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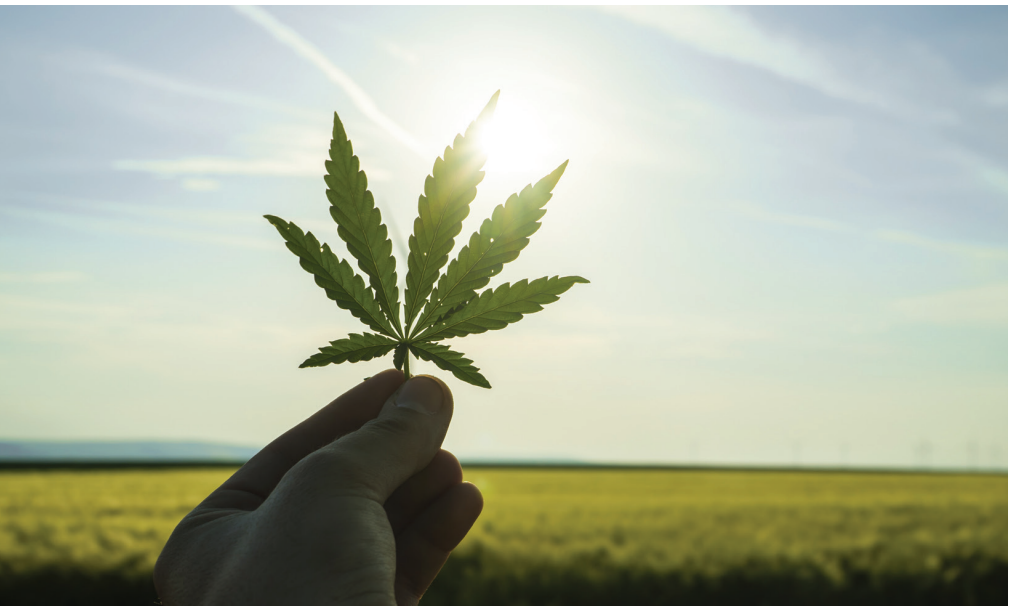

Epidiolex Approval Covers 'One Specific Cannabidiol, Not Marijuana'

MICHAEL CIPRIANO michael.cipriano@informa.com

The buzz has been high around the US FDA's approval of **GW Pharmaceuticals PLC** *Epidiolex* (cannabidiol) for the treatment of Lennox-Gastaut syndrome (LGS) and Dravet (DS) syndrome, in what the agency is calling "the first FDA-approved drug that contains a purified drug substance derived from marijuana."

But in a response geared toward the broader public perception that is bound to take place, Commissioner Scott Gottlieb did his best to tamp down any hype suggesting that FDA was issuing a broad approval to pot.

"This is an important medical advance," Gottlieb said in a June 25 statement accompanying the approval. "But it's also important to note that this is not an approval of marijuana or all of its components. This is the approval of one specific CBD medication for a specific use. And it was based on well-controlled clinical trials evaluating the use of this compound in the treatment of a specific condition."

The quality aspects are also important. "This is a purified form of CBD," the commissioner added. "It's being delivered to patients in a reliable dosage form and through a reproducible route of delivery to ensure that patients derive the anticipated benefits."

Lennox-Gastaut syndrome and Dravet syndrome are forms of rare and severe childhood-onset epilepsies. It is the first agency green light for a Dravet syndrome therapy, although there are six approved treatments for the treatment of seizures associated with LGS.

The mechanism of action of Epidiolex – which is approved for patients ages 2 and older – is not completely understood, although it is not believed it involves an interaction with cannabinoid receptors. This stands in contrast with tetrahydrocannabinol (THC), the compound responsible for most of marijuana's psychological effects. There are several synthetic versions of THC that have been backed by FDA, including **AbbVie Inc.**'s *Marinol* (dronabinol) and **Mylan NV**'s *Cesamet* (nabilone).

In April, FDA's Peripheral and Central Nervous System Drugs Advisory Committee unanimously backed the risk/benefit profile for Epidiolex by a 13-0 margin, as both panelists and FDA agreed that there were no obstacles precluding approval. *(Also see "Epidiolex Enjoys Mellow Advisory Cmte. Meeting" - Pink Sheet, 19 Apr, 2018.)*

CONCERNS ABOUT UNAPPROVED MARKETING

Gottlieb made no secret about the agency's concerns that accompany the approval: that companies will illegally market unapproved products containing cannabidiol with unproven medical claims.

"The FDA has taken recent actions against companies distributing unapproved CBD products," Gottlieb said in the statement. These products have been marketed in a variety of formulations, such as oil drops, capsules, syrups, teas, and topical lotions and creams. These companies have claimed that various CBD products could be used to treat or cure serious diseases such as cancer with no scientific evidence to support such claims."

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Competitive showdown looming (p20-21)

Data Scattered
EY on the challenge of getting access (p12-13)

Forgotten Blockbusters
Old products that continue to rake in billions (p10)

from the editor

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The US approval of GW Pharma's *Epidiolex* is an important advance towards regularizing the use of marijuana-based products with medicinal benefits within a health-regulation framework that lays down and enforces stringent rules about safety, efficacy, quality and consistency.

Should approval ensue in Europe (it is expected to come next year), it should give at least some desperate patients an alternative to the irregular use of unlicensed products, which has led to confrontations with governments such as the UK's, where the recent struggles of families with children with severe seizure disorders to obtain cannabidiol products have been hitting the headlines.

Separating the regulation of cannabidiol from the regulation of the recreational drug is only one element: to protect patients as well as to ensure their medication is sufficiently safe, effective and reliable in its formulation, the products must meet the same exacting standards as other medicines labelled to treat specific conditions. This should include evidence of efficacy in particular indications through clinical trials, not just demonstration of good manufacturing practice.

The case of cannabidiol highlights the fragmentation of regulation around cannabis and cannabis-based products (medical or otherwise) across different countries. Swiss generics giant Sandoz, for example, has already teamed up with Canada's Tilray to sell and develop non-smokable medical cannabis products in Canada. While the initial focus appears to be on co-branded product sales, Sandoz says the partners will also invest in research studies. Adding rigorous clinical studies to cGMP accreditation has to be the most appropriate route for anyone serious about selling cannabis-derived medicines as a suitable option for patients.

Scrip

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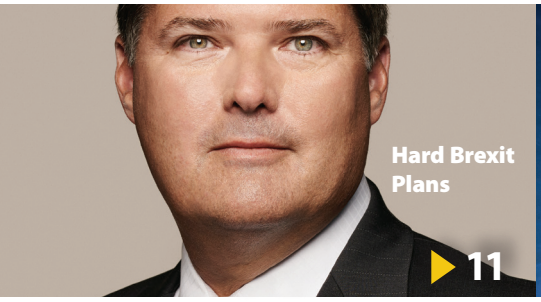

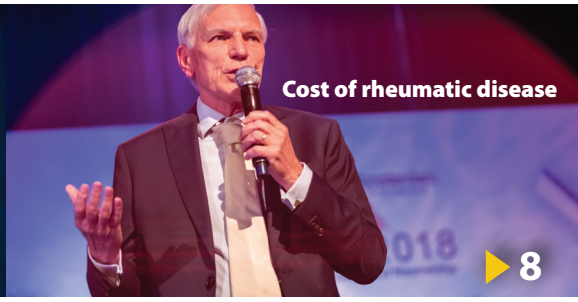

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Alexion Gets Speedy Review For Soliris Successor
https://bit.ly/2IDufyc
Switching patients from the very expensive ultra-rare disorder drug to ravulizumab will be a key strategy for Alexion if the latter is approved. Recent compelling data in paroxysmal nocturnal hemoglobinuria patients suggests the long-acting C5 complement inhibitor could offer more benefit than its predecessor with more convenient dosing.

Akero Thinks It Will Produce A Next-Wave Therapy For NASH With Former Amgen Compound
https://bit.ly/2MujSrV
Akero is entering the NASH race with a mechanism it thinks will be more powerful than current Phase III candidates and offer better efficacy than two other FGF-targeted candidates now in Phase II.

Interview: Eisai India Unit's Pivotal Role As Japan Genericizes
https://bit.ly/2KoIc0D
Eisai India chief Dr. Sanjit Singh Lamba outlines the competitive edge that the Japanese group's Indian site offers under the deal with Nichi-Iko; the site has also never "depended" on active pharmaceutical ingredients from China.

Array Celebrates BEACON Of Hope For Anti-BRAF/MEK/EGFR Triplet In Colorectal Cancer
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New data on Array BioPharma's encorafenib and binimetinib together with cetuximab add hopes for its future in colorectal cancer. Recent strong data in melanoma for the BRAF/MEK combo are expected to be followed by its first US approval.

Learning From Human Cell Hijacking Masters: ENYO Pharma Takes Virus Tricks Into Drug Discovery
https://bit.ly/2KeI3Pp
Emerging Company Profile: ENYO Pharma has been around for barely four years, but it is already advancing its lead programs into Phase II trials in hepatitis B and NASH, and anticipates many more uses for its virology-based platform that will go way beyond treating virus infections.

Finance Watch: Dementia Discovery Fund Exceeds Fundraising Goal By $150m
https://bit.ly/2yPhzNM
The Dementia Discovery Fund started in 2015 with plans to raise $200m to fund early-stage development of disease-modifying drugs, but recently closed its fundraising with $350m in commitments. Also, Kaleido's $101m Series C is among three recent $100m-plus rounds.

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BI's Business Development Focus Remains On Early Collaboration

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Whatever the prevailing winds are in biopharma M&A, privately held **Boehringer Ingelheim GMBH**'s deal-making approach will remain centered on early-stage collaborations to bolster its therapeutic focus areas, such as cancer, immunology and cardiometabolic disease, US business development head Ioannis Sapountzis said during an interview at BIO's 2018 International Convention in Boston earlier this month.

Other than a deal that took about 14 months to close from late 2015 to early 2017, in which the German pharma swapped its consumer health unit in exchange for Sanofi's animal health business, BI maintains a focus on what Sapountzis calls "classical business development and licensing" transactions. But BI does not look to large-scale acquisitions as a source of R&D transformation, he said.

"We're focusing on partnerships where we jointly develop [something] with a partner, so I think our focus generally is on more classical BD&L types of deals," said Sapountzis, who leads business development and licensing for the US and specialty care. "M&A is something we should not exclude. Two years ago, BI did an M&A deal with Sanofi on the animal health business, but for us organic growth is something that we favor."

