink, analysts issued a note on 2 July saying that "we were wrong [as] we viewed the testicular toxicity signal story as a big and bounded uncertainty for filgotinib." Still, it remains to be seen how well it can compete with upadacitinib, which Leerink stated will have "the full might of AbbVie's pharma commercial machine behind it."

The analysts concluded by noting that after attending EULAR, they were "struck by one simple reality: the RA problem remains unsolved. Only less than 10% of patients achieve drug-free remissions despite being heavily bombarded by biologics. While the antibodies will not be disappearing anytime soon, it may be time to reconsider new modalities more broadly, increasing the opportunity for great oral drugs."

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GSK's Otilimab Goes Head-To-Head To Crack Rheumatoid Arthritis

JOHN DAVIS john.davis@informa.com

The Phase III clinical trial program for GlaxoSmithKline PLC's novel mechanism-of-action rheumatoid arthritis candidate, otilimab (GSK3196165), will include head-to-head comparisons with marketed RA therapies including Pfizer Inc.'s oral JAK inhibitor, Xeljanz (tofacitinib), and Sanofi/Regeneron Pharmaceuticals Inc.'s injectable anti-interleukin-6 Mab, Kevzara (sarilumab), the UK big pharma announced on 3 July.

The breadth of the program is one of the clearest signs yet of the effort GSK is continuing to put into developing the investigational rheumatoid arthritis therapy, which, as an anti-granulocyte macrophage colony stimulating factor (GM-CSF) monoclonal antibody, has a mechanism of action that would be novel for an antirheumatic.

GSK has previously signaled a strong interest in immune-inflammation, and its drive to extend its activities in the sector beyond the marketed lupus product, Benlysta (belimumab). However competition in this field is strong, with new products like Gilead Sciences Inc./Galapagos NV's JAK inhibitor filgotinib and AbbVie Inc.'s upadacitinib nearing the market.

All development and commercialization rights for otilimab (then MOR-103) were licensed from MorphoSys AG in 2013, in a deal that included a €22.5m upfront, up to €423m in milestones, and royalties on sales.

The Phase III program for otilimab was designed in collaboration with regulators, explained GSK chief scientific officer Hal Barron, and has now started in patients with moderate-to-severe rheumatoid arthritis who have had an inadequate response to disease modifying antirheumatic drugs (DMARDs) or targeted therapies. The program, called ContRAst, is the first in RA to include head-to-head comparisons with current treatments in all three pivotal studies. The primary endpoint will be the proportion of patients achieving the American College of Rheumatology criteria (ACR20) at week 12 with otilimab versus placebo. Otilimab is being given as 90mg or 150mg subcutaneous weekly injections.

The cytokine, GM-CSF, is believed to play a central role in immune-mediated diseases, acting on macrophages and other immune cells to cause inflammation, joint damage and pain. Otilimab is believed to block the interaction of GM-CSF with its cell surface receptor.

In a Phase II dose-ranging study, BAROQUE, reported at the October 2018 meeting of the American College of Rheumatology, otilimab added to methotrexate therapy in 222 patients with an inadequate clinical response to methotrexate, was associated with an encouraging rapid onset in reducing pain and tender joint counts. Although the primary endpoint of the study was missed, secondary endpoints produced statistically significant improvements, Biomedtracker analysts noted.

Preclinical data suggests otilimab may have a broader range of therapeutic activities than conventional biologics, including a specific effect on pain, and although the treatment of rheumatoid arthritis has benefited from the development of TNF inhibitors and other biologic therapies, there is still an unmet need for effective therapies. GSK noted that with multiple targeted therapies, only around 30% of patients treated with marketed therapies achieve remission, and daily pain is a key driver of switching between biological and oral therapies.

While the worldwide RA market for anti-TNFs has been slowly declining since 2016-17 because of the launch of biosimilars, GSK expects the market for RA drugs with alternative (non-TNF) mechanisms of action to increase from just under £7bn in 2019 to around £9bn in 2024. Few other companies are developing anti-GM-CSF antibodies for rheumatoid arthritis; UK biotech Izana Bioscience is preparing to conduct a Phase II trial in ankylosing spondylitis with its anti-GM-CSF Mab, IZN-101.

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Hanmi Faces Another Licensee U-Turn, This Time Janssen On Obesity/Diabetes Drug

JUNG WON SHIN jungwon.shin@informa.com

Janssen Pharmaceutical Cos. has returned the rights to obesity/diabetes therapy HM12525A (JNJ-5111), a long-acting GLP/GCG analog to originator Hanmi Pharmaceutical Co. Ltd., after Phase II studies achieved their weight reduction targets, the primary evaluation indicator, but not their glycemic control goals for obese diabetics.

The South Korean firm was upbeat however. "Through the results of Phase II trials Janssen has conducted, the compound has sufficiently proven its efficacy as an obesity drug," it declared. "This has proven the glycemic control needs for obese diabetics, so we will reflect this need and determine future development directions of the compound after an internal review."

The company will be able to retain the upfront payment of $105m that its US partner paid under the license deal.

HM12525A is a novel ultra-long-acting dual agonist comprising a chemically synthesized GLP-1/GCG peptide conjugated with a human IgG Fc fragment via a flexible PEG linker. The once-weekly product is site-specifically conjugated using Hanmi's proprietary LAPSCOVERY technology for sustained duration of activity.

Under the agreement signed in 2015, Janssen gained exclusive worldwide rights to the therapy excluding in South Korea and China. Hanmi was also eligible for a total of up to $810m in milestone payments plus double-digit sales royalties after commercialization.

Janssen told *Scrip* that it had decided to end the program because the results of the Phase II studies did not meet all of the desired endpoints. "Metabolism remains a critical part of the Cardiovascular & Metabolism therapeutic area at Janssen, and our strategy to advance new therapies for metabolic disease states, including obesity, has not changed," it stressed.

OBESITY/DIABETES A CHALLENGING SPACE

Even so, this is disappointing news for Janssen. While the cardiovascular/metabolic area is core, with blockbusters such as blood thinner Xarelto (rivaroxaban) and Invokana (canagliflozin) for diabetes, it has only a limited pipeline in diabetes/obesity.

> Despite the rising prevalence of obese individuals globally, the area has been challenging for pharmaceutical therapies, as patients generally want more weight loss than medications are able to provide.

Despite the rising prevalence of obese individuals globally, the area has been challenging for pharmaceutical therapies, as patients generally want more weight loss than medications are able to provide and safety is so critical, Peter Chang, principal scientific analyst at Biomedtracker, told *Scrip*.

Obese diabetics are an important segment, along with drugs that treat both the diabetes and cause weight loss, as they are more apt to be treated medically. Novo Nordisk AS has started to be more successful with Saxenda (liraglutide, a higher dose version of Victoza) for obesity, though it is still used in only a limited number of patients, of which an estimated 20-30% are diabetics, the analyst explained.

Another challenge for competitors is that other new drugs such as Novo's GLP-1 agonist Ozempic (semaglutide) and its oral formulation, as well as Eli Lilly & Co.'s GLP-1/GIP co-agonist tirzepatide, are raising the bar on weight loss and glycemic control. Novo is hoping that combination use of Ozempic and the amylin analogue AM833 could lead to weight loss of 20%-plus, Chang said.

"So if HM12525a fell short on glycemic control, it is not too surprising that Janssen dropped it. That issue has been a major limitation of combined GLP-1/glucagon agonists, because glucagon agonism increases blood glucose. Companies have been trying to find combinations where the added weight loss leads to enough improvement in glycemic control that it overcomes the negative effects of glucagon agonism, and apparently that was not seen here," he said.

Janssen does have earlier stage candidates in Phase I and preclinical studies, which could be interesting, but there is still significant uncertainty about their prospects. In a recent R&D call for the CV/metabolic space, they instead highlighted retinal disease and a collaboration on Factor XIa inhibition, where the candidates are more advanced, Chang commented.

HANMI HIT AS FOURTH COMPOUND RETURNED

Meanwhile for Hanmi, this is the fourth time to face a return of licensed-out compounds following a series of massive licensing deals with global pharmas over the past few years.

In January this year, Eli Lilly & Co. returned rights to the novel Bruton's tyrosine kinase inhibitor LY3337641 (HM71224) it had licensed in from Hanmi in 2015, after the US giant decided to halt its Phase II program in 2018 due to what it saw as weak data. *(Also see "Hanmi To Step Up Global Drug Development As Lilly Returns BTK Rights" - Scrip, 23 Jan, 2019.)*

In 2018, Hanmi decided to stop all further development of its third generation EGFR inhibitor Olita (olmutinib) following Zai Lab Ltd.'s return of rights in the China region to the drug and Boehringer Ingelheim GmbH's cancellation of an earlier licensing deal.

In Seoul, shares in Hanmi fell more than 20% in early trading on 4 July on disappointment over the news, which the firm disclosed to the stock market late on 3 July. Hanmi reassured investors that the return of the rights frequently occurs in the process of new drug development. "Although it is a difficult road ahead to develop global new drugs, its challenges will not stop us," it said.

The South Korean firm said it is progressing nearly 30 new drugs in its pipeline and still has collaborations with various other big pharma partners such as

Sanofi, Spectrum Pharmaceuticals Inc. and Genentech Inc.

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Boehringer Adds Yuhan's First-In-Class Dual Agonist To NASH Portfolio

JUNG WON SHIN jungwon.shin@informa.com

South Korea's Yuhan Corp. and Boehringer Ingelheim GmbH have inked a collaboration and license agreement for the global development of a first-in-class GLP-1/FGF21 dual agonist for the treatment of non-alcoholic steatohepatitis (NASH) and related liver diseases, in a deal worth as much as $870m, including $40m in upfront and near-term payments, plus royalties.