Since moving into his current role at the family-owned firm a couple years ago – after roughly a decade working on the research side at BI – Sapountzis has focused his efforts mainly on advancing the company's R&D efforts in immuno-oncology and cardiometabolic health, specifically non-alcoholic steatohepatitis.

(Also see "Boehringer Ingelheim's Partnering Focus: An Interview With Ioannis Sapountzis" - Scrip, 30 Jun, 2017.) It uses three processes – the BD&L deals he oversees, the corporate venture arm, and its Research Beyond Borders effort to look into therapeutic areas such as hearing loss and infectious disease where it may place future emphasis, he said.

"There also is the opportunity to combine these," Sapountzis added. "Sometimes an investment leads to a partnership and that from time to time may lead to an acquisition. But we want to be involved early on in driving science forward."

"We do not have a need for adding a lot of top-line sales at this time," the exec continued. "We had double-digit growth on pharma sales last year. I think many M&A deals are transformational for the top-line and not so much for entering [new] therapeutic areas. BI, through our long-term focus, does not have to act on a market that, honestly, is quite high-priced at the moment. There is a lot premium being paid and being expected. We may not be able to wrap our head around some of the valuations that we currently see."

But in smaller deal-making, BI has remained busy focusing on collaborations to build up its focus therapeutic areas. *(Also see "Boehringer Ingelheim Confident Of A Happier Ending In NASH Than HCV" - Scrip, 5 Jan, 2018.)* "We are using our insights in fibrotic mechanisms in NASH," he explained. "We continue to be a leader in idiopathic pulmonary fibrosis [with *Ofev* (nintedanib)] and have learned a lot about fibrotic diseases and hope to capitalize on this for our NASH program. What we've done in the last year is entered into two new partnerships – one with **MiNA Therapeutics Ltd.** and the other with **Dicerna Pharmaceuticals Inc.** – both using RNA-interference to target mechanisms that we thought were not druggable."

The partnerships with MiNA and Dicerna add to the AOC3 inhibitor BI-146733 – obtained via a 2015 option deal with **Pharmaxis Ltd.** – now in Phase II in NASH, as well as in diabetic retinopathy. "With this new modality we are opening up new treatment options for patients," Sapountzis continued. "We are partnering with both companies on advancing the science in this area, from a NASH and a new therapeutic modality perspective."

Those deals reflect the thinking that BI looks to advance treatment paradigms in its therapeutic focus areas, whether by looking for better molecules, new modalities or both, he said. In the cardiometabolic space, the company's focus includes type 2 diabetes, obesity and diabetic complications.

IMMUNO-ONCOLOGY R&D EMPHASIZES FOUR PILLARS

Similarly, in immuno-oncology, BI has looked to early-stage collaborations in an effort to catch up in a hyper-competitive space, with an emphasis on solid tumors. BI has its own PD-1 inhibitor in development in case it is needed for internal combination therapy approaches, but also is looking to lead in novel immunotherapy mechanisms, Sapountzis said. In terms of indications, the company's IO work focuses on the busy lung cancer arena, but also the somewhat less competitive gastrointestinal cancer space, he added.

In IO, BI has identified four therapeutic types as pillars of its R&D effort: oncolytic viruses, cancer vaccines, T-cell engagers and immune regulatory receptor modulators. In April, it licensed global rights to **OSE Immunotherapeutics SA**'s novel SIRP alpha receptor antagonist OSE-172, which Sapountzis said the company hopes to combine with its own IO candidates. *(Also see "OSE Immunotherapeutics Adds Boehringer Ingelheim To Its Pharma Partnering List " - Scrip, 9 Apr, 2018.)* Expected to enter clinical development in 2019, OSE-172 is thought to work by turning myeloid suppressor cells into anti-tumor cells.

On the T-cell engager side, BI partnered last November with Boston-area biotech **Siamab Therapeutics Inc.** to develop antibody therapeutics for solid tumors that target tumor-associated carbohydrate antigens (TACAs). Sapountzis said the goal of this collaboration is to develop bispecific antibodies that can harness the immune system by re-directing T-cells to a specific site in the body or a tumor. Siamab's approach combines a glycoprotein therapeutic with a targeting antibody.

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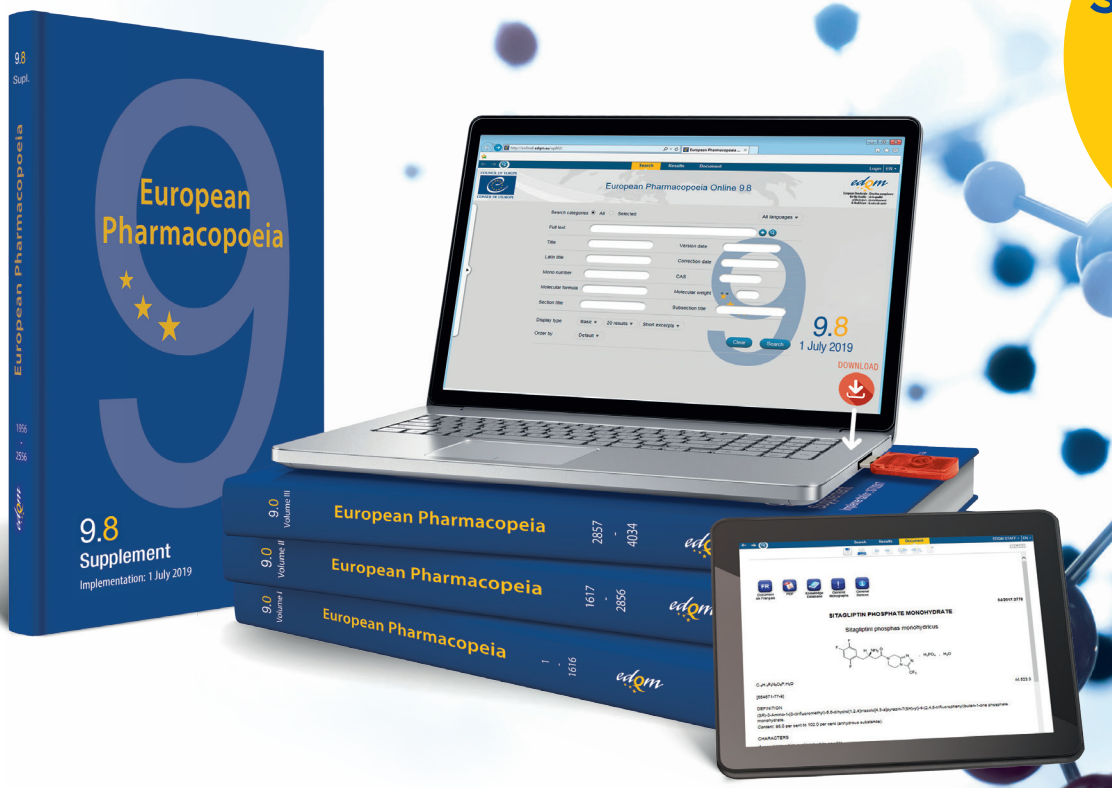

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Samsung, Celltrion Aim For Biosimilar Confidence, Convenience With New Studies

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Two major South Korean biosimilars companies have released new study results that appear aimed at increasing switching rates away from the branded originator therapies by addressing prescriber concerns over the equivalence of their products or improving administration convenience.

Samsung Bioepis Co. Ltd. and its partner **Biogen Inc.** released a pooled analysis of three anti-TNF biosimilars, while Celltrion showcased preliminary results for a new subcutaneous formulation of its infliximab product in patients with rheumatoid arthritis, at the recent European League Against Rheumatology (EULAR 2018) meeting.

Among major global markets, the European Commission is looking to boost confidence in biosimilars to support their use on a much wider scale across Europe, where uptake and levels of patient access still vary widely due to factors like payer attitudes, physician incentives, information and education, along with originator pricing policies.

Europe is generally seen as being well ahead of other large markets like the US in terms of approvals and the regulatory framework for biosimilars.

DESIGNING POOLED ANALYSIS

Samsung Bioepis and Biogen announced at EULAR a pooled analysis of results for three anti-tumor necrosis factor (TNF) biosimilars – *Benepali* (SB4, etanercept), *Flixabi* (SB2, infliximab), and *Imraldi* (SB5, adalimumab).

The analysis is the first of its kind and combined and analyzed data from three separate Phase III randomized, double-blind trials that compared the efficacy and safety of the anti-TNF biosimilars to their reference biologics, in patients with moderate to severe rheumatoid arthritis despite previous methotrexate treatment.

The main aim was to assess the impact of anti-drug antibodies (ADAbs) on efficacy and treatment tolerability, and to assess and compare radiographic progression by disease activity state at week 24 (for etanercept and adalimumab) or week 30 (for infliximab) in terms of DAS28 (a composite disease activity score). Each clinical study had a similar design and population demographics, and the same primary endpoint of ACR20 response rate (patients with at least a 20% improvement in the number of tender/swollen joints and in at last three of five other criteria).

Patients with radiographic data from each Phase III study were pooled and grouped based on their disease activity state (remission, low disease activity (LDA), moderate disease activity (MDA), and high disease activity (HDA)) at week 24 or 30 in terms of DAS28.

The mean change in mTSS and the proportion of radiographic non-progressors of higher disease activity groups (LDA, MDA, and HDA) in reference to remission were summarized descriptively and odds ratios (OR) compared using a 95% confidence interval (CI) obtained from a logistic model with baseline DAS28; 1,263 patients from the studies had radiographic assessment available.

IMMUNOGENICITY DATA

In a finding that might address some of the concerns about biosimilars' activity, immunogenicity data from 1,710 patients with RA pooled from the three studies revealed that the incidence of ADAbs was comparable between the biosimilars and their reference products – indicating that the biosimilars were equally effective as their biologic counterparts.

In addition, efficacy and injection site reactions/infusion-related reactions (ISR/IRR) were evaluated in relation to the presence of ADAbs, the data suggesting that the development of ADAbs is associated with reduced clinical efficacy and increased incidence of ISR/IRR in patients with RA.

Across treatment groups, efficacy was greater in patients without ADAbs compared to those with. In all treatments combined, the ACR20 response rate was lower in the presence of ADAbs (OR 2.06, 95% CI: 1.63–2.60, p<0.0001) and the mean improvement in DAS28 was significantly greater in patients without ADAbs (estimated difference: 0.383, 95% CI: 0.24–0.52, p<0.0001).

The effect of ADAbs on reducing ACR20 response rates as well as other efficacy parameters was similarly observed in other treatment groups.