The worldwide deal, excluding South Korea, marks the second NASH license-out deal for Yuhan following that with Gilead Sciences Inc. in January, validating its competitiveness in the therapy space and reflecting the strong global interest in the yet unconquered area. *(Also see "Asia Deal Watch: Boost For Esperion's Cholesterol Candidate As Daiichi Brought On Board" - Scrip, 8 Jan, 2019.)*

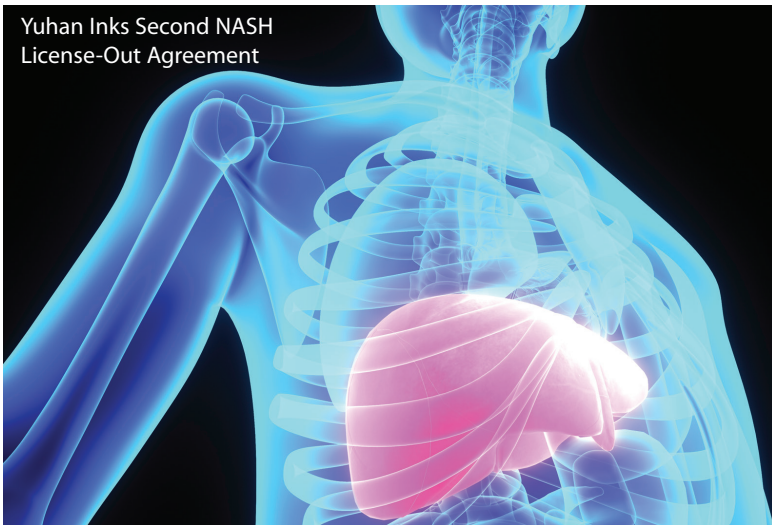
The leading South Korean pharma's main therapeutic focus is on cancer as well as metabolic diseases such as NASH and diabetes, and its efforts to transform into an R&D innovator now appear to be recognized globally after a series of deals since last year with global firms including Janssen Biotech Inc.

LANDMARK DEAL

The new collaboration brings together Yuhan's expertise in FGF21 biology, obesity and NASH with Boehringer's global experience and commitment to bringing innovative medicines to patients with cardiometabolic diseases, said Yuhan.

The deal also marks Yuhan's first external partnership for a biologic and is the first licensing out of a biologic targeting NASH by a Korean firm, noted Jung Hee Lee, CEO and president of Yuhan.

In a research note on the alliance, Mirae Asset Daewoo pointed to the large deal value and upfront payment, even though it is for a still preclinical-stage molecule that hasn't completed toxicity tests. Boehringer is considered as a good partner with biologics



manufacturing capability, and in the cardiometabolic disease sector already sells the DPP-4 inhibitor Trajenta (linagliptin) and SGLT-2 inhibitor Jardiance (empagliflozin). It is also progressing clinical trials of a GLP-1R/GCGR dual agonist, and so is a suitable partner for Yuhan, the brokerage said.

Hana Financial Investment said that the deal also derived from Yuhan's collaboration with a domestic biotech partner, and pointed to Yuhan's pipeline immuno-oncology drug YH24931, which it brought in from its joint venture with Sorrento Therapeutics Inc., as another asset worth keeping an eye on.

The compound licensed to Boehringer is a fusion protein utilizing the long-acting hybrid (HyFc) technology of Korean venture Genexine, and was developed in-house by Yuhan. Preclinical evidence suggested high efficacy when combining the gut-derived

hormone GLP-1 with FGF21. As Yuhan applied Genexine's technology, it has to pay 5% of the license deal value, excluding sales royalties, to Genexine.

The dual GLP1R/FGF21R agonist approach is expected to reduce liver cell damage and hepatic inflammation by resolution of steatohepatitis, as well as having direct antifibrotic effects. The addition will complement Boehringer's existing R&D portfolio in NASH, adding another potential first-in-class opportunity.

DEAL BUOYS BI'S PRESENCE IN CARDIOMETABOLIC DISEASE

For the private German group, the addition of Yuhan's preclinical molecule will further beef up its R&D expertise in cardiometabolic diseases, including NASH. The deal is also in line with its deal-making strategy to focus on early-stage collaborations to bolster its therapeutic focus in selected areas including cardiometabolic diseases.

In late May, BI inked a second obesity deal with Danish biotech Gubra ApS to develop poly-agonist peptides for obesity and concomitant diseases. *(Also see "BI Inks Second Obesity Pact With Denmark's Gubra" - Scrip, 31 May, 2019.)*

Boehringer believes that in many cases approaches targeting one of the features of NASH will not be able to achieve the desired outcomes in patients with advanced stages of the disease. Thus the company has built a comprehensive program to develop next-generation therapy approaches targeting all three key drivers of the condition - steatosis, inflammation and fibrosis.

Boehringer has a long history of R&D for cardiometabolic disease and has established a broad portfolio of marketed products for thromboembolic disorders, type 2 diabetes, acute myocardial infarction, hypertension and cardio-renal risk reduction. The pipeline also extends beyond type 2 diabetes and anticoagulation with a focus on innovative drugs for the treatment of the consequences of diabetes and contributing factors like obesity.

Yuhan has already been a commercial partner for Boehringer's diabetes products in South Korea for many years, providing an existing link for the new alliance.

NASH NEEDS

NASH is generally caused by the accumulation of fat in the liver, giving rise to inflammation and finally leading in many patients to liver fibrosis and cirrhosis. It has an especially high prevalence among obese and diabetic patients and remains an area of high-unmet medical need with no currently approved treatments.

According to Informa's Datamonitor Healthcare, NASH is considered to be an ongoing burden to society with the number of prevalent cases projected to increase by over 13% from 2016 to 2035. The possible progression of patients to cirrhosis and hepatocellular carcinoma in particular will result in an increased burden on overall healthcare systems.

Several diabetes and other drugs such as pioglitazone, rosiglitazone, losartan and metformin are used off-label to treat non-alcoholic fatty liver and NASH patients, as various new dedicated therapies progress globally through development.

Genfit SA, for one, is ready to begin combination therapy studies of its Phase III candidate elafibranor with two classes of already marketed diabetes drugs. *(Also see "Genfit Assesses Optimal Elafibranor NASH Combo Therapy Opportunity" - Scrip, 24 Jun, 2019.)*

After multiple Phase IIb trial failures, Conatus Pharmaceuticals Inc. said in June it will wrap up its obligations related to its pan-caspase inhibitor emricasan with partner Novartis AG and consider its strategic alternatives going forward. *(Also see "Conatus Accepts Defeat For Emricasan In NASH" - Scrip, 25 Jun, 2019.)*

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Karyopharm's Xpovio In Multiple Myeloma Priced At $22,000 Per Four-Week Cycle

JOSEPH HAAS joseph.haas@informa.com

Karyopharm Therapeutics Inc. obtained approval for Xpovio (selinexor) to treat penta-refractory multiple myeloma patients on 3 July, with a full approval hinged on the ongoing Phase III BOSTON trial, despite safety concerns and other issues overhanging the drug.

Pessimism reigned regarding the chances for the first-in-class nuclear export inhibitor to gain accelerated approval following a US FDA advisory committee review in February, but investors turned optimistic as the agency's decision was announced.

In fact, Karyopharm's stock surged 36% to $11.09 per share even before trading of the company's stock was halted just after 11 a.m. Eastern – a few hours before Xpovio's approval was announced. The stock resumed trading and was up another 6% in the after-hours market.

Karyopharm's 3 July news also included an announcement that chief commercial officer Anand Varadan will depart the company effective 5 July. Vice president of sales Perry Monaco was promoted to a senior VP position to oversee Xpovio's launch.

Executives said during a same-day investor call that the drug should be available to patients by 10 July, noting that a considerable amount of Xpovio already has been manufactured. Karyopharm set the drug's wholesale acquisition cost at $22,000 per four-week dosing cycle, which will be the same for all four approved dosing regimens.

"We wanted to make sure that cost was not going to be a factor in determining the optimal dose for a patient," CEO Michael Kauffman told *Scrip*. "It would be absolutely the wrong thing to do medically. The price itself was basically placed at the higher end of what's currently done in myeloma now with Pomalyst (pomalidomide) and with Darzalex (daratumumab), particularly in the late stage, and it's a bit lower than some of the other drugs in hematologic malignancies for these patients who unfortunately have ex-

hausted all available options. But what we didn't want to do was provide an incentive to get the wrong dose."

Celgene Corp.'s Revlimid (lenalidomide) is the top-selling multiple myeloma drug globally, but it is expected to face generic competition in 2022. That means the Xpovio launch will occur in an indication with significant branded drug competition and expectations of increased genericization, adding to the potential challenges posed by the departure of Karyopharm's CCO.

The company did not comment on why Varadan is leaving the company, but Kaufmann wished the outgoing executive well during the investor call and noted that Varadan "played an integral role in our commercial preparedness."

OUTLOOK WAS BLEAK AFTER ADVISORY COMMITTEE

Commercialization of Xpovio appeared uncertain after a 26 February meeting of the FDA's Oncologic Drugs Advisory Committee (ODAC), during which the panel voted 8-5 that approval of selinexor should wait until the Phase III BOSTON data were available. At that point, chances for accelerated approval did not look good, Kauffman admitted. But near-immediate dialogue between the company and the agency addressed issues of concern, he noted, enabling the accelerated approval to go forward. *(Also see "Keeping Track: Poteligeo, Onpattro, Galafold And Annovera Approved; Selinexor Submitted" - Pink Sheet, 12 Aug, 2018.)*

FDA officials told Karyopharm that despite the vote recommending against accelerated approval, they also took note of other commentary in favor of the approval, including those by the one multiple myeloma expert on ODAC. "They also listened very carefully to the patients and the doctors who spoke during the public session," Kauffman said. "There was a definite sense at FDA that the ODAC vote, which was reasonably close, maybe didn't quite reflect the reality" of the drug's risk-benefit profile in a patient population with very limited options.

The discussions also identified additional data that the agency wanted to see, which Karyopharm provided, the exec said, and clarified that the company, which had no commercial products, was not able to offer patients an expanded access program while approval was pending. The FDA had indicated that Karyopharm was capable of doing such a program, which may have swayed the votes of some ODAC panel members, Kauffman said.

Going into the advisory committee, briefing documents mentioned concerns about drug toxicity and also questioned how clear the benefit of selinexor was in a combination regimen with dexamethasone. *(Also see "Karyopharm's Selinexor: US FDA Unconvinced By Efficacy In Single-Arm Trial" - Pink Sheet, 22 Feb, 2019.)* The new drug application (NDA) was backed by the Phase IIb STORM study, which showed a 25.3% overall response rate in a subgroup of 83 patients. However, those responses included one stringent complete response, no other complete responses, four very good partial responses and 16 partial responses.

WARNINGS AND PRECAUTIONS, BUT NO BLACK BOX

The accelerated approval – for combination therapy with dexamethasone in multiple myeloma patients who have received at least four prior therapies and whose disease is refractory to at least two proteasome inhibitors, two immunomodulators and anti-CD38 antibody therapy – includes a label with no black box warning.

However, there is language regarding monitoring instructions, recommended concomitant therapy, and warnings and precautions about thrombocytopenia, neutropenia, gastrointestinal toxicity, hyponatremia, infections, neurological toxicity and embryo-fetal toxicity. Prescriptions will be accompanied by a medication guide, Karyopharm noted.

Addressing the safety and tolerability language in the label, Kauffman pointed out that penta-refractory myeloma patients are very sick, with an average life expectancy of three-to-five months, [so adverse events when introducing a new medicine isn't unexpected]. [He noted that while] Xpovio has side effects, including numerically more incidents of nausea and anorexia than seen with other myeloma therapies like Pomalyst and Kyprolis (carfilzomib), [they aren't of a magnitude of concern to doctors Karyopharm has spoken with].

"What we didn't have was major organ toxicities or major adverse reactions," Kauffman said. "We did have a number of serious adverse events, but the percentage was similar to Pomalyst and Kyprolis and the nature of those serious adverse events were really what happens to people who have three-to-five months to live. I think FDA's safety group understood early on that there was nothing that was going to be of sufficient magnitude or concern to a physician that they would need a black box."

A 70-PERSON TEAM TO CALL ON MYELOMA DOCTORS

On Karyopharm's call, Monaco outlined a launch strategy in which 70 sales reps and nurse liaisons will call on 1,300 key physicians, including about 400 who treat more than 50% of the projected patient base. Karyopharm said an estimated 69,000 myeloma patients currently are on drug therapy and about 6,000 of those individuals fall into the penta-refractory group. Xpovio represents the first approval against a new myeloma target since 2015, the company pointed out, since Bristol-Myers Squibb Co.'s anti-SLAMF7 therapy Empliciti (elotuzumab). *(Also see "BMS/AbbVie Empliciti Leaps Ahead, Wins Fast FDA Nod" - Scrip, 30 Nov, 2015.)*

While it awaits data from the BOSTON trial, an event-driven study that could read out later this year or early in 2020, Kauffman said the study offers the potential to quickly advance Xpovio to second-line myeloma therapy. The drug is a good candidate for earlier lines of therapy, he asserted, because it offers a new mechanism of action, is oral and combines well with other agents. Karyopharm also has studies underway investigating first-line myeloma therapy with Xpovio, he said.

Datamonitor Healthcare analyst David Dahan suggested that early uptake of Xpovio will be limited.

"Since doublet regimens are typically reserved for heavily pretreated patients who are not fit enough for more rigorous triplet therapies, it is likely that selinexor's initial target patient population will be limited," Dahan told *Scrip*. "However, Xpovio is also being evaluated in the Phase III BOSTON trial as part of a triple combination with Velcade (bortezomib; Takeda Pharmaceutical Co. Ltd./Johnson & Johnson) and dexamethasone in the second- to fourth-line settings, which will help the drug increase its commercial potential."

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Amarin Will Double Vascepa Sales Team In Big Bet On Supplemental Approval

JOSEPH HAAS joseph.haas@informa.com

Amarin Corp. PLC previewed its second quarter sales performance on 2 July, pointing to a sizeable increase for Vascepa ahead of an anticipated US approval that would increase the purified fish oil pill's market exponentially, and revealed plans to double its sales force for the product.

Ireland-headquartered Amarin said sales of Vascepa (icosapent ethyl), approved by the US Food and Drug Administration in 2012 to reduce very high triglyceride levels, totaled $97m-$101m during the second quarter and $170m-$174m in the first half of 2019. The company anticipates major growth in the product's indicated population following FDA approval expected this fall; the label expansion would be based on cardiovascular outcomes data in patients with high triglycerides, including less severe triglyceride levels than outlined in Vascepa's current label.

The company's record revenue during the first two quarters of this year was attributed to increased demand for Vascepa, approved in the US to reduce triglyceride levels in patients whose levels are 500mg/dL or greater. Still subject to auditor review, estimated sales of the proprietary formulation of the omega-3 eicosapentaenoic acid (EPA) rose 84-92% year-over-year during the second quarter and by 76-80% during the first six months of 2019.

Vascepa has a 28 September action date at the US FDA for a supplemental new drug application (sNDA) that if approved would make it the first drug with an indication to reduce residual cardiovascular risk in patients who are managed for LDL cholesterol on statin therapy, but need treatment for persistently elevated triglycerides. *(Also see "Keeping Track: A Busy Week For Regenerative Medicine, A Surprise Priority Review For Vascepa, And Tazemetostat Aims For Accelerated Approval" - Pink Sheet, 1 Jun, 2019.)*

Jefferies analyst Michael Yee wrote optimistically in a 2 July note about Vascepa's chances for the expanded label based on the REDUCE-IT cardiovascular outcomes

The company's record revenue during the first two quarters was attributed to increased demand for Vascepa.

study results unveiled in September, which showed an ability to reduce cardiovascular risk by 25% on top of statins. *(Also see "'That's Huge, Folks': Amarin's Vascepa Cuts CV Risk By 25% On Top Of Statins" - Scrip, 24 Sep, 2018.)* The projected second quarter sales of Vascepa indicate "robust demand" with dollar figures "well above even bullish expectations, so this is a strong result," the analyst added.

SALES GUIDANCE INCREASED TO $380M-$420M

Amarin increased its full-year sales guidance to a range of $380m-$420m from a previous $350m projection, which Yee called conservative based on current trends for the product. "We see [the] lower end of new guidance as conservative as math shows even minor increases in the second half would get to $380m and sales should pick up big, especially in the fourth quarter with label expansion," he said. "The $420m high end suggests healthy quarter-over-quarter increases from the second quarter."

In REDUCE-IT, an 8,179-patient study in statin-treated patients with elevated cardiovascular risk, Vascepa as an adjunct to dietary changes yielded a 25% reduction in relative risk of cardiovascular outcomes, including a 20% decrease in risk of cardiovascular disease-related mortality. *(Also see "Amarin's REDUCE-IT Data For Vascepa May Be Game-Changing, But Not Without Controversy" - Scrip, 12 Nov, 2018.)* In a key secondary endpoint assessing first cardiovascular death plus non-fatal heart attacks and/or strokes, the trial also demonstrated a 26% relative risk reduction.

These reductions were greater than what was seen in CVOT trials for PCSK9 inhibitors such as Amgen Inc.'s Repatha (evelocumab) and Sanofi/Regeneron Pharmaceuticals Inc.'s Praluent (alirocumab), although Amarin points out that Vascepa does not compete directly with the PCSK9 class of drugs.

In an email exchange, Amarin CEO John Thero declined to say whether the company is seeking a labeling update that would include the key secondary endpoint from REDUCE-IT. "It is premature to discuss label details," the exec said. "We are pursuing FDA approval of an expanded indication

for Vascepa for cardiovascular risk reduction in patients with elevated triglyceride levels, despite statin therapy."

While the outcome of FDA's review of the sNDA filing is uncertain, Amarin is moving forward with a confident outlook. Although previously it planned to build up incrementally to a headcount between 600 and 800 sales representatives, it now is working to double the team to 800 by October. The decision is based partly on positive feedback from doctors about the REDUCE-IT data, Amarin noted, along with a need to reach doctors not yet informed about the drug as well as data suggesting the potential benefits of calling on targeted physicians more frequently.

The company also benefited from American Diabetes Association treatment guidelines issued in March that recommend Vascepa therapy for diabetes patients with high triglycerides. *(Also see "Amarin's Vascepa Gets ADA Recommendation For Patients With Diabetes And High Triglycerides" - Scrip, 28 Mar, 2019.)*

PHYSICIAN EDUCATION, DTC CAMPAIGN PLANNED FOR EXPANDED LABEL

Key parts of Amarin's planned commercial ramp-up are physician education efforts as well as a direct-to-consumer (DTC) advertising campaign the company plans to submit to the FDA's Office of Prescription Drug Promotion by October. The company hopes to be able to roll out DTC advertising by the second quarter of 2020.

Thero told *Scrip* that most physicians "have limited or no awareness of Vascepa."

"Our focus in educating physicians and other health care professionals regarding Vascepa after label expansion will begin with reminding them that cardiovascular disease is an enormous and growing health care burden; that existing standard-of-care therapy is important but insufficient (e.g. cholesterol lowering lowers cardiovascular risk by 25%-35% but this leaves 65%-75% remaining risk); that other products seeking to address this residual cardiovascular risk have failed; and that Vascepa provides a new cost-effective treatment options for such patients," he said.

Amarin's board of directors is fully supportive of the plan for a quick ramp-up of the commercial team, he noted, and the expense of adding that much staff should benefit investors quickly if the label expansion is approved and sales grow as anticipated based on the expanded label, Thero said. Getting the sNDA approved would add "millions of patients in the United States, alone" as potential customers for Vascepa, he noted.

Investors responded positively to Amarin's announcements on 2 July, as the company's stock closed up 16% at $22.37 per share.

Amarin also stated that it remains on track to file Vascepa for approval in the EU by the end of 2019. The company is not partnered on development or commercialization of the product in Europe at present, and Thero indicated that potential partnering in Europe is not a priority right now.

"While Amarin has been approached by various companies which seek to promote Vascepa in the EU, the timing and specifics of Vascepa commercialization in the EU is under review and, although important, a lower priority at this time than ensuring [expanded] approval and successful launch of Vascepa in the US and preparing for the EU submission," he said.

Amarin has lined up partners for Vascepa in Canada, China and the Middle East; in addition to the US, the drug also is approved in Lebanon and the United Arab Emirates. Eddingpharm International Holdings Ltd. paid $15m up front, with the potential for $154m in milestones as well as sales royalties in 2015 for rights to market the product in China, Hong Kong, Macau and Taiwan. HLS Therapeutics Inc. obtained Canadian rights to Vascepa in 2017.