In all treatments combined, the presence of ADAbs was associated with increased ISR/IRR (OR 1.73, 95% CI: 1.02–2.96, p=0.043), predominantly with the infliximab combined (OR 2.67, 95% CI: 1.04–6.89, p=0.041) rather than the etanercept combined (OR 1.72, 95% CI: 0.38–7.77, p=0.478) or adalimumab combined (OR 1.00, 95% CI: 0.35–2.88, p=0.998) results.

In conclusion, the pooled analysis found the development of ADAbs to TNF to be associated with reduced clinical efficacy and increased incidence of ISR/IRR in patients with RA.

Across all treatment groups, radiographic progression was the highest in HDA followed by MDA, LDA, and remission. In all treatments combined, the mean change in mTSS was 0.03, 0.38, 0.27, and 1.27 and the proportion of non-progressors was 79.7% (181/227) in the remission group, 78.1% (125/160) in LDA, 74.1% (473/638) in MDA, and 58.4% (139/238) in HDA.

In all treatments combined, compared to the remission group, the estimated difference in mTSS was greater in HDA (1.15, 95% CI: 0.63-1.66) than MDA (0.20, 95% CI: –0.22-0.62) and LDA (0.36, 95% CI: –0.20-0.91) groups and the OR of the proportion of the non-progressors was the smallest in HDA (OR 0.40, 95% CI: 0.26-0.61) followed by MDA (OR 0.76, 95% CI: 0.52-1.10) and LDA (OR 0.90, 95% CI: 0.55-1.49). This trend was similarly observed in other treatment groups.

The analysis concluded that pooled radiographic assessment data from the three different biosimilar studies showed radiographic progression to be greater as disease activity worsened.

"This analysis presents a unique opportunity to compare the efficacy of three anti-TNFs in slowing the progression of joint erosion in patients with moderate to severe RA, as measured by radiographic progression," said Ian Henshaw, vice president, Head of Biosimilar Business Unit at Biogen.

"We look forward to continuing to collaborate with Samsung Bioepis to provide

guidance on treatment algorithms and as we work toward our goal of expanding access to biosimilars for patients who may benefit in Europe and around the world."

Since the European Commission granted marketing authorization for Benepali and Flixabi in 2016, the two biosimilars have treated nearly 80,000 patients across 23 countries. As a result of European marketing authorization of Imraldi in 2017, Samsung Bioepis and Biogen expect to launch the product in Europe in October 2018.

This means the companies are now on track to becoming the first to bring biosimilars that reference products for all three original first-generation anti-TNF therapies to European patients and healthcare systems.

CELLTRION INFLIXIMAB SC

Celltrion also showcased at EULAR a study showing its subcutaneous (SC) formulation of CT-P13 (biosimilar infliximab) is comparable in terms of efficacy and safety with the intravenous (IV) formulation of CT-P13 for the treatment of patients with RA up to week 30. The company's launched infliximab biosimilar, *Remsima*, held 52% of the European market for the drug in the fourth quarter of 2017.

The objective of the randomized, controlled Phase II/III study was to evaluate the efficacy, pharmacokinetic properties and safety profile of CT-P13 SC over the first 30 weeks of treatment and optimal dosing. Patients were randomly assigned into four cohorts, one group receiving CT-P13 IV and the other three receiving different doses of CT-P13 SC (90mg/120mg/180mg) bi-weekly.

The initial 30-week results from the study showed comparable efficacy of the subcutaneous and intravenous regardless of the route of administration or dosage with similar DAS28 and ACR20 scores. The safety profiles in the SC cohorts were also comparable to IV.

The positive preliminary results indicate that CT-P13 SC could become a future alternative and easier to use infliximab treatment, giving patients more independence, the Korean company's marketing and distribution arm Celltrion Healthcare said.

Professor Rene Westhovens, rheumatologist at the University Hospitals KU Leuven, Belgium said in a statement: "These preliminary results are encouraging as they show that CT-P13 SC is safe and has comparable efficacy to the well-established intravenous version. This new injection formulation of infliximab would give patients the opportunity to self-inject, saving their time and giving them more autonomy."

Hyoung-Ki Kim, vice chairman at Celltrion Healthcare added: "While the treatment of intravenous CT-P13, an infliximab biosimilar, is effective and well-tolerated, a new SC formulation would provide added patient convenience. Subsequently, based on the positive week 30 results presented today, we are planning to launch CT-P13 SC next year if approved as part of our 'twin-track' strategy to create more choice and synergy across the healthcare system."

However, it is not yet clear what approach regulators in Europe (and elsewhere) might take to a biosimilar with a changed formulation, and Celltrion's product would present the first such case.

The company told *Scrip* that "there are no clear regulations on this in each country, so Celltrion is discussing this [the SC approval] with regulators in each country."

Celltrion's *Truxima* (rituximab), which launched in Europe in the second quarter of 2017, is now available in 18 European countries, and the company plans to sell it across Europe by the end of this year.

Celltrion has recently submitted additional data to the US FDA for the regulatory approval of Truxima in the US and also plans to submit additional data for *Herzuma* (trastuzumab) to the FDA in June.

Earlier this year, Celltrion and its partner **Teva Pharmaceutical Industries Ltd.** received complete response letters for trastuzumab (CT-P6) and rituximab (CT-P10) - biosimilars for *Herceptin* and *Rituxan* respectively - over GMP issues at Celltrion.

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From the editors of PharmAsia News.

CONTINUED FROM COVER

On a June 25 media call discussing the approval, the commissioner noted that one company was claiming that cannabidiol "could actually promote shrinkage of certain forms of cancer." He went on to shed some light about how the agency would go weed out bad actors.

"I think with respect to how we're going to prioritize enforcement going forward, I think we are still going to prioritize it based on a public health assessment where we think that claims are being made around the use of CBD in situations where patients could be put at particularly significant harm because there's otherwise effective, available therapy for those patients," Gottlieb said.

"We've focused on areas where there's claims being made around CBD for the treatment of significant health conditions, things like cancer," he added.

On the call, both Gottlieb and Douglas Throckmorton, deputy center director for regulatory programs in the Center for Drug Evaluation and Research (CDER), stressed the importance of the clinical trial process as the way to bring marijuana-based products to market.

DEA RESCHEDULING NEEDED

The launch of Epidiolex will be determined by the Drug Enforcement Agency's rescheduling of cannabidiol from its current schedule I status, which is expected to occur within 90 days. GW Pharma expects patients to have access to the drug in the fall.

FDA did not believe Epidiolex to have a high abuse potential. Stephen Schultz, vice president of investor relations at GW Pharmaceuticals, told *Scrip* in an interview that the active ingredient will likely be rescheduled to "a very unrestricted level, Schedule IV or Schedule V, likely."

Schultz said the company has not yet set a list price. The commercial launch team is "nearly in place and ready to go," he said, as the company is finalizing the hiring of the last of the approximately 70 sales reps.

According to Schultz, the company is estimating a target population of around 8,000 DS pediatric patients in the US, along with roughly 35,000 pediatric and adult LGS patients. With the approval, the company also picked up a rare pediatric disease designation, which it will "likely monetize," Schultz added.

GW Pharmaceuticals also has Epidiolex in Phase III development for tuberous sclerosis complex (TSC) and Phase II/III development for infantile spasms (Phase II/III). The TSC study is expected to be completed in the first half of 2019, although the company has said it will likely not continue to pursue the infantile spasms indication, as it has not seen a strong response to the primary endpoint in the patient population.

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Interview: EULAR Head Counting The Cost Of Rheumatic Disease

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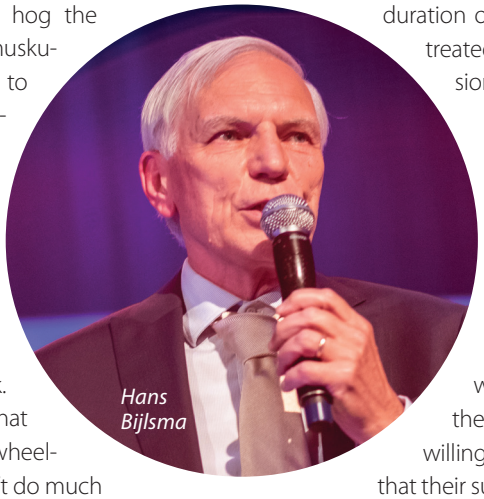
As other diseases, notably oncology, hog the headlines, the area of rheumatic and musculoskeletal diseases (RMD) is coming to the fore with innovative treatments transforming patients' lives and payers waking up to the burden on society in terms of morbidity, long-term disability and cost.


Hans Bijlsma

Someone well equipped to comment on the changes over the last few decades is Hans Bijlsma, president of the European League Against Rheumatism which held its annual conference in Amsterdam last week. He told *Scrip* in an interview at the meeting that "when I started, my waiting room was full of wheelchairs and now there are zero. Before I couldn't do much for my patients, now we sit down and look at the options."

Bijlsma noted that "in the last 20 years, we have seen enormous progress in the treatment of rheumatoid arthritis but that has levelled off." The reason for this, he argued, is that researchers in RA know so much about the disease, coming up with solutions for around 80% of patients, that they need to weigh up where more gains can be made.

Instead, the focus has shifted to areas in RMD "which still have a long way to go, which is good – we should be looking at areas where greater innovation is needed," Bijlsma said. One such field is systemic autoimmune disease, particularly lupus, and he noted promising data presented at the EULAR meeting – highlights included **Eli Lilly & Co.**'s oral Janus kinase (JAK) 1 and 2 inhibitor *Olumiant* (baricitinib) and **Johnson & Johnson**'s interleukin-12 and -23 antagonist *Stelara* (ustekinumab).

Before, RMDs were divided up by the symptoms of patients and "some signal in the blood," he said, but now researchers look at the genetic and molecular patterns in patients and the overlap in diseases. Bijlsma gave the example of osteoarthritis (OA), saying that it is not just one disease – "it could involve activity of cartilage, activity of the bone, joint issues, weaknesses of ligaments and muscles – if you treat them in the same way, it is clear you will not go far."

Researchers are studying the phenotypes of OA "in order to see what is the driving force of the disease in a particular patient" and whether treatments for other diseases may help, he said. An example of this was an abstract at EULAR which showed that a one-yearly infusion of the osteoporosis drug zoledronic acid did not significantly reduce knee pain or bone marrow lesion size overall in knee OA patients over two years, but it may have symptomatic benefit in milder disease.

Bijlsma went on to talk about the importance of early treatment for RMDs, saying it is not enough to talk about the clinical benefits but stress the benefits to society. He cited a study he led in his home country of the Netherlands, "where we have quite a well sorted out healthcare system," in RA patients who presented with a median duration of symptoms of only four weeks – they were treated and after three months, 50% achieved remission and after a year, that rose to 80%.