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EU Ultomiris Approval Rounds Off A Good Week For Alexion's Complement Franchise

ALEX SHIMMINGS alex.shimmings@informa.com

The European Commission has approved Alexion Pharmaceuticals Inc.'s Soliris successor, Ultomiris, for its first indication, paroxysmal nocturnal hemoglobinuria, just days after the US Food and Drug Administration approved Soliris for its fourth indication, neuromyelitis optica spectrum disorder (NMOSD).

In April, the EMA's Committee for Medicinal Products for Human Use recommended approval of Ultomiris (ravulizumab) for the treatment of adult patients with PNH with hemolysis and clinical symptoms indicative of high disease activity, and also for adult patients who are clinically stable after having been treated with Soliris for at least the previous six months. *(Also see "ViiV's Potential HIV Blockbuster Among Latest Drugs To Win EMA Nod " - Pink Sheet, 29 Apr, 2019.)* Ultomiris has EU orphan drug designation. It was also approved in Japan last month.

Ultomiris is a longer-acting C5 complement inhibitor than Soliris (eculizumab), being dosed every eight weeks rather than every two weeks (following a weekly induction period for four weeks), and the company is hoping it will become the new standard of care for patients with paroxysmal nocturnal hemoglobinuria (PNH).

Alexion has previously said that the first EU launch of Ultomiris was expected in Germany around mid-year. The new product was first approved in the US in December 2018, and its first quarter sales performance was promising, showing a good conversion rate. Combined Q1 revenues from Soliris/Ultomiris were up by 23% year-on-year to $987m, with Soliris contributing $962m (versus $977m in 4Q18) and Ultomiris $25m.

The C5 franchise accounts for around 87% of Alexion's revenues and the company is relying on its combined growth ahead of

first competition from generic versions of Soliris expected from 2021. Alexion said during its Q1 earnings call that Ultomiris was well on its way to achieve the company's guidance of >70% switching of US PNH patients by the end of 2020.

Alexion has already filed Ultomiris in the US for use in Soliris's second indication, atypical hemolytic uremic syndrome (aHUS), and will further submit it for the expanded indication in the EU and Japan later this year. Positive Phase III data in this setting were released in January. *(Also see "Alexion Looks To Broaden Complement Inhibitor Market With Next-Generation Ultomiris" - Scrip, 29 Jan, 2019.)*

Soliris meanwhile has been shoring up its sales with its new indications, particularly generalized myasthenia gravis (gMG), a label it got in the US in late 2017.

Jefferies analysts reckoned that Q1 Soliris sales for the gMG indication were roughly $150m. "Assuming steady new gMG patient adds (~200/quarter), we estimate Soliris sales in gMG could reach ~$700m in FY19 (~17% of Soliris/Ultomiris sales)," they said in a Q1 earnings notes in late April.

NMOSD MAKES FOUR

Now, Soliris can exploit its fourth indication, NMOSD, in the US. The FDA has approved Soliris for use in adult NMOSD patients who are anti-aquaporin-4 (AQP4) antibody positive, ie, about 73% of NMOSD patients following an expedited six-month priority review. *(Also see "Keeping Track: US FDA Closes Out First Half Of 2019 With CRL For Edsivo, But A Burst Of Supplemental Approvals" - Pink Sheet, 29 Jun, 2019.)*

NMOSD is a rare, severe autoimmune disease that can cause progressive and irreversible damage to the brain, optic nerve and spinal cord, which may lead to long-term disability. Complement activation due to anti-AQP4 antibodies is one of the primary underlying causes of the destruction in these patients, Alexion says.

The expanded approval was based on the results of the Phase III PREVENT trial recently published in the *New England Journal of Medicine*. In the 143-patient study, "treatment with Soliris reduced the number of NMOSD relapses by 94% over the 48-week course of the trial" compared with placebo, the FDA summarized. "Soliris also reduced the need for hospitalizations and the need for treatment of acute attacks with corticosteroids and plasma exchange."

The product is currently under review for the same indication in the EU and Japan; it has orphan drug status for NMOSD in all three markets.

Analysts at SVBLeerink commented that the latest indication given by the US agency was broader than they had expected. In the pivotal trial, Soliris was given to patients who had prior immunosuppressive therapies and had multiple relapses over the previous one to two years, but the approved indication has no restrictions by prior treatment, they noted in a 27 June research note.

"Despite the label, we don't think Soliris will capture significant use in front line treatment given Rituxan's favorable cost-benefit profile (~70% disease control under Rituxan and ~$60K first year cost compared ~$700K first year cost for Soliris)," they said. "We expect most insurance payers to require evidence of Rituxan failure before reimbursing for Soliris in this disease but do expect relatively open access to Soliris for relapsed patients in late line treatment."

Analysts at Wedbush said in a 28 June research note that their estimates assumed around 4,000 NMOSD addressable patients in the US, based on the anti-AQP4 status. They forecast FY19-FY22 NMOSD revenue of $9m, $41m, $75m and $179m, respectively. "With additional approvals anticipated in other geographies (e.g. EU, Japan), our furthest out year estimate (FY26), projects NMOSD revenue will reach $1.3bn."

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Sanofi's Libtayo Lands In EU With Skin Cancer Nod

JO SHORTHOUSE joanne.shorthouse@informa.com

Regeneron Pharmaceuticals Inc. and Sanofi's PD-1 inhibitor Libtayo (cemiplimab) has been given the nod by the European Commission, making it the first treatment available in Europe for adults with advanced cutaneous squamous cell carcinoma (CSCC) who cannot have surgery or radiation treatment.

Already approved in the US since September 2018, the EU approval was based on data from the pivotal EMPOWER-CSCC-1 trial, which along with two advanced CSCC expansion cohorts from a Phase I trial, provide the largest prospective clinical data set to date to evaluate a systemic therapy in patients with advanced CSCC.

Libtayo's runway has been cleared for landing

The conditional approval recognizes the extreme unmet need in advanced CSCC. As part of the conditional approval, Sanofi and Regeneron will add a new patient group to EMPOWER-CSCC-1 to further support the benefit-risk profile of Libtayo, and report the results to the EMA. The EMA will review any new information at least every year and update product labelling as necessary.

Libtayo's current recommended dose is 350mg IV infusion every three weeks.

Treatment may be continued until disease progression or unacceptable toxicity.

Although CSCC is the second most common form of skin cancer, accounting for about 20% of all skin cancer cases, the therapy approvals in the US and EU are for patients who are not candidates for curative surgery or radiation. Approximately 95% of CSCC patients are effectively managed with surgery, greatly reducing the number of treatable patients.

"With no competition in this indication, Libtayo has shown a strong initial launch in the US, with $27m in sales in Q1 2019," said Michael Ramirez, analyst at Datamonior Healthcare. "[Leerink analyst Geoffrey] Porges has estimated global sales of $1.4bn in 2021, with $600m of that total coming from US sales," he said. In addition to the US and EU, Libtayo is also currently approved in Canada and Brazil.

Advanced CSCC includes both patients with locally advanced disease, where the cancer cannot be cured by surgery and/or radiation, and patients with metastatic disease. Patients with advanced CSCC have a life expectancy of approximately one year.

UK PRICING

The UK's The National Institute for Health and Care Excellence (NICE) has recommended cemiplimab to be available within the Cancer Drugs Fund.

In the UK, it is estimated that around 560 people per year with locally advanced or metastatic cutaneous squamous cell carcinoma in adults, where curative surgery or curative radiotherapy is not appropriate, are eligible for treatment with cemiplimab.

The list price of cemiplimab is £4,650 per 350mg vial (1 treatment cycle). The list price for one year of treatment with cemiplimab is £80,877.

"Although there is significant uncertainty around the evidence for cemiplimab, the committee noted that the overall response rates reported in the trials are very promising," NICE said in a statement.

John Stewart, NHS England's director of specialized commissioning, said: "NHS England has worked closely with Sanofi and NICE to reach a deal to make this hugely promising innovative drug available, meaning NHS patients in England will be among the first in Europe to benefit."

OTHER INDICATIONS

Libtayo is also in Phase III trials for cervical and non-small cell lung cancer, in Phase II trials for basal cell carcinoma, brain and prostate cancer, and Phase I trials for hematologic cancer, melanoma, renal cell cancer and solid tumors.

"While approvals for use in NSCLC and cervical cancer certainly have the potential to drive growth for the drug, Libtayo will be met with significant competition in these areas," said Ramirez. Merck & Co. Inc.'s Keytruda (pembrolizumab) has been approved for second-line use in cervical cancer for over a year and enjoys substantial physician familiarity in multiple indications.

Four PD-1/PD-L1 inhibitors are currently approved for NSCLC. However, Ramirez told *Scrip* that if positive results were obtained for the three ongoing Phase III trials, particularly the trial comparing Libtayo combinations to Keytruda monotherapy in first-line NSCLC patients with PD-L1 expression ≥ 50%, the drug could compete despite its late market entry. This trial is among the first head-to-head trials between PD-1/PD-L1 inhibitors. "Jorge Insuasty of Sanofi has previously disclosed that he believes Libtayo has the opportunity to be positioned third among the PD-1/PD-L1 inhibitors in NSCLC, behind Keytruda and Opdivo," Ramirez concluded.

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CHMP Delivers More Good News For Sanofi's Dupixent

KEVIN GROGAN kevin.grogan@informa.com

The opinions issued at the latest monthly meeting (24-27 June) of the European Medicines Agency's drug evaluation committee revealed more good news for Sanofi's Dupixent, its Regeneron Pharmaceuticals Inc.-partnered therapy which is expected to comfortably pass the €1bn sales barrier this year.

The Committee for Medicinal Products for Human Use (CHMP) has adopted a positive opinion for Dupixent (dupilumab) recommending extending its approval to also include adolescents aged 12 to 17 years of age with moderate-to-severe atopic dermatitis (AD) who are candidates for systemic therapy. If approved, and the European Commission's formal thumbs-up should come in the next few months, it would be the first biologic approved to treat these patients.

The expanded approval is based on data from the LIBERTY AD program, including a pivotal Phase III trial which showed that Dupixent significantly improved skin lesions, reduced itching, and helped clear the skin of adolescent patients. Specifically, at 16 weeks, the average improvement in the Eczema Area and Severity Index (EASI) from baseline was 66% compared to 24% for placebo and more than 10 times as many patients had clear or almost clear skin with Dupixent compared with placebo (24% versus 2%). 37% of patients on drug achieved a clinically meaningful improvement in itch compared with 5% with placebo.

Sanofi will be hoping that getting the expanded label for Dupixent, which is currently approved in the EU for use in adults with moderate-to-severe AD and for adults and adolescents as an add-on maintenance treatment for severe asthma with type 2 inflammation, will boost sales of what is becoming its flagship product. First-quarter revenues from the drug were €329m (+186.9%), with the US making up €266m of that, driven by a successful asthma launch – it became commercially available for adolescent AD in mid-March in the US.

Sanofi and Regeneron also have an ongoing Phase III trial in children with AD aged six to 11. They are also running a pediatric AD study in children aged six months to five years old which is in Phase II/III.

In an investor note issued 1 July, analysts at Morgan Stanley gave some insight into a discussion with Bill Sibold, head of Sanofi's Genzyme unit from an investor roadshow in Paris about Dupixent. He stressed that the company was "at the beginning of

building a broad presence across multiple indications and across physician groups," according to the broker, but is "not overly concerned by emerging competition in AD," notably from oral JAK inhibitors.

Although there are no JAK inhibitors approved yet for AD patients, there are a number vying to be first to market, notably Eli Lilly & Co.'s Olumiant (baricitinib) and Pfizer Inc.'s abrocitinib, which have posted promising Phase III data, with AbbVie Inc.'s upadacitinib and Incyte Corp.'s topical version of Jakafi (ruxolitinib) further back. However there are lingering safety concerns about JAK inhibitors and the Morgan Stanley report cited Sibold as stressing Sanofi's belief those fears and the clinical data seen so far for emerging injectibles "do not suggest significant differentiation to Dupixent which has set a very high efficacy/safety bar and established real-world experience (50,000 patients treated)."

The AD expansion in Europe came a couple of days after Sanofi and Regeneron received the US Food and Drug Administration's approval for a third indication for the IL-4/IL-13 blocker, chronic rhinosinusitis patients with nasal polyposis (CRSwNP). The green light, granted on 26 June, expands Dupixent's reach to a new set of patients, making it the first biologic approved by the FDA to treat CRSwNP, although there is some overlap in patients who also experience asthma.

> Although there are no JAK inhibitors approved yet for atopic dermatitis patients, there are a number vying to be first to market.

SVB Leerink analyst Geoffrey Porges wrote in a 26 June investor note that sinusitis is "a nice addition for Dupixent, but won't move the needle," noting that while CRSwNP is not a significant indication, "it does broaden Dupixent's usage in different therapeutic areas and demonstrates the product's growing portfolio of indications." He added that he expected insurance companies "to have a very high bar for paying for maintenance treatment with a high-priced injectable medicine when low priced generic intranasal steroids and one-time surgical options are widely available."

Porges went on to say that "ultimately the sweet spot for Dupixent in this indication is most likely to be for patients who have other allergic symptoms, such as asthma or AD, in which case the sinusitis improvement is likely to be viewed as further justification" for using the drug.

While asthma and AD will continue to drive the commercial prospects for Dupixent, it is being studied for an additional four indications, namely eosinophilic esophagitis (Phase III), chronic obstructive pulmonary disease (Phase II), grass allergy (Phase II) and peanut allergy (Phase II). Consensus estimates for global Dupixent sales are $5.1bn by 2023 and $5.8bn by 2025.

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LSKB Still Upbeat On Rivoceranib Despite ANGEL Failure In Late-Line Gastric Cancer

JUNG WON SHIN jungwon.shin@informa.com

After preliminary top line results showed that a Phase III study for rivoceranib (also known as apatinib) in later line gastric cancer failed to meet its primary endpoint, US-based LSK BioPharma Inc. (LSKB) is planning to seek an alternative development path, but still believes it can gain the US FDA's approval of the VEGFR-2 inhibitor.

"Although the trial didn't meet the overall survival endpoint, it doesn't mean we believe that the technology or rivoceranib has failed. It has already successfully been used for a number of years in China," said Arlo McGinn, managing director of business and product development at LSKB, which is a subsidiary of South Korea's HLB Co. Ltd.

"We are disappointed that the study missed the primary endpoint and didn't provide the data we need to file for the approval based on a single study at this time, but the biggest challenge this will create for LSBK is that it delays filing for the first market approval outside China," he added.

McGinn's video clip was posted on the website of HLB after shares of HLB plunged in the wake of the announcement of the top line data from the ANGEL study. LSKB intends to publish the full report within the next few months.

Rivoceranib is a vascular endothelial growth factor receptor 2 (VEGFR2)-targeted small molecule inhibitor under development for third-line treatment of advanced or metastatic gastric cancer, in which it acts to inhibit angiogenesis, a critical process in cancer growth and proliferation.

LSKB holds the global rights, excluding China, and has partnered for development and marketing in South Korea. The molecule was approved in third-line gastric cancer in China in 2014 through Jiangsu Hengrui Medicine Co. Ltd.

ADDITIONAL ANALYSES, STUDY TO DETERMINE APPROVAL PATH

LSKB has completed the unblinding and preliminary review of the top line data from ANGEL, which enrolled 460 advanced or metastatic gastric cancer patients.

While the rivoceranib arm did achieve better median overall survival (OS) compared with placebo, and a result comparable to other approved drugs in this indication, the result against this primary endpoint was not statistically significant. However, the drug did demonstrate a highly significant improvement in median progression-free survival (PFS), a secondary endpoint, and was also generally well tolerated, and safety results were consistent with prior studies.

LSKB will conduct further analyses as additional data become available, such as overall response rate (ORR) and time to progression, will follow surviving patients, and will keep an open dialog with regulatory agencies to determine the appropriate path to approval for rivoceranib in the gastric cancer monotherapy indication.

The company also plans to continue ongoing clinical development programs in other indications including earlier lines of therapy for gastric cancer as part of combination treatment, and in colorectal cancer and hepatocellular carcinoma.

McGinn said the main impact from missing the primary endpoint is the likely delay in a US NDA filing. "We need to take a step back and work on a plan that is most efficient way to get the required data for filing in the gastric cancer as a third-, fourth-line indication."

"One option for strategy would be to leverage the positive data that we do see in the ANGEL study and conduct a confirmatory study. We believe it could be a smaller, faster clinical study. We will be working internally in the coming weeks to develop the whole plan for the possible confirmatory study," he said. HLB said it expects an additional one-year period will be required to conduct such an additional smaller trial. It pointed to the fact that some other like Cyramza (ramucirumab) had been approved after additional studies were conducted after failing in a Phase III program.

ONGOING FAITH IN MOLECULE

The South Korean firm reassured investors that it doesn't expect to face any financing issues from the failure, as LSKB had already prepared funding of KRW48bn ($41m) for clinical trials and HLB has also secured more than KRW30bn in financing. A planned merger between HLB and LSKB is expected to go ahead.

LSKB still believes rivoceranib is an active cancer drug because the vast body of data it has acquired from Hengrui's development in China indicates this is the case. Because of the positive signals from the ANGEL study, McGinn said the issue of overall survival may actually be related to the changing way that gastric cancer is being treated. Even over the short period of time for the trial, the standards of care for the disease have changed significantly.

"We still believe the ANGEL study was designed correctly, but considering the changes in gastric cancer treatments, the ANGEL study didn't fully provide the data necessary to file for the approval. I believe we will get a lot of good data out of the ANGEL study and this will help us identify a path for filing an NDA in the third- or fourth-line gastric cancer indication," he said. LSKB also feels that the ANGEL data will be extremely helpful and will inform the design of clinical studies in other indications such as the planned second-line gastric cancer use and for colorectal cancer as well.

LIKELIHOOD OF APPROVAL LOWERED

Even so, Informa's Biomedtracker said the news is "highly disappointing" for LSKB. Although rivoceranib trended toward an OS improvement and significantly improved PFS, missing the primary endpoint will likely delay regulatory submission, it noted. LSKB had hoped to file by late 2019, but without further data it is difficult to determine the full impact of the poor outcome in an area of unmet need within gastric cancer.

Given LSKB's signals that it would still continue to discuss rivoceranib's potential in this indication with regulatory agencies, Biomedtracker said it is not suspending the drug in this indication but lowered the likelihood of approval by 5 percentage points to 30% versus the average of 35%.

In its gastric cancer pipeline report published in December 2017, Datamonitor Healthcare predicted that the uptake of the drug would likely be low due to the relatively small eligible patient population in the third-line setting. The buildup of toxicity may also preclude heavily pretreated patients from further drug therapy, and as a result, many patients who fail multiple therapies are often treated with best supportive care only, it noted.

Furthermore, rivoceranib will likely face significant competition from established targeted therapies such as ramucirumab, pembrolizumab and nivolumab. Nonetheless, the lack of effective options in later line settings continues to make this an area of limited competition and high unmet need, and the drug could find a role in patients who fail to respond to immunotherapies, Datamonitor said.

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AstraZeneca Gets Imfinzi Boost From CASPIAN Lung Cancer Trial

ELEANOR MALONE eleanor.malone@informa.com

AstraZeneca PLC's Phase III CASPIAN study of Imfinzi (durvalumab) in patients with first-line extensive-stage small-cell lung cancer has met its primary endpoint.

An interim analysis showed a significant and clinically meaningful positive overall survival benefit for patients treated with Imfinzi in combination with standard-of-care etoposide and platinum-based chemotherapy options versus chemotherapy alone. "We see this as a positive surprise for a study that has received very little investor attention," commented Credit Suisse analysts in a 27 June note. They believe the checkpoint inhibitor could achieve peak annual sales of $500m in this indication should it be approved.

The trial is also studying Imfinzi in combination with AstraZeneca's CTLA-4 inhibitor tremelimumab and chemotherapy but results for this arm are not yet available.

Full data are expected to be presented at a scientific meeting later in 2019, such as World Conference on Lung Cancer or the European Society for Medical Oncology (ESMO) annual congress, both of which are being held in Barcelona in September.

Small-cell lung cancer (SCLC) accounts for only about 15% of all lung cancer deaths but is an area of significant unmet need as the prognosis is poor: only 6% of all SCLC patients will be alive five years after diagnosis. About two thirds of SCLC patients are diagnosed with extensive-stage disease.