"Look at it like this. If it takes half a year for diagnosis and half a year for the medication to work, a patient will lose their job. If you are only 'out' for three months, you don't lose your job," he said. "With early diagnosis we can do so much more."

Bijlsma is of course well aware of the restrictions on healthcare budgets in Europe where long-term financial planning is hardly the norm. He noted that finance ministers are unwilling to invest heavily at the start of an intiative so that their successor will enjoy the kudos a couple of years down the line, adding with a smile that "the pharmaceutical industry makes drugs that are not that cheap and you can't say everybody with RA should have a €15,000 treatment."

However, "if you hit hard in the beginning, and then reduce treatment, we can get patients into drug-free remission – governments need to do the calculations," he said.

PATIENTS' BIOSIMILAR WORRIES

One way of bringing down the cost of treating RMD is the increasing use of biosimilars. Bijlsma told *Scrip* that "nearly all physicians are convinced but patients are still worried" about them "and I understand perfectly – if you have been taking a drug that makes you feel on top of the world, you don't want to lose that and switch." The challenge is to show patients the evidence that biosimilars are as effective and safe, if not more so, than the original, he added.

Moving RMD up the agenda remains tricky, Bijlsma acknowledged, especially given that "oncology and child healthcare tug at the heartstrings." However, he noted that "we are dealing with patients who have these diseases for 30 years, not for a week," and the cost is not just financial. A number of abstracts at EULAR this year looked at the rising rates of depression, anxiety and even self-harm in patients suffering from RA, knee OA and ankylosing spondylitis.

He added that the RMD field was progressing well, and expressed pleasure that the attendance at EULAR in Amsterdam – over 14,500 participants – was larger than last year and the year before that. Bijlsma and his executive committee colleagues had been worried it could go down, given that guidelines have seen the pharma companies sponsor fewer medical professionals to attend medical conferences.

He was also pleased to note that a lot of younger scientists are getting involved in RMD. "We need bright minds with enthusiasm," he told *Scrip*, laughing that 20 years ago, the younger generation were asked "you seem to be clever, why are you specializing in that, what's wrong with you?!"

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ViiV CEO: "We Aim To Be Top HIV Player By Mid-2020s"

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ViiV Healthcare aims to combine its promising pipeline of HIV-fighting drugs with its strategy of using less burdensome forms of treatment to displace **Gilead Sciences Inc.** and become the top player in the £20bn-a-year market by the mid-2020s, its CEO says.

The global specialist HIV company, majority owned by **GlaxoSmithKline PLC**, with **Pfizer Inc.** and **Shionogi & Co. Ltd.** as shareholders, is pursuing two-drug regimes to fight HIV and says demographic trends will reinforce that business approach and help form ViiV's defense against rival Gilead and its new triple combination Biktarvy.

Outlining her strategy to reporters in London, ViiV CEO Deborah Waterhouse explained that "in the developed world, the real challenge is that half the people living with HIV will be above fifty years of age."

"This is the population that is now asking, 'Can I take less medication? Can I make sure there is minimal co-drug interaction between the drugs I'm taking for my HIV and my diabetes, and my cardio-vascular issues?' whatever those issue might be. That really does raise the issue of what is the easiest HIV regimen to take with the least medicines possible and with the least side effects," she said.

She said positive topline results recently released from ViiV's Phase III GEMINI 1 and GEMINI 2 studies were a major breakthrough in ViiV's strategy to gain an advantage in the highly competitive HIV market through the development of two-drug single-tablet regimens, with the target of reducing long-term health burdens associated with antiretroviral therapy. These studies tested a combination of *Tivicay* (dolutegravir) and the older anti-HIV drug *Epivir* (lamivudine).

"The aging population, the desire to take less medicine, the fact that this is still a growing market, currently worth £20bn and growing at about 7%-8% in value and 4%-5% volume annually at the moment [makes it] a very attractive market but it's one that's really demanding medicines with different tolerability and safety profiles as people are living up 50 to 70 years on medication. That has led us to the belief that the two-drug regimen could be a valuable addition to the medication that patients have."

ViiV has calculated that an HIV patient that moves from a three-drug regime to a two-drug regimen would over a full lifetime need to take 20,000 fewer doses of medicines than if they stayed on a three-drug regimen.

> 'Our aim is to become the leading HIV company by the mid-2020s, if our pipeline plays out as we're expecting and our competitors' pipelines play out as we're expecting'

John Pottage, ViiV's chief scientific and medical officer, told the media round table that while that statistic was not necessarily accurate "it does illustrate that there's a lot of medicine that you're not taking by moving to a two-drug regimen."

This year has already seen the authorization in the US and the EU of ViiV's two-drug HIV regimen *Juluca* for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults who are virologically suppressed on a stable antiretroviral regimen for at least six months with no history of virological failure and no known or suspected resistance to any non-nucleoside reverse transcriptase inhibitor or integrase inhibitor.

Juluca is composed of ViiV Healthcare's *Tivicay* (dolutegravir), the most widely prescribed integrase inhibitor worldwide, and **Janssen Pharmaceutical Cos.**'s *Edurant* (rilpivirine).

Analysts say the GEMINI studies are the first large trials to demonstrate that a two-drug regimen can be just as effective as three-drug regimens at suppressing HIV in treatment-naïve patients.

ViiV and partners are also evaluating an investigational long-acting, injectable regimen comprising ViiV's cabotegravir and rilpivirine for the treatment of HIV-1 infection. The two studies, FLAIR (First Long-Acting Injectable Regimen) and ATLAS (Antiretroviral Therapy as Long-Acting Suppression), are examining the safety and efficacy of monthly dosing with the two-drug, injectable regimen in both treatment-naïve and treatment-experienced patients.

"Those are studies that will read out in the third quarters of this year and we'll be filing [regulatory submission for the combo] in the first part of 2019," Pottage said.

CEO Waterhouse told reporters that Gilead's product offering since its launch of Biktarvy had not dented ViiV's market share or sales performance. "Dolutegravir-based regimes have continued to grow and have continued to gain market share," she said.

"There had been some concern from shareholders that with Biktarvy being launched in the US, that that would stem our growth and cause our market share to decline, but in fact … our market share continues to grow, and we'll continue to do that." She said ViiV now holds "approximately" 22.3% of the US market while Gilead is at 52%, with the remainder held between Johnson & Johnson and **Merck & Co. Inc.**.

"You've got a £20bn market that now actually only has four players in it, as you've got **AbbVie Inc.** who have moved out, **Roche** have moved out and you've got **Bristol-Myers Squibb Co.** that have moved out. So you've got Janssen and Merck and then you've got Gilead and ViiV. We're the challenger and our objective given the pipeline … is to gain a leading place in this market."

Waterhouse added that "it's a competitive market, but not from a volume of players perspective as you see in other markets."

She said ViiV aims to become the top player in the HIV therapy market in less than 10 years. "Our aim is to become the leading HIV company by the mid-2020s, if our pipeline plays out as we're expecting and our competitors' pipelines play out as we're expecting. That's when you'd see us move to the number one position," the CEO predicted.

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The Blockbusters No One Talks About

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Just because a drug loses patent protection and faces generic competition doesn't mean it disappears in a puff of smoke from big pharma's balance sheet.

Drug makers have become quite adept at managing patent expirations and preserving some revenues post-generic entry, usually by launching their own branded generics and focusing on geographic expansion in emerging markets that are largely cash-pay.

In some cases, commercial winners continue to bring in blockbuster-level sales years after losing patent protection in the US market.

Those revenues may only be a fraction of what the drugs generated at their peak, and the products certainly aren't considered growth drivers, but in today's increasingly fragmented drug market – where the launch trajectory for new drugs has slowed – they pad the bottom line and remain important products. In some cases, they even remain top-sellers.

Here is a look at drugs that remain blockbusters even after generics have launched in the US, based on 2017 revenues.

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In some cases, commercial winners continue to bring in blockbuster-level sales years after losing patent protection in the US market.

CRESTOR, $2.37BN

Rosuvastatin kept its brand exclusivity well after statin peers like *Lipitor* (atorvastatin) and *Zocor* (simvastatin) went generic, and it was a critical bandage to help **AstraZeneca PLC** through a challenging growth period while the company waited for its new R&D strategy to deliver. Sales of the drug peaked in 2011 at $6.22bn, but it still generated $5.07bn in 2015, the last full year before the first generics launched in the US in May 2016.

GLEEVEC, $1.94BN

The blood cancer drug *Gleevec* (imatinib) remained **Novartis AG**'s top-selling cancer drug in 2017, despite facing the first generic competition in the US and Europe in mid-2016. Sales of Gleevec had already begun to chip away prior to the generic entry as Novartis turned its attention to follow-on drug *Tasigna* (nilotinib), which was the company's second best-selling cancer drug in 2017.

NEXIUM, $1.92BN

The proton pump inhibitor esomeprazole faced the first generic competitor in the US in February 2015. It generated $3.65bn in 2014, the last full year before it faced generic competition in the US. In markets like China and Japan, use of Nexium grew in 2017. It remained one of AstraZeneca's best-selling brands, behind *Symbicort* (budesonide/formoterol) and Crestor.

LIPITOR, $1.92BN

Pfizer Inc.'s blockbuster statin Lipitor was the number one selling drug in the world when it lost US patent protection in November 2011. It generated more than $11bn in sales in 2010, but today it remains an important blockbuster for Pfizer, outpacing sales of newer growth drivers like *Xeljanz* (tofacitinib) and *Xtandi* (enzalutamide). In fact, in 2017, sales of Lipitor grew 9% worldwide, driven by growth outside the US and Europe.

LOVENOX, $1.84BN

Sanofi's all important insulin franchise *Lantus* (insulin glargine) continues to rule the roost, but after Lantus, *Lovenox* (enoxaparin) was the French pharma's second top revenue generator in 2017. That's pretty impressive given that the first generic versions of the low molecular weight heparin product launched in the US in 2010. *(Also see " FDA approval of generic Lovenox sparks debate and lawsuit" - Scrip, 27 Jul, 2010.)* Biosimilar copies were only approved in Europe in 2017, however. Although Lovenox is considered a complex drug, copies were approved as generics, not biosimilars, in the US.

PLAVIX, $1.71BN

The clot-buster *Plavix* (clopidogrel) faced generic competition in the US in 2012, but the drug continues to deliver for Sanofi's top line five years later – despite pressure from a slew of novel oral anticoagulants. Plavix was the leading anti-platelet in China in 2017, and most of the product sales come from China and Japan.