Imfinzi was approved by the US Food and Drug Administration for previously treated metastatic bladder cancer in May 2017 and for unresectable Stage III non-small cell lung cancer that has not progressed following chemoradiation in May 2018. It was approved for the same NSCLC indication in Europe in September 2018 and is also approved in several other countries including Japan. Sales of the product amounted to $633m in 2018 and $295m in the first quarter of 2019.

PLAYING CATCH-UP

In advanced SCLC it is playing catch-up to Roche's rival PD-L1 inhibitor Tecentriq (atezolizumab), which gained US FDA approval for first-line treatment along with etoposide and carboplatin in March 2019. Merck & Co. Inc.'s Keytruda (pembrolizumab), a PD-1 inhibitor, is also being studied in this indication, in the Keynote-604 study, due to read out in December 2019.

But Bristol-Myers Squibb Co.'s Phase III CheckMate-451 trial of PD-1 inhibitor Opdivo (nivolumab) in combination with CTLA-4 inhibitor Yervoy (ipilimumab) failed to meet its primary endpoint of overall survival in November 2018. *(Also see "BMS SCLC Chances Dive After Opdivo, Yervoy Combo Flunks Checkmate-451" - Scrip, 27 Nov, 2018.)* However, the FDA had already granted Opdivo accelerated approval in third-line or later metastatic SCLC settings in August 2018.

Analysts at Biomedtracker commented that the positive results shown by Tecentriq and Imfinzi as first-line therapy contrasted with the disappointing results from Opdivo in later lines of treatment, suggesting "the benefit [of the PD-1/PD-L1 class] may be more pronounced when used as an upfront therapy." They raised their estimated likelihood of approval for Imfinzi in the indication from 35% to 39%.

The Credit Suisse analysts cautioned against comparing Tecentriq and Imfinzi in the extensive SCLC setting because of differences between CASPIAN and Roche's IMpower133 study, notably the fact that patients in the CASPIAN control arm received more intensive therapy and IMpower133 included relapsed less-advanced stage patients, unlike CASPIAN.

INTEREST REVITALIZED IN INFIMZI STUDIES

They view the CASPIAN results as having a broader benefit beyond its specific setting, "revitalising interest in the long tail of IMFINZI Phase III studies." AstraZeneca's checkpoint inhibitor had suffered a blow when it failed in the key MYSTIC study in first-line Stage IV metastatic NSCLC, even though it succeeded in gaining approval for Stage III unresectable lung cancer on the basis of its PACIFIC study. *(Also see "Mystic Miss Not Make Or Break For Imfinzi" - Scrip, 16 Nov, 2018.)*

Credit Suisse points out that the company has "a rich catalyst stream of other Phase III studies" with results due over the next 18 months, both as a monotherapy and in combination with tremelimumab and/or chemotherapy, many of which are focused on first-line therapy.

Among imminent Imfinzi mono- and combination therapy Phase III trial read-outs based on which - if positive - AstraZeneca anticipates filing for approval extensions in the US, EU and Japan by the end of 2019 are:

- KESTREL, studying Imfinzi and tremelimumab in first-line head and neck squamous cell carcinoma, for which Credit Suisse predicts peak annual sales of $1bn and a 25% probability of success;
- DANUBE, combining Imfinzi and tremelimumab for first-line bladder cancer; Credit Suisse forecasts a 50% probability of success and $400m peak sales;
- NEPTUNE, also combining Imfinzi and tremelimumab, this time in first-line non-small cell lung cancer, with a 10% probability of success according to Credit Suisse and the potential for $1bn in peak annual sales; and
- POSEIDON, combining Imfinzi and chemotherapy with or without tremelimumab in first-line non-small cell lung cancer, which Credit Suisse assigns a 10% probability of success and up to $500m in annual sales.

Imfinzi is also being studied following concurrent chemoradiation therapy in limited-stage SCLC in the Phase III ADRIATIC trial.

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Dainippon's Lead Boston Asset Hits Wall In Pancreatic Cancer

IAN HAYDOCK ian.haydock@informa.com

Sumitomo Dainippon Pharma Co. Ltd.'s (SDP) novel oral investigational cancer agent napabucasin has failed in a Phase III study in one its main lead indications, after the futility of continuing the trial was determined in an interim analysis.

The development marks a major setback for the Japanese company in its effort to build out a cancer pipeline and business against the background of the looming loss of US exclusivity in early 2023 for its current top seller globally, the atypical antipsychotic Latuda (lurasidone).

Sales of this product in North America, its main market, were $1.66bn (+3%) in the fiscal year ended 31 March, and SDP is bidding to become a "global specialized player", helped by planned M&A activity, in its defined core area of psychiatry and neurology, as well as oncology.

The failure is also a strategic miss for SDP's past acquisition strategy given that napabucasin was originated by Boston Biomedical, acquired for $2.63bn in 2012 in a bid to strengthen the Japanese firm's oncology pipeline.

SDP had until recently been anticipating a US launch in pancreatic cancer in fiscal 2021, saying it expected napabucasin "to become a blockbuster at peak revenue" in total across all indications, while stopping short of providing detailed forecasts.

Part of its US business development plans for the product included building a specialist sales and marketing organization, and it looks likely that these will be affected by the setback.

FUTILITY FINDING

The company's wholly owned US subsidiary Boston Biomedical received a recommendation on 1 July from the independent data and safety monitoring board for the CanStem111P study with napabucasin to discontinue the Phase III trial in pancreatic cancer.

This came after an interim analysis – conducted upon 50% of total events being reached – and determined "futility", which usually means that statistical significance and the primary endpoint were unlikely to be met. Neither SDP or Boston are providing any further details at this stage.

The open-label trial was assessing napabucasin in combination with weekly nab-paclitaxel and gemcitabine, versus the latter two drugs alone, for the first-line treatment of patients with metastatic pancreatic adenocarcinoma.

SDP said it had "accepted the recommendation and has decided to discontinue the study," and noted that no new safety concerns were raised by the board. The company added it is "currently evaluating the impact that this matter will have on its consolidated financial results" for the current fiscal year ending next 31 March.

"The failure is also a strategic miss for SDP's past acquisition strategy given that napabucasin was originated by Boston Biomedical, acquired in 2012 to strengthen the Japanese firm's oncology pipeline.

The company's share price dipped immediately after the announcement but has since recovered ground, perhaps given that napabucasin remains in a Phase III US/Japan trial for its potentially larger indication of colorectal cancer, and is in earlier clinical development for various other indications, all as part of combination therapy. These include hepatocellular carcinoma (HCC), gastrointestinal cancer and solid tumors (all in Phase I/II in the US).

The colorectal study is looking at combination use with Folfiri (folinic acid, fluorouracil and irinotecan) with or without Avastin (bevacizumab), an approach adopted after an earlier monotherapy trial was stopped on monitoring board advice after it stumbled on efficacy at an interim analysis.

SDP noted recently that an interim analysis by the trial board had allowed the study to continue.

Napabucasin (BBI608) acts an an oral cancer stemness inhibitor and is bioactivated by the cancer cell enzyme NQO1, which generates reactive oxygen species to inhibit cancer stemness and tumor progression-related pathways including STAT3, resulting in cancer cell death.

In the colorectal indication, Datamonitor Healthcare is forecasting global sales of $72.7m in 2025, constrained by expected initial approval only in the second-line or later setting.

MORE DEALS TO FILL PIPELINE?

Pancreatic cancer is a particularly tough oncology target with a low disease survival rate, although promising results for AstraZeneca PLC/Merck & Co. Inc.'s PARP inhibitor Lynparza (olaparib) in metastatic patients with germline BRCA mutations were reported at ASCO this year. *(Also see "AZ/Merck & Co's Lynparza POLO Study 'Practice Changing' For Pancreatic Cancer Subgroup " - Scrip, 3 Jun, 2019.)*

For SDP, there are no other late-stage projects in its oncology pipeline, while the company's core neurology and psychiatry

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CONTINUED FROM PAGE 16

pipeline is dominated by line extensions. One bright spot is imeglimin (licensed from Poxel SA), an antidiabetic for which positive results have been reported this year. *(Also see "Positive Phase III Data Set Stage For Japan Imeglimin Filing" - Scrip, 10 Apr, 2019.)*

The other main ex-Boston asset is amcasertib (BBI503), a first-in-class oral cancer stemness kinase inhibitor in US Phase I/II trials for HCC and solid tumors (the latter including as monotherapy).

SDP's share price has already come under sustained pressure this year, falling by around 40% and hit particularly hard in late January after Japanese bioventure partner SanBio Co. Ltd. unveiled disappointing results for a novel cell therapy in ischemic stroke.

It is not yet clear whether napabucasin's failure in pancreatic cancer will affect SDP's strategic mid-term plan to spend JPY300-600bn ($2.68-5.36bn) on M&A over the next five years, in terms of revenue generation to support this, or a harder focus on new deals to fill the oncology pipeline.

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Sarepta Shares Bounce As Pfizer's DMD Gene Therapy Sparks Safety Concerns

JO SHORTHOUSE joanne.shorthouse@informa.com

Pfizer Inc. has allowed a peek into its Phase Ib clinical data on PF-06939926, its investigational gene therapy for Duchenne muscular dystrophy (DMD), and while it does show some signs of efficacy, safety is a concern.

The primary endpoint of the ongoing Phase Ib study is to assess the safety and tolerability of the gene therapy, and one of the six boys participating had a severe immune reaction to the therapy; even so Pfizer is continuing its plans for a Phase III trial.

The patient in question developed a rapid antibody response with activation of the complement system associated with acute kidney injury, hemolysis and reduced platelet count. This participant was promptly admitted to a pediatric intensive care unit and received intermittent hemodialysis, as well as two intravenous doses of Alexion Pharmaceuticals Inc.'s complement inhibitor Soliris (eculizimab). The boy spent 11 days in hospital and his renal function returned to normal within 15 days.

No other participants will be dosed until the specific additional safety monitoring, which has been endorsed by the external data monitoring committee, has obtained all appropriate approvals at the clinical research sites.

Other side effects seen in the trial included nausea, vomiting and fever in four out of the six patients.

To complete the Phase Ib study Pfizer aims to enrol approximately 12 boys with DMD who are ambulatory and aged from five to 12. To date, six study participants ranging in age from six to 12 years have received the one-time intravenous dose of PF-06939926 at either 1E14 vector genomes/kilogram (vg/kg) or 3E14 vg/kg.

COMPETITORS

Pfizer is not the only party to have had safety wobbles with its DMD gene therapy. In May, Solid Biosciences Inc. announced that a patient had experienced a serious adverse event while in a trial for its lead DMD product SGT-001, and had been reported to the FDA. *(Also see "Solid Biosciences' DMD Gene Therapy Undermined By Safety Wobbles " - Scrip, 15 May, 2019.)*

And while the news of Pfizer's so-so results were being digested by the markets, the shares in Sarepta Therapeutics Inc. soared by 17%. It is in Phase II development with its micro-dystrophin gene therapy program for AAVrh74.MHCK7.micro-Dystrophin, otherwise known as SRP-9001.

"We believe Sarepta remains in the driver's seat with its AAVrh74 micro-dystrophin gene therapy, with its 24-patient placebo-controlled study almost fully enrolled (23 patients now enrolled), and its confirmatory study (with commercial supply) targeted to begin by year end," said BTIG analysts in a 28 June note.

Sarepta bounces on Pfizer data but will it win the game?

"We believe Sarepta could be the first company to enter the US market with its gene therapy for treating DMD in 2021. We estimate Sarepta to generate annual sales of around $2bn from its gene therapy segment by 2024."

PTC's non-gene therapies Emflaza (deflazacort), and Sarepta's Exondy 51 (eteplirsen) are the only products approved in the US, while PTC Therapeutics Inc.'s Translarna (ataluren) is the only approved therapy in the EU.

EFFICACY DATA

Secondary endpoints of the clinical study include measurement of expression of mini-dystrophin distribution within muscle fibers by immunofluorescence and concentration by liquid chromatog-

raphy mass spectrometry (LCMS). There was efficacy in muscle fiber distribution and mini-dystrophin concentration demonstrated. Preliminary results from open muscle biopsies of the biceps taken two months after dosing show detectable mini-dystrophin immunofluorescence signals with a mean of 38% and 69% positive fibers taken from participants who received PF-06939926 at 1E14 vg/kg and 3E14 vg/kg, respectively.

Biomedtracker analysts said: "Initial data from multiple sites on muscle fiber distribution, minidystrophin concentration, and signs of potential clinical benefit are encouraging but warrant further investigation, and the safety profile of the investigational therapy is acceptable for continued development.

"As the safety concerns may well be manageable, we are increasing our likelihood of approval, but with the small number of patients treated, limiting that to 1%," said Biomedtracker. "The safety issues could place the drug at a competitive disadvantage, though, depending on how relative efficacy turns out and whether similar issues turn up with competitors."

Pfizer is continuing to collect data from this ongoing open-label study in boys with DMD, and is also in the planning stages for a global, randomized, placebo-controlled Phase III study, expected to begin in the first half of 2020 with commercial-scale manufacturing processes using multiple 2000-liter bioreactors.

The study will use the lessons from the ongoing Phase Ib study to make decisions about the optimal dose, assay, method of administration, concomitant medications, participant selection and safety monitoring.

PF-06939926 is a rhAAV vector that delivers a shortened, but functional copy of the dystrophin gene, called mini-dystrophin. Pfizer on-boarded the therapy as part of a 2016 deal with Bamboo Therapeutics. *(Also see "Pfizer Advances Duchenne Drug As It Prioritizes Gene Therapy" - Scrip, 12 Apr, 2018.)*

Pfizer will present these data at the 25th Annual Parent Project Muscular Dystrophy (PPMD) Connect Conference in Orlando, FL.

GOTTLIEB JOINS BOARD

In other news, Pfizer announced 27 June that the ex-Food and Drug Administration commissioner Scott Gottlieb would be joining its board, effective immediately. He was also appointed to the regulatory and compliance committee and the science and technology committee of Pfizer's Board.

Prior to serving as commissioner, Gottlieb held several roles in the public and private sectors, including serving as the FDA's deputy commissioner for medical and scientific affairs and as a senior adviser to the administrator of the centers for Medicare and Medicaid services, where he helped implement the Medicare drug benefit, advance policies to improve healthcare quality and promote the effective use of new medical technologies.

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Versant's Century Aims For Off-The-Shelf Cancer Cell Therapies

JOSEPH HAAS joseph.haas@informa.com

Century Therapeutics debuted on 1 July with $250m in backing for its strategy to develop off-the-shelf cell therapies for cancer using induced pluripotent stem cells (iPSCs), an approach it says will give it technological advantages over much of the cell therapy field. Bayer AG's venture capital arm – provided $215m in funding, with Versant Ventures and technology partner Fujifilm Cellular Dynamics Inc. kicking in the remainder.

Versant founded the company with seed funding in 2018, followed shortly thereafter by a deal with Fujifilm that gives Century exclusive access to immune effector cell-differentiation protocols and intellectual property that will enable it to manufacture its cell therapies at commercial scale. Specifics of the partnership with Fujifilm were not detailed, but the Japanese firm will be the primary manufacturer of Century's therapeutic products.

Century CEO Lalo Flores noted the previous history between Versant and Bayer, which together launched BlueRock Therapeutics with $225m in series A funding in late 2015 to develop stem cell therapies for cardiovascular and neurodegenerative disease. Flores, who was hired to helm the new company last year, has his own history with Versant. The VC firm was among the investors in hepatitis B-focused biotech Novira Therapeutics Inc. where Flores was the CEO when it was bought out by Johnson & Johnson in 2015.

Versant was pondering the game-changing potential of cell therapy in cancer and "quickly came to the conclusion that to make a difference, we need to develop off-the-shelf products," Flores told *Scrip*. The venture firm also determined that iPSCs were an ideal platform for such products, he added. "They recruited me to join as CEO in the summer of 2018; I had reached the same conclusion that I wanted to be in cell therapy and with a company that can distinguish itself from all of the other players," he said.

The versatility if iPSCs should prove ideal for cell therapy, the exec explained, because of their "self-renewing" capacity and the fact that they can go through multiple rounds of cellular engineering. This process can yield master cell banks of modified cells that then can be expanded and differentiated into immune effector cells – such as T-cells or natural killer (NK) cells – that can become allogeneic therapeutics, he asserted.

"The main power of these cells is that they offer unlimited replication capacity, they can propagate indefinitely in cell culture," Flores said. "The cells themselves don't have drug-like utility; their utility is that we can take advantage of this indefinite replication capacity *ex vivo* to incorporate multiple different types of genetics

or engineering that the ultimate effector cells of interest will have in their genome."

Other cell therapy companies, working from donor-derived primary cells, get one shot at engineering the cells to have the desired characteristics, he noted, because they need to work at a high efficiency to produce enough cells to have a therapeutic end product. With rejection being a primary issue with using cell therapies in patients with solid tumors, Flores and his team believe the multiple rounds of engineering they'll be able to do will allow the production of cells that won't be rejected by a patient's immune system.

"That why CAR-Ts haven't worked very well in solid tumors, because the field believes that all these other molecules that tumors secrete inhibit the activity of these cells," he added.

Flores declined to offer timelines for Century's work or be specific about which types of cancer it wants to target. However, the firm does plan to work first to obtain proof-of-concept in hematologic cancers, where cell therapies have a better track record of success. The company hopes that will de-risk its approach before moving on to solid tumors.

> "The main power of these cells is that they offer unlimited replication capacity, they can propagate indefinitely in cell culture." - Lalo Flores

APPROACH INCLUDES PROPRIETARY GENE-EDITING TECHNOLOGY

In addition to Fujifilm's iPSC capabilities, Century will employ some proprietary technology of its own, including multiple gene-editing processes its scientists have developed, Flores said. The company still needs to determine which of those methods will work best, but as of now, it won't need to license CRISPR-Cas9 access to do its gene-editing.

"Because we're working with iPSCs, we can use methods that are not possible for cell products that rely on primary cells," the exec explained, "because they don't replicate effectively. So, we have access to other gene-editing approaches that work quite well with iPSCs and that's why, for the moment, we're not licensing CRISPR-Cas9."

Despite Bayer's significant investment in Century, Flores stressed that his firm is independent and free to develop wholly owned candidates and partner with whomever it can attract. He expects that Century will collaborate with academic institutions, other biotechs and possibly big pharma companies "that can complement our technology and add value beyond what we have with our existing platform."

Flores conceded, however, that Bayer does hold some limited rights to innate immune cell products that emerge from Century's pipeline. He did not elaborate further on those rights.

Bayer previously entered the gene-editing and cellular therapy space in 2015 via a joint venture with CRISPR Therapeutics AG. That resulted in the inception of Casebia Therapeutics, focused on hemophilia, blindness and congenital heart disease. *(Also see "Bayer And CRISPR Form Cutting Edge Gene Editing JV" - Scrip, 22 Dec, 2015.)*

At an Alliance for Regenerative Medicine conference last fall, Casebia reported that it will be selecting candidates for advancement to clinical development this year, with a goal of filing an investigational new drug (IND) application in 2020. *(Also see "Early-Stage Cell And Gene Therapy Progress: Updates From Casebia, BlueRock, Athersys, Cynata" - Scrip, 11 Oct, 2018.)* At the same meeting, Bayer- and Versant-backed BlueRock highlighted its preclinical stem cell program to reverse motor deficits in Parkinson's disease.

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Korea Eases Stock Rules To Help Bioventures Stay Listed, Focus On R&D

JUNG WON SHIN jungwon.shin@informa.com

South Korea has revised initial public offering and stock listing management rules to lower the barriers for innovative companies, including bioventures, seeking to go public. The changes are designed to enable such firms to remain listed and focus on R&D and continued growth without having to worry about meeting revenue requirements.

At present, biotech firms which debuted on the Kosdaq market under the special listing systems, which allow companies that don't meet standard profitability requirements to list if they met technology parameters, or allow companies with strong growth potential to float upon a recommendation from IPO lead managers, must meet an annual KRW3bn ($2.6m) revenue requirement five years after listing. If they don't, their stocks will be placed under the supervision of the exchange and face possible delisting.

To meet the requirement, companies have sometimes engaged in other businesses such as beauty or functional health foods, rather than their core new drug development activities, in order to raise sales.