ZETIA, $1.34BN

The first generic versions of the cholesterol-lowering medicine *Zetia* (ezetimibe) launched in December 2016, and *Vytorin,* a combination pill with simvastatin, only went generic in April 2017. The franchise remains important to **Merck & Co. Inc.** since the two drugs together generated $2.1bn in 2017, outpacing many other brands excluding *Keytruda* (pembrolizumab), *Januvia/Janumet* (sitagliptin) and the *Gardasil* vaccine. All but $476m in sales of the two drugs came from outside the US, however.

SANDOSTATIN, $1.61BN

The first generic version of Novartis' *Sandostatin* (octreotide acetate) for the rare hormonal disorder acromegaly launched in the US in 2011, but the product continues to bring in rather consistent sales. The drug generated $1.61bn in 2017, roughly on par with where sales of the drug have been since 2014.

BARACLUDE, $1.052BN

Bristol-Myers Squibb Co.'s antiviral for hepatitis B, *Baraclude* (entecavir), faced generic competition in the US in 2014, but the drug always generated more sales outside the US anyway. Sales declined 12% in 2017 as international revenues experienced lower demand.

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Ipsen CEO: 'I Assume a Hard Brexit', But Remain Bullish On UK Life Sciences

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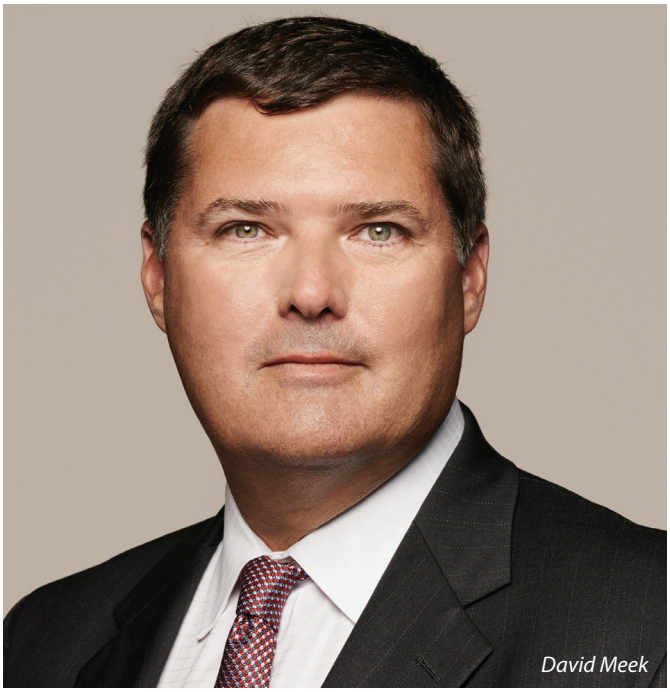
To best protect his company and patients relying on its medicines, **Ipsen**'s CEO David Meek says he's preparing the big pharma to best cope with a "hard Brexit" under which the UK gives up full access to the EU's single market and withdraws from the EU's customs union.



David Meek

> 'We're preparing for a hard Brexit. That's the most prudent assumption'

Despite the dangers Brexit poses, the American CEO has nonetheless underscored Ipsen's commitment to the UK by making it one of the France-based group's three global hubs to reflect the country's overall promise in the life sciences sector.

"The ecosystem in the UK is thriving and offers all the needed ingredients for a biopharma company like Ipsen – great academic centers, top hospitals and talent along with patient advocacy and a friendly government environment that when combined drive innovation," Meek told *Scrip*.

Still, Brexit is the key management topic for the group.

"We're preparing for a hard Brexit. That's the most prudent assumption," he said in an interview, adding:"We have plans in place to prepare for that hard Brexit and I feel confident about them.

"For me, the most important thing is to ensure there's no disruption to patient supply of medicines. That's critical. So if a patient is on therapy today and Brexit does hit, we need to make sure they remain on that therapy. We have drugs which are manufactured in the UK, and we need to make sure that we have the proper regulations in place so drugs can flow out of the UK for patients around the world, and we need to ensure that products that are manufactured outside the UK are able to enter the UK for those patients that are there," he said.

"We're in the fields of cancer, neuroscience and rare disease and the UK is a top ecosystem for generating innovation in those therapeutic areas." - Ipsen CEO David Meek

"We have an internal team working on our Brexit strategy. Besides being Ipsen CEO I also sit on the board of directors of EFPIA, the European Federation of Pharmaceutical Industries and Associations, and on the board of the Pharmaceutical Research and Manufacturers of America (PhRMA), so Brexit is the key topic for us."

No-one can be fully confident yet that breaks in patient supply won't happen under Brexit, he added.

"We're not going to be completely confident until Brexit actually happens. So, we're preparing for a hard Brexit and I want to ensure that a break in patient supply does not happen."

Longer term though, Meek - who has been CEO at Ipsen since 2016 - says the UK offers all the promise a global biopharmaceutical company needs to thrive and grow.

"We're in the fields of cancer, neuroscience and rare disease and the UK is a top ecosystem for generating innovation in those therapeutic areas. The country's importance has gotten bigger for Ipsen since my arrival as CEO two years ago and we see this progressing still in the UK," he said.

The group's facility in Slough, Berkshire in England now serves as one of Ipsen's three international hubs, the other two being in Paris, France and Boston, Massachusetts.

"We do R&D in these global hubs and they all interact. The head of R&D for these three hubs lives in the US, while our global head of specialty care lives in the UK, the global head of externalization lives in the US, and we have other top people living in Paris," he explained.

"What differentiates the UK is that it definitely can be a global hub for us – it can cover Asia, it can cover Europe, it can cover North America and South America; that's one of the benefits of the UK, and a lot of that has to do with the talent base," Meek concluded.

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Access To Widely Scattered Data A Major Challenge For Evolving Health Care Industry: EY Report

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Power in the health care sector is moving away from the product and toward the compilation and understanding of data, London-based consultant firm EY contended in a recent report. But data is siloed and difficult to access. Life sciences companies looking to evolve with new technology will need to recognize shifts in power and consolidate substantial and scattered health care data, the advisory firm said.

The challenge of getting access to and then making sense of voluminous health care-related data is made greater because that information is held by so many different stakeholders. EY pointed to seven critical silos of health care data, including that compiled and controlled by biopharma and medical device companies, by physicians and hospitals, by pharmacies, by health care payers and by government and non-governmental organizations (NGOs), among others *(see graphic)*.

Life sciences companies are used to innovation, EY Global Life Sciences Industry Leader Pamela Spence acknowledged in an interview with *Scrip,* but the next wave of innovation should involve finding ways to connect, combine and share data among stakeholders.

"These innovations will be valued based on their ability to satisfy a common purpose linked to health quality, cost and outcomes," EY's *Life Sciences 4.0: Securing value through data-driven platforms* report states. "In other words, to create future value, life sciences companies must develop systems that align objectives and share value among stakeholders."

SHIFTING POWER

Spence posited that the move toward outcomes-driven, holistic health care platforms is already shifting power within the health care sphere away from providers and biopharma/medtech companies, which, along with payers, were the traditional centers of power in health care. The good news for drug and device makers is that they control a significant pool of valuable data, including preclinical research, clinical data, biomarker analyses and post-market data, EY notes.

But other stakeholders hold key pieces of the overall data puzzle too, the report states. Physician practices and hospitals have health records as well as admissions and longitudinal patient outcomes data; pharmacies compile such information as product sales, prescription volume and medication adherence; laboratories can offer diagnostic results and biomarker and genetic assessments; payers gather actuarial analyses and claims and cost data; governments and NGOs collect and maintain statistics on costs and demographics along with biomedical and environmental data. Patients and their caregivers also hold valuable information. This can include sensor data, quantified self and fitness tracking, and even social media commentary on their health and care.

Because of the detailed patient care data they control, payers retain a strong place of power in the developing paradigm, Spence says, but power is shifting to stakeholders such as patients and consumers, policy makers and other sectors, including technology firms, retail and manufacturing.

"The rise of super consumers and technologies that deliver data-fueled insights to other health stakeholders (e.g., artificial intelligence and the internet of everything) disrupt entrenched relationships and shift power away from life sciences companies. To regain positional power, life sciences companies must invest strategically and

Health data are siloed across many different organizations

One key challenge for life sciences companies: accessing and integrating different data, which are stored in multiple locations in the health ecosystem.

Biopharma and medtech companies	Physicians and hospitals	Pharmacies	Laboratories	Payers	Governments and NGOs	Consumers and caregivers
• Preclinical research	• Health record data	• Product sales	• Diagnostic results	• Claims data	• Cost data	• Social media commentary
• Clinical trial data	• Hospital admissions	• Script volumes	• Biomarker and genetic assessment	• Actuarial analyses	• Demographic data	• Sensor data
• Biomarker analyses	• Longitudinal patient outcomes	• Medication adherence		• Cost data	• Biomedical data	• Quantified self/fitness tracking
• Post-market analyses					• Environmental data	

differentially in the capabilities that create future value and that can be shared broadly by all stakeholders," the report states. "Moreover, to achieve significant improvements in outcomes, companies must unlock the power of diverse data streams that reside outside the traditional health ecosystem."

Partnerships are the best way to incorporate data-driven technology applications into the biopharma/medtech business model, EY contends, whether that's aimed at creating a new product or service, improving an existing product or service, or collecting real-world data.

IT PAYS TO HOLD PATIENT DATA

One type of company gaining in influence in data-driven business development is the pharmacy benefit manager, Spence noted. "Seeing the number of pharmacy benefit managers doing tech-type deals, I believe that's because tech companies really see the opportunity in owning and understanding the data that PBMs have about patients," she said.

The patient-level data payers have could be valuable to tech companies whether they are interested in the disease-management or lifestyle-management business, or even want to do their own product R&D, she explained. "The tech companies have spotted the power of the payer as becoming even more dominant in the industry," Spence added. "I just didn't see that a few years ago."

There has been lots of excitement around what online retail/tech giant Amazon.com could bring to health care – including working in the PBM sector – and how that could be a catalyst for further disruption. In recent years, PBMs have been leveraging their data, either for outcomes-based reimbursement or harvesting data for partners.

UnitedHealth Group Co. acquired the PBM **Catamaran Corp.** in 2015 for nearly $13bn, in part to add its patient-centric platform and expand United's in-house PBM **OptumRx Inc.** OptumRx has a business around allowing partners to tap into their data.

DST Systems, Inc., a technology firm self-described as focusing on the speed of technology and influx of data, operates a PBM formerly known as Argus Health Systems – now DST Pharmacy Solutions. The broader firm has introduced a suite of data-driven health outcomes optimization and health administration services.