Under the new rules unveiled by the Financial Services Commission (FSC), companies won't be placed under the exchange's supervision even if they don't meet the annual KRW3bn revenue requirement, if their combined sales in the last three years exceed KRW9bn.

In addition, companies which are officially designated as "innovative pharmas"

by the Ministry of Health and Welfare, or companies that are performing well in the stock market with a daily market capitalization above KRW400bn, will be exempt from the revenue requirements.

To evaluate bioventures' business continuity, the exchange will conduct more detailed reviews that reflect the characteristics of the biotech industry. These will include whether firms possess proprietary technologies, experience in licensing-out deals, multiple pipeline assets and clinical stage projects, experience or plans in co-research or co-development with partners, as well as the past research performance of their core research workforce.

In addition, the country will now allow scale-up companies as well as foreign companies to be listed on Kosdaq using the listing system for special technology entities, which at present only permits local small- and medium-sized companies. Scale-up refers to non-small or medium-sized firms whose average sales in the past two fiscal years rose by more than 20%.

Foreign companies listed under the special technology system will be subject to external audit rules, and will need to receive an A rating or above in technology from multiple recognized rating agencies.

The latest rule changes, which are in line with the South Korean government's ongoing support for the broad bio-health sector, will help many bioventures currently traded on Kosdaq to remain listed without having to worry about raising revenues.

According to local media, 19 bioventures that debuted on Kosdaq under the special technology listing system reported sales of less than KRW3bn in 2018, although it hasn't yet been five years since they floated on the market. Companies such as Helixmith (formerly known as ViroMed Co. Ltd.), CrystalGenomics Inc., Genexine Inc., Alteogen Inc. and ABL Bio Corp. are "innovative pharmas" designated by the health ministry and whose market capitalization exceeds KRW400bn. *Published online 1 July 2019*

UK's O'Neill 'Frustrated' By G20's 'Paltry' AMR Message

STEN STOVALL sten.stovall@informa.com

The man who led the UK's high-profile, government-backed review on antimicrobial resistance, Lord (Jim) O'Neill, said the lack of AMR progress at last week's G20 summit has left him feeling "annoyed and frustrated" and that countries that are truly committed to tackling the health threat should now band together to push the issue forward.

Leaders from G20 countries gathered in Osaka, Japan, from 28-29 June during which they discussed economic and geopolitical issues and the climate crisis. But they gave little – if any – attention to combating the rising threat of antibiotic resistance and the related need to find viable market mechanisms to promote creation of new antibiotics.

O'Neill told *Scrip* in an exclusive interview conducted after the Japan G20 summit that the lack of concrete action or suggestions regarding AMR in the concluding communique "seems to leave us dead in the water at the global policy level."

"I'm nonplussed and frustrated by their declaration because it doesn't take us any further than where we were two years." – Jim O'Neill

The O'Neill Review On Antimicrobial Resistance, launched in 2014 under the sponsorship of former Conservative Party Prime Minister David Cameron, was integral in getting AMR discussed at the Chinese hosted G20 in 2016, and which led to it being on the German-hosted G20 meeting agenda in 2017 and the subsequent establishment of a Global AMR R&D Hub aimed at promoting research into combating antimicrobial resistance.

"But the statement that came from the Osaka declaration this weekend regarding AMR is a bland single paragraph, the wording of which makes clear that none of the G20 countries want to commit to offering financial incentives to advance this effort," O'Neill told *Scrip*.

"I'm nonplussed and frustrated by their declaration because it doesn't take us any further than where we were two years."

He continued, saying the situation today "leaves a crucial gap because no pharmaceutical company wants to treat the search for new antibiotics as an unprofitable – or at best a low-profit business."

He voiced particular disappointment with the declaration sentence that said: "We call on interested G20 members and Global AMR R&D Hub to analyze push and pull mechanisms to identify best models for AMR R&D and to report back to relevant G20 Ministers."

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Scrip's weekly **Pipeline Watch** tabulates the most recently reported late-stage clinical trial and regulatory developments from the more than 10,000 drug candidates currently under active research worldwide.

Click here for the entire pipeline with added commentary: http://bit.ly/2mx4jY3

PIPELINE WATCH, 28 JUNE – 4 JULY 2019

Event Stage	Lead Company/Partner	Drug Name	Indication	Comments	Change To LOA (%)	LOA (%)
Phase III Published Results	Regeneron/Sanofi	Praluent (aliracumab)	Cardiac And Metabolic Outcomes	ODYSSEY OUTCOMES; The Lancet Diabetes & Endocrinology, 1 July, 2019	0	100
Phase IIIb Updated Results	Novartis/Amgen	Aimovig (erenumab)	Episodic Migraine, Refractory	LIBERTY; Sustained Efficacy	0	100
Phase III Updated Results	Novartis/Amgen	Aimovig (erenumab)	Episodic Migraine, Refractory	STRIVE; Durable Responses	0	100
Phase IIb Updated Results	Merck KGaA	evobrutinib	Multiple Sclerosis, Relapsing	Reduces Disease Activity	0	17
Phase II/III Updated Results	Akcea Therapeutics, Inc.	Tegsedi (inotersen)	hAATR Amyloidosis With Polyneuropathy	NEURO-TTR (Ext.); Durable Safety, Efficacy	0	100
Phase III Top-Line Results	Pfizer Inc.	Revatio (sildenafil) IV	Persistent Pulmonary Hypertension	Neonates; Missed Efficacy Endpoint	0	100
Phase III Top-Line Results	Roche/Shionogi	Xofluza (baloxavir marboxil)	Influenza, In Children	MINISTONE-2; Positive Results	0	100
Phase III Top-Line Results	ImmuPharma PLC	Lupuzor (rigerimod)	Systemic Lupus Erythematosus	Extension Study; Safety Endpoint Met	0	51
Phase III Trial Initiation	Hengrui Medicine/Incyte	camrelizumab	Hepatocellular Cancer	A PD-1 Mab, w/rivoceranib	0	35
Phase III Trial Initiation	GlaxoSmithKline/MorphoSys	otilimab	Rheumatoid Arthritis	contRAst-1,2,3,X; Head-To-Head Studies	39	56
Phase III Trial Initiation	Beijing Northland Biotech	donaperminogene seltoplasmid, gene therapy	Peripheral Arterial Disease	NL003; In 20 Centers	0	42
Phase III Trial Initiation	Merck & Co., Inc.	V114, vaccine	S pneumoniae Infections	PNEU-PLAN; Catch-Up Regimens	0	66

Source: Biomedtracker | Informa, 2019

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"That sentence is, for me, almost annoying because in conducting our [O'Neill AMR] review we probably devoted around 50% of our time analyzing such incentives, and since our review the small grouping of people who actually focus on these issues have embraced our recommendations, so I'm not sure what further analysis is going to do."

O'Neill – ex-chair of Goldman Sachs Asset Management and a former UK treasury official – said that had the G20 been more detailed on how to address AMR collectively, "then they would have needed to come up with the money to do it, something that the leaders were still not prepared to do. The G20 result is thus a diplomatic nothing, really."

He added that "this lack of movement is scary, because the market failure problem is getting bigger."

COMPLICATED GEOPOLITICS

O'Neill said the G20 Osaka declaration on AMR reflected the current, complicated geopolitical situation.

"The power of the UK voice has disappeared. And crucially, some of the countries that opposed wanting AMR as an agenda focus in the first place four years ago – particularly India, Brazil and Russia – were trying to actually stop it from being in the Osaka communique at all."

"They [India, Brazil and Russia] had tried to stop its inclusion in the 2017 G20 communique as well. But back then the UK had the support of the Obama Administration. From what I understand, the US in Osaka didn't want to offer any real comments or views [on AMR]."

He concluded: "This seems to leave us dead in the water at the G-20 level."

Still, going forward, he said there remained real hope and potential for progress on addressing the global AMR threat.

"It's not all completely gloom and doom; there is some progress taking place in some countries, noticeably in the UK and the US, where we see a reduction in the use of antibiotics in agriculture, largely because consumers have started to tell food distributors and wholesalers that they don't want antibiotics-fed meat. And there are other areas where there is some progress, too," he said. "The key is to deal with the market failure in catalysing R&D aimed at developing new antibiotics," he stressed.

SAYS 'LIKE-MINDED' AMR COLLABORATION NEEDED

"We need a like-minded group of countries to take the initiative themselves to develop viable market models."

He noted that the UK under health minister Matt Hancock, in proposals announced in January, had introduced a new formula for paying drug companies for NHS drugs aimed to encourage them to invest in antibiotic research and development, by linking payment to the potential "health value" of the drug.

"I hope that pilot by Matt Hancock testing a version of market entry reward continues [after the selection of a new Conservative Party leader and hence prime minister occurs], because it could prove to be the basis for the UK to cooperate with like-minded countries, such as the Scandinavian countries, as a way to demonstrate ways of developing novel market mechanisms to address problems posed by AMR," O'Neill said.

Published online 2 July 2019

APPOINTMENTS

Executive	To Company	New Role	From Company	Previous Role	Effective Date
Megan Sniecinski	BioCryst Pharmaceuticals Inc	Chief Business Officer	PTC Therapeutics	Senior Vice President, Business Operations and Program Management	1-Jul-19
Mihaly Hajos	Cognito Therapeutics Inc	Chief Scientific Officer	Biogen	Head, Experimental and Translational Neurophysiology	26-Jun-19
Shin Jung-Beom	LEO Pharma Korea	Chief Executive Officer	Roche Korea	Head, Oncology	18-Jun-19
Elizabeth Garner	ObsEva SA	Chief Medical Officer	Agile Therapeutics Inc	Chief Medical Officer and Senior Vice President, Clinical Development	15-Jul-19
David A. Esposito	ONL Therapeutics	Chief Executive Officer and Director	Armune BioScience Inc	Chief Executive Officer	18-Jun-19
Jack V. Talley	Squarex LLC	Chief Executive Officer	Mitotherapeutix	Director	1-Jul-19
Jens-Peter Marschner	Zelluna Immunotherapy AS	Chief Medical Officer	AbbVie	Lead, Oncology-Western Europe and Canada	25-Jun-19

Click here for all appointments: https://bit.ly/2oHWRYn

Source: Medtrack | Informa, 2019

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