VALUE IN CONNECTING, COMBINING, SHARING

Only about 50% of available health-related data is used, Spence told *Scrip*, and a significant portion of relevant data is recently created, meaning there are opportunities both for efficiency and for capturing and using data that is currently underutilized.

"With the advances of technological change and the opportunities these advancing technologies present to really unlock data, [EY asked] how can organizations both inside the industry and outside the industry unlock the power of data for connecting, combining and sharing that data," she said.

The report concludes that "success requires the adoption of flexible business models that allow life sciences companies to develop data-driven improvements to health outcomes."

But the isolation of data throughout the health care ecosystem poses one of the greatest challenges in value creation, the report asserts. "Because of the way these databases are structured, it's difficult to interpret and use the data to improve health outcomes," it states. "Even when companies have significant reservoirs of health information within their own organizations, a significant proportion of it goes unused."

The report notes that at the 2018 J.P. Morgan Healthcare Conference, one senior pharmaceutical executive estimated that his company uses less than 40% of the data it collects.

"Although life sciences companies currently house only a small amount of data tied to health outcomes and the total cost of care, the data they do hold are incredibly rich," the report states. "If life sciences companies combined these clinical data with environmental, behavioral and financial insights, they could position themselves as one of the primary owners of the outcomes data that drive future value."

That could also establish life sciences companies as key health technology providers in a wider network of stakeholders exchanging information and services aimed at delivering better outcomes across the board – to patients, providers, insurers and governments, EY concludes.

"If life sciences companies do not take this step, it's already clear that they may lose the ability to control the direction — and value creation — of future platforms."

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Speedy Review For Soliris Successor

Having just presented more strong data for ravulizumab, also known as ALXN1210, **Alexion Pharmaceuticals Inc.** is cashing in a priority review voucher (PRV) to get a faster assessment in the US for the successor to its blockbuster *Soliris* (eculizumab) for the treatment of paroxysmal nocturnal hemoglobinuria (PNH).

The Biologics License Application to the FDA for the investigational long-acting C5 complement inhibitor has been made with a rare disease PRV, which means an expedited eight-month evaluation instead of the standard 12 months.

The application is supported by data from two Phase III trials in more than 440 patients. The first saw ravulizumab demonstrate non-inferiority to Soliris in complement inhibitor treatment-naïve patients on the co-primary endpoints of transfusion avoidance and lactate dehydrogenase (LDH) normalization, while the second study showed that patients with PNH can be effectively and safely switched from Soliris every two weeks to ravulizumab every eight weeks.

Last weekend at the European Hematology Association meeting in Stockholm, a late-breaking abstract on ravulizumab included incremental data from the PNH-naïve results. Analysts at Leerink said in a note the presentation suggested that in addition to more consistent efficacy, with less frequent dosing, ravulizumab resulted in much faster C5 inhibition and LDH normalization than Soliris, "while maintaining each of these parameters to a greater effect and with more consistency through nearly all timepoints."

Alexion's strategy is to quickly switch PNH patients on Soliris, which is also approved for atypical hemolytic uremic syndrome, over to ravulizumab before the patents start to expire on the blockbuster. One of the most expensive drugs in the world, Soliris had first-quarter 2018 sales of $800.1m.

kevin.grogan@informa.com, 21 June 2018

Sarepta Outlines A Fast Path Forward For Its DMD Gene Therapy

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Sarepta Therapeutics Inc. is poised to get a second chance to deliver a treatment to children with Duchenne muscular dystrophy, this time perhaps with a stronger efficacy result. The company unveiled the first data on a new gene therapy in three boys that could represent a breakthrough in the treatment of the debilitating disease – if the results can hold through to a broader patient population.

It's a familiar situation for the DMD pioneer, which eventually gained approval from the US FDA for the first DMD therapy, *Exondys 51* (eteplirsen), after generating strong early evidence and less support from a later study. And, once again, it is paving the way for a new endpoint.

The initial data on the gene therapy – called AAVrh74.MHCK7.micro-Dystrophin – was outlined at Sarepta's inaugural R&D day June 19, showing impressive efficacy on multiple measures, particularly increased levels of dystrophin, the dysfunctional or missing protein in DMD patients, which builds and maintains muscle. The first cohort of the Phase I/IIa clinical trial is enrolling six boys ages 4 to 7 with confirmed DMD mutation between exons 18-58. Four boys have been treated so far.

In the first three boys to undergo a post-treatment biopsy at 90 days, the level of micro-dystrophin as measured by Western blot showed robust increases, with a mean of 38.2% compared to normal using Sarepta's method (which does not take into account adjustments for fat and fibrotic tissue). The level was 53.7% using the Nationwide Children's Hospital quantification method, which adjusts for fat and fibrotic tissue. Nationwide Children's Hospital developed the gene therapy and partnered with Sarepta on worldwide development in 2017.

As a contrast, the 12-patient trial supporting FDA approval of Sarepta's Exondys 51 showed a mean change in baseline of .28%. Investors had been hoping to see the gene therapy deliver micro-dystrophin production of at least 10%.

"Our challenge on Western blot? Our challenge is we are making too much darn protein," CEO Doug Ingram joked during the R&D briefing. "We had to come up with a new standard curve." For prior studies, the standard curve only went up to 4%, he said.

Exondys 51 is Sarepta's antisense oligonucleotide that was controversially approved by FDA in 2016 for DMD patients amenable to exon 51 skipping, despite questionable efficacy data.

In Europe, the Committee for Medicinal Products for Human Use (CHMP) rejected eteplirsen earlier in June. Now, Sarepta could be the first to deliver a gene therapy to DMD patients, although there are still a lot of hurdles to cross. Investors pounced on the news, and analysts were enthusiastic. The company's stock opened 52% higher on June 19 at $160; it closed at $143.93, up 36.76% over the prior day's close.

Leerink Partners' analyst Joseph Schwartz called the results a home run. "With strong expression and wide distribution across the biopsied sample and complemented by dystrophin-associated protein complexes, today's data, in our view, highlight the strong promise of the company's rh74-delivered gene therapy and should position Sarepta as a leader in the field," he said in a same-day research note.

The news is certainly encouraging and could represent an important breakthrough for the hope of developing a gene therapy for DMD. But the dataset is very small and the results are only measured out to 90 days. The company did not provide any data on functional improvements in patients, though the company did show patients climbing stairs before and after with notable improvements post-treatment. A placebo-controlled clinical trial will be needed to confirm the early efficacy.

"This is a day you would envision for those of us at Sarepta where we could be arrogant and thump our chest, but it is not that day for us," Ingram said. "All this opportunity is nothing but obligation." He said the company is now focused on executing on a broader clinical development program for AAVrh74.

The next steps will require input from FDA, but Ingram said the company plans to act quickly and is already preparing to begin enrolling a new placebo-controlled cohort of patients. The cohort has already been cleared by FDA to begin trials, so that arm will begin enrolling patients as soon as reasonably possible, he said. It will enroll 24 patients and run about one-year and could serve as the basis for approval.

"It would be a mistake for us to claim that we know that that's the path. That is going to require a discussion with FDA," Ingram said. One question will be if FDA will accept micro-dystrophin as a surrogate endpoint or require some combination of a surrogate endpoint and biomarker like decreases in serum creatine kinase (CK), an enzyme associated with muscle damage, or a surrogate endpoint and functional endpoint.

All three boys initially treated with the gene therapy also experienced significant decreases in CK levels, with a mean reduction of over 87% at Day 60. Patients with DMD uniformly exhibit high levels of CK.

Lead investigator Jerry Mendell, Nationwide Children's Hospital, presented the positive results from the Phase I/IIa trial. He worked to optimize the AAVrh74.MHCK7 vector specifically for DMD in collaboration with gene therapy specialist Louise Rodino-Klapac, who joined Sarepta in June to lead the company's new gene therapy business unit as VP for gene therapy. She previously led the laboratory for gene therapy research for muscular dystrophies at Nationwide Children's Hospital.

Pfizer Inc. and **Solid Biosciences Inc.** are also racing to develop a gene therapy for DMD. Pfizer initiated a Phase Ib open-label trial for its candidate, PF-06939926, in boys ages five to 12 in March, with data expected in early 2019.

Meanwhile, Solid announced June 18 that FDA had lifted a clinical trial hold for its candidate, SGT-001, and it can resume the Phase I/II IGNITE DMD trial.

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Incyte Will File Jakafi For Acute GVHD In US Based On Phase II Success

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Incyte Corp. is drawing closer to a third US indication for its JAK1/2 inhibitor *Jakafi*, reporting successful top-line data from the Phase II REACH1 study in steroid-refractory, acute graft-versus-host disease (GVHD). The company intends to file a supplemental new drug application (sNDA) for that application during the third quarter of 2018.

Jakafi (ruxolitinib) is also being testing for GVHD in the Phase III REACH2 and REACH3 studies, in acute steroid-refractory GVHD and chronic steroid-refractory GVHD, respectively, which are expected to report data in 2019. Those studies are being funded by **Novartis AG**, Incyte's European partner for ruxolitinib (where it is branded as *Jakavi*).

The drug met the primary endpoint of overall response rate at 28 days in 54.9% (39/71) of patients enrolled in REACH1, a single-cohort, pivotal Phase II study. It also achieved a best overall response rate – illustrating the number of patients who achieved a response at any time during the study – of 73.2% (52/71), which Chief Medical Officer Steven Stein called the best metric for evaluating the results compared to other trials in steroid-refractory GVHD, including small, investigator-sponsored studies using ruxolitinib.

The drug yielded treatment-emergent adverse event rates during the trial of 61% for both anemia and thrombocytopenia and of 56% for neutropenia. Stein told a June 21 investor day, however, that this was "nothing unexpected from this population."

LACK OF EFFECTIVE THERAPIES

While Incyte plans to present full trial data at a medical conference later this year, Stein broke out the primary endpoint a bit more by noting that of the response rates, 26.8% of the overall enrollment achieved a complete response, 9.9% had a very good partial response and 18.3% had a partial response. He added that responders had relapse-free rates of about 80% at three months and 67% at six months.

For an important secondary endpoint – duration of response at six months – the median has not yet been reached, the exec noted. When Incyte presents the full dataset, it will also detail secondary endpoints including ORR at different time intervals (14, 56 and 100 days) during treatment, non-relapse mortality and progression to chronic GVHD, he said.

Ruxolinitib has FDA breakthrough therapy designation and orphan disease status for this specific indication. Stein noted that of approximately 7,500 allogeneic stem cell transplants occurring annually in the US, about 1,700 patients have acute, steroid-refractory GVHD. Chronic, steroid-refractory GVHD is seen in about 1,500 US patients annually, he added.

GVHD in patients receiving allogeneic stem cell transplants results in first-year mortality rates ranging between 25% and 75%, said Madan Jagasia, who directs the hematology-stem cell transplant center at Vanderbilt University Medical Center. This underscores the lack of efficacy of currently available therapies, the researcher added.

Morgan Stanley analyst Matthew Harrison concluded the REACH1 data look promising, even though other smaller studies produced higher response rates. A study led by Robert Zeiser of Germany's Freiburg University in the same disease setting produced an 88% (44/54) ORR, but was not a prospective study, the analyst pointed out. Meanwhile, other smaller studies testing other agents in this indication yielded ORRs ranging from 40% to greater than 80%, but many of these enrolled only between 10 and 30 patients, Harrison wrote in a June 21 note.

"Thus, given the more robust study for Jakafi, we believe the ORR is competitive," he said. The Novartis-led REACH2/3 studies each have enrollments of roughly 300 patients.

PRIMARY ENDPOINT, TRIAL DESIGN OKAYED BY FDA

The company is confident in its plan to file on the basis of the single, open-label Phase II study in part because of the drug's breakthrough therapy status – which does bring greater interaction with the agency throughout development.

"First [within FDA], there's a huge interest in the disease itself," Stein said. "The endpoint is agreed. The study is agreed. So it's as robust as it can be. Day 28 response is felt to be a really good surrogate for long-term benefit, particularly survival. And then in terms of the endpoint, it was felt that anything north of 50% would be a really good surrogate for clinical benefit, coupled with … durability of response."

The secondary endpoint of best ORR also is "pretty predictive" for long-term benefit, he asserted, but there's not as much agreement on that as on the value of 28-day response rate. He added that Incyte believes its sNDA will enjoy a "very high probability of success."

Biomedtracker gives ruxolitinib a 59% likelihood of approval, which is average for a Phase II candidate for this indication, and unchanged from before the top-line REACH1 data were unveiled. Biomedtracker's take on the data was that the REACH1 results "demonstrated the potential of ruxolitinib to meaningfully improve the outcomes of allogeneic transplant patients who develop steroid-refractory acute GVHD and further underscored the promise of JAK inhibition to advance the treatment of this condition."

SOLID START FOR GVHD PROGRAM

The first JAK1/2 inhibitor on the market, Jakafi currently is approved in the US to treat patients with polycythemia vera who have an inadequate response or are intolerant of therapy with hydroxyurea and in patients with intermediate or high-risk myelofibrosis. While the GVHD program is off to a solid start, the drug has seen multiple clinical failures in label-expansion efforts, included unsuccessful trials in colorectal and pancreatic cancer.

Incyte has another JAK1 inhibitor, itacitinib, in a pair of Phase II trials for GVHD.

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Array Celebrates BEACON Of Hope For Anti-BRAF/MEK/EGFR Triplet In Colorectal Cancer

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Overall survival data from **Array BioPharma Inc.**'s Phase III BEACON CRC safety lead-in trial of its BRAF inhibitor encorafenib, MEK inhibitor binimetinib, and **Eli Lilly & Co./Merck KGaA**'s anti-EGFR antibody *Erbitux* (cetuximab) suggest the triplet combination could prove valuable as a treatment for BRAF V600E-mutant metastatic colorectal cancer (mCRC).

Array reported at the European Society of Medical Oncology's gastrointestinal cancer conference (ESMO-GI) in Barcelona June 23 that the combo had a 62% observed overall survival rate at one year from the 30-patient safety lead-in of BEACON CRC, which investigated efficacy as well as safety. Median overall survival had not yet been reached. Presenting the study, Axel Grothey of the Mayo Clinic's division of hematology/oncology noted that with current approved standards of care half of patients with BRAF-mutant mCRC will succumb to their disease within four to six months. BRAF-mutant CRC accounts for around 10%-15% of CRC cases.

Median progression-free survival (PFS) for patients treated with the triplet was eight months (95% CI 5.6-9.3), and was similar between patients receiving one prior line of therapy and those receiving two prior lines of therapy. The current standard of care benchmark in this patient population is about two months.

The confirmed overall response rate was 48%, and among patients who only received one prior line of therapy it was 62%.

Array reported that the triple combination was generally well tolerated with no unexpected toxicities.

FUTURE STANDARD OF CARE?

"Every parameter, whether it's response rate, progression-free survival or overall survival, does compare favorably with chemotherapy data, standard of care, but also over the results that we've seen with encorafenib plus cetuximab. So there seems to be the idea that a triplet could be superior to the doublets of a BRAF inhibitor plus an EGF receptor inhibitor. In the Phase III study, we'll actually try to show exactly that," said Grothey. "I think this has a great potential to really become a new standard of care in this setting."

"The efficacy data presented for the safety lead-in phase of the study are indeed very promising. Furthermore, the tolerability of the triple combination is also encouraging," commented Hardik Patel, therapeutic area director for oncology with Datamonitor Healthcare. "Although we will have to wait for the results of the randomized portion of the study to definitively outline the magnitude of benefit this combination has, these results bode well for its chances of approval for BRAF V600E-mutant CRC patients."

Array is enrolling patients for the randomized portion of the BEACON CRC trial, evaluating patients with BRAF V600E-mutant metastatic CRC whose disease has progressed after one or two prior regimens in the metastatic setting in one of three arms: triplet therapy with encorafenib, binimetinib and cetuximab; doublet therapy with encorafenib plus cetuximab; and investigator's choice of either irinotecan/cetuximab or FOLFIRI/cetuximab. The estimated enrollment is for 615 patients with 205 to be assigned to each arm, to be fully enrolled by the end of 2018, with an estimated completion date of July 2019 and an overall survival endpoint. Grothey noted that FOLFIRI-cetuximab and irinotecan-cetuximab represent "from a regulatory perspective, the established control worldwide in the US, in Japan and in Europe."

The ESMO-GI presentation also referenced updated mature Phase II results for encorafenib plus cetuximab, showing a median overall survival of 9.3 months, median progression free survival of 4.2 months and an overall response rate of 24%. A more detailed presentation will take place at a future medical meeting.

APPROVALS ON THE HORIZON

Array is in discussions with regulators for accelerated approval in BRAF-mutant mCRC. CEO Ron Squarer said the company was looking at the prospect of conducting an interim analysis on a subset of the full Phase III patient population, potentially assessing surrogates "like a durable response or PFS."

And the company looks likely to study its triplet also in the front-line setting for BRAF-mutant mCRC: Chief Medical Officer Victor Sandor commented at ESMO-GI that "we're very excited by the prospect of doing that." He said the firm was still working out how to approach conducting clinical trials in the first line from a regulatory point of view, suggesting that options could "range from doing sort of small randomized studies to even potentially looking at trying to show a good response rate that's durable in a single-arm study." Grothey added: "This is really targeting the underlying oncogene mechanism of this cancer, so it really screams for a first-line treatment."

The combination is ahead of **Novartis AG**'s BRAF/MEK combination *Tafinlar* (dabrafenib)/*Mekinist* (trametinib) combination, which already is approved in melanoma, but is only in Phase I/II for BRAFV600E-positive CRC and CRC with secondary resistance to prior anti-EGFR treatment, in a trial begun in 2012 with an estimated primary completion date of October 31, 2018, according to clinicaltrials.gov. That trial includes a Phase II part with three arms for comparison: dabrafenib plus **Amgen Inc.**'s *Vectibix* (panitumumab); trametinib plus dabrafenib plus panitumumab; and chemotherapy (FOLFOX, FOLFIRI or irinotecan with or without *Vectibix* or **Roche**'s *Avastin* (bevacizumab)).

The combination of encorafenib and binimetinib already is shaping up as a strong likely competitor in melanoma with compelling updated overall survival data from the Phase III COLUMBUS trial in BRAF-mutant advanced melanoma recently reported. US approval is expected by the end of June in melanoma. Read the full article here

Separately, binimetinib is being investigated in combination with **Merck & Co. Inc.**'s PD-1 checkpoint inhibitor *Keytruda* (pembrolizumab) and chemotherapy in first- and second-line CRC and with **Bristol-Myers Squibb Co.**'s *Opdivo* (nivolumab) and *Yervoy* (ipilimumab) in second- and third-line RAS-positive CRC.

Array BioPharma licensed back rights to binimetinib and encorafenib from Novartis in 2015.

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HVIVO Seeks Big Pharma Partner For 'Phase III-Ready' Universal Flu Vaccine

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Speaking after unveiling positive Phase IIb data on the universal flu vaccine candidate FLU-v, Trevor Phillips, executive chairman of UK firm hVIVO, told *Scrip* the company expects to begin partnering talks shortly with big pharma companies operating in the vaccines space.

The main players in the seasonal and pandemic flu vaccines market are **Sanofi**, **GlaxoSmithKline PLC**, **Merck & Co. Inc.**, **CSL Ltd.**, **AstraZeneca PLC** and **Pfizer Inc.**.

Phillips said various parties had approached hVIVO at recent conferences, expressing interest in the Phase II data, and the aim was now to secure a deal "in the very near future." In the event that it is not possible to license the product out or to sell the Imutex joint venture that has developed FLU-v (which is 49% owned by hVIVO and 51% by **SEEK**), the partners will seek non-dilutive funding for ongoing development, from bodies such as the World Health Organization, National Institutes of Health, BARDA or the UK government.

The company announced that the Phase IIb FLU-v 003 field study met its primary and secondary endpoints, inducing T- and B-cell immunological responses versus placebo at 42 and 180 days post vaccination in healthy volunteers. The randomized, double-blind, single-center trial, funded by the EU under the European Universal Influenza Vaccines Secured Consortium (UNISEC) project, tested 176 subjects aged 18-60 randomized to four arms: a single adjuvanted dose of FLU-v versus adjuvanted placebo and two non-adjuvanted FLU-v doses administered 21 days apart versus non-adjuvanted placebo. The single adjuvanted dose produced the strongest response in terms of T- and B-cell response and number, severity and duration of symptoms.

Phillips noted that there was a 60% reduction in influenza infections in the people receiving a single dose of FLU-v, and an 83% reduction in the severity of the symptoms of those who were infected who received the single dose (although the study was not powered to show significance). "So not only did we reduce the risk of being infected, but those who were infected had a very downgraded illness which is exactly what the vaccine is designed to do," he said. The partners noted that FLU-v was safe and well tolerated, with the main adverse events being mild and moderate, and severe ones at the site of injection only. The adjuvant formulation was associated with an increased rate of transient injection-site reactions.

With only 17 people confirmed with flu infection, though, the results need verifying in a larger Phase III trial, of the order of 10,000 patients or more. However, the Phase IIb studies show that the single adjuvanted dose of FLU-v would be the one to take forward, Phillips said.

STUDY 004

The data from the field study has boosted hopes for FLU-v after earlier initial data from a separate Phase IIb study run by the NIH's National Institute of Allergy and Infectious Diseases (NIAID) failed to reach statistical significance in its primary endpoint, even though it trended towards statistical significance. At the time the company noted that further sample testing was ongoing; Phillips said the final primary endpoint result from those tests was expected to be announced in the next few weeks, after which he hoped a big pharma partner could be secured. That study (004) was a flu challenge study in which 123 healthy volunteers were exposed to flu in hVIVO's quarantine facilities; the 003 study was conducted in the real world.

"We had previously written of FLU-v on the back of the mixed data from the challenge chamber study [004], but this new information based on a real world study of healthy volunteers prompts us to reconsider this," Numis analyst Paul Cuddon commented in a June 18 note. Numis holds a long position of more than 0.5% in hVIVO and has received payment for investment banking services from hVIVO in the past 12 months.

Phillips and Gregory Stoloff, CEO of London-based SEEK, explained that FLU-v targets influenza A, B and pandemic strains with a standalone, single injection expected to provide protection for three to five years or more. Unlike some other vaccines in development, it is not designed as a booster to current seasonal vaccines given annually, and need not be linked to or limited by annual vaccines.

Rival UK firm **Vaccitech**, a spin-out of the University of Oxford, is developing a prime boost universal flu vaccine. *(Also see "Vaccitech Will Seek Partners For Its Universal Flu Vaccine" - Scrip, 16 Jan, 2018.)* Other firms working on universal flu vaccines include big hitters like **Janssen R&D LLC**, GlaxoSmithKline and Sanofi in collaboration with **SK Chemicals Co. Ltd.** of South Korea, and small players like **Inovio Pharmaceuticals Inc.**, which has announced positive preclinical results, and **BiondVax Pharmaceuticals Ltd.** of Israel, which has tested its M-001 peptide vaccine candidate in six Phase I/II and Phase II trials in 698 participants and is preparing a Phase III trial. *(Also see "Israel's BiondVax To Take 'More Global View' With NASDAQ-Only Listing" - Scrip, 31 Aug, 2017.)*

FLU-v is an equimolar combination of four individual synthetic polypeptides covering conserved immunogenic regions in M1, M2, NP-A and NP-B proteins inside and on the surface of flu proteins.Other vaccines that target HA head/stem or stalk only targets on the surface of the flu protein are specific to particular strains.

LOW-COST MANUFACTURING

As a freeze-dried chemical powder made up at point of administration with water and a water/oil-based emulsion adjuvant, it is stable and does not require cold chain distribution, Stoloff said. The synthetic manufacturing process can be carried out year-round at low cost in existing chemical factories without the need for specialized plants. The time it takes to manufacture current seasonal vaccines means that they are based on estimated forecasts about the strains that are expected to prevail during a flu season, which may be more or less accurate at the time they are actually used.

Imutex is also developing a vaccine that creates an immune response in humans

against mosquito saliva, to prevent infection with mosquito-born illnesses including Zika, malaria, dengue and West Nile virus.

Another company developing synthetic vaccines is Emergex Vaccines.

Phillips said hVIVO, whose CEO Kym Denny departed in April, hoped to "monetize" FLU-v and invest the funds in growing its business as a specialized development services company. "We're experts in the development of human challenge models using RSV [respiratory syncytial virus], influenza or common cold. We've been running those services for a long time now: the company was founded in 1989 and went public in 2012. We're looking to broaden the horizon now, beyond viral challenge for the development of antivirals, to become the development services organization for airway diseases." Phillips, who was formerly chief operating officer for UK firm **Vectura Group PLC**, which specializes in formulation, device and development of inhaled therapeutics, said hVIVO would move into asthma and COPD.

"If we are able to gain a lot of benefit from monetization of FLU-v we might seek to do something more strategic … possibly acquiring or combining with other businesses, to further enhance the service offerings that can be made available and then build a really strong airways disease organization," he said.

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Erytech Pulls Graspa ALL Filing In The EU

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It will be quite a while yet before France's **Erytech Pharma SA** gets a product on the market after pulling its European submission for *Graspa* (eryaspase) for acute lymphoblastic leukemia (ALL) and deciding that solid tumors, particularly pancreatic cancer, represent the best way forward for the compound.

The Lyon-headquartered group said in a statement that "despite having observed favorable efficacy results and safety profile in multiple clinical trials of eryaspase in patients with ALL," it now believes, based on recent feedback from the regulators in Europe and the US that "significant additional investment would be required in order to seek regulatory approval" for the therapy, which consists of the enzyme L-asparaginase (L-ASP) which is encapsulated inside donor-derived red blood cells.

Erytech added that "in the context of the rapidly changing and increasingly competitive landscape with newly-approved treatment options for ALL, the regulatory requirements," and what the company "observes to be a limited market opportunity," it has ceased further clinical development efforts in this indication.

Erytech has also decided to withdraw its European marketing authorization application and the resources that will become available as a result of this decision will be allocated to "significantly larger unmet medical needs and market opportunity for the potential treatment of solid tumors." On a conference call, CEO Gil Beyen said "it is a pity" to be exiting ALL "and the European filing put us on the map," as well as providing proof of concept but the move is strictly a business one, given the small and shrinking ALL market.

He added that around $20m would be freed up from jettisoning the ALL work, some of which would be used on a Phase III trial of Graspa combined with chemotherapy in patients suffering from second-line metastatic pancreatic cancer, which is expected to begin enrollment in the third quarter of 2018. Enrollment for a Phase II trial in first-line pancreatic cancer should commence in the first half of 2019.

The decision to quit the ALL space got the thumbs-up with analysts at Jefferies. In an investor note, they said that the decision to focus on Graspa for solid tumors "is logical from a commercial and strategic standpoint," although it "removes a possible near-term sentiment boost from EU approval," while also validating Erytech's technology platform for encapsulating therapies inside red blood cells which is called ERYCAPS.

The broker had expected potential EU approval by the end of 2018 for ALL relapsed/refractory patients or those hypersensitive to current L-ASP therapies, and a global Phase III was also to be initiated this year. Still, Jefferies added that given the rapidly evolving ALL market with novel therapies, "the commercial opportunity is insufficient to justify the spend."

The aforementioned novel therapies include Novartis' *Kymriah* (tisagenlecleucel) which became the first chimeric antigen receptor T cell (CAR-T) therapy to receive US regulatory approval in August 2017 for B-cell precursor ALL. Only last week, European regulators awarded Amgen's bispecific T-cell engager (BiTE) *Blincyto* (blinatumomab) full approval for Philadelphia chromosome-negative (Ph-) relapsed or refractory B-cell precursor ALL, while Pfizer's CD22-directed antibody-drug conjugate *Besponsa* (inotuzumab ozogamicin) is also approved for that indication.

The Jefferies analysts spoke about the compelling benefit in pancreatic cancer shown to date with Graspa, citing data which revealed that the drug significantly reduced the risk of progression-free and overall survival by 41% and 40%, respectively, in the all-comer analysis of a Phase IIb second-line pancreatic cancer study. They believe "there remains a chance of an expedited regulatory path in Europe," but conservatively assume launches in 2022 and peak worldwide sales of $500m.

Erytech chief financial officer Eric Soyer said on the conference call that the company had enough cash - €171.8m as of March 31 this year - to keep operations going through 2020/21 and was constructing a large-scale manufacturing facility in Princeton, New Jersey and expanding its capacity in Lyon. Both plants are expected to be operational for clinical production at the expanded capacity in the first quarter of 2019.

In addition to pancreatic cancer, a Phase II trial in triple negative breast cancer is expected to commence by the fourth quarter of 2018 and Beyen added that Erytech was also looking at Graspa for aggressive tumors with high rates of metastases – these include colorectal and ovarian cancers, as well as mesothelioma and hepatocellular carcinoma.

While analysts were pleased with Erytech's sole focus shifting to solid tumors, investors were less than impressed and the company's stock fell just over 30% to close at €10.90.

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New Drugs Jockey For The Multi-Billion Dollar CDK4/6 Pie

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Three cyclin-dependent kinase (CDK) 4 and 6 inhibitors are now on US market for the treatment of hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2-) advanced or metastatic breast cancer in various combinations with hormonal therapy, setting the category up for a competitive show down.

Novartis AG's *Kisqali* (ribociclib) and **Eli Lilly & Co.**'s *Verzenio* (abemaciclib) are the drugs that are coming from behind to take on the dominant leader in the category, **Pfizer Inc.**'s *Ibrance* (palbociclib), which had a more than two-year head start in the market. Another drug maker, **G1 Therapeutics Inc.**, is working to develop what it believes could be a best-in-class CDK4/6 inhibitor that could offer continuous dosing with less toxicity. The company's G1T38 is being tested in a Phase I/II trial in combination with fulvestrant, showcasing the lengthy tailwind the company believes the category will have.

ROOM FOR MULTIPLE BLOCKBUSTERS

Novartis and Lilly hope to build Kisqali and Verzenio into blockbuster brands mirroring Ibrance, which generated an impressive $3.13bn in 2017, its second full year on the market. Forecasts for the category suggest the goal isn't out of reach. Sales of CDK4/6 inhibitors are expected to reach $8bn in 2024 in the US, Japan and five major European markets, according to Datamonitor Healthcare.

The commercial market is attractive because HR+/HER2- breast cancer is the most common form of breast cancer, accounting for about 70% of all cases; advanced and metastatic breast cancer has spread to the lymph nodes or other sites. HER2- breast cancer tends to be less aggressive than HER2+ breast cancer, however, where **Roche**'s *Herceptin* (trastuzumab) is the standard of care.

Building new blockbusters in a category dominated by Ibrance will be a commercial test for Novartis and Lilly, however. Ibrance is expected to maintain a significant lead; sales are expected to peak at $4.4bn in the US, Japan and five major EU markets in 2022, while Verzenio and Kisqali are expected to reach $2.4bn and $2.5bn in sales, respectively, according to Datamonitor. Kisqali generated $44m in the first quarter of 2018, while Verzenio generated $29.7m.

"Verzenio and Kisqali are expected to see significant future uptake and become blockbuster drugs in HR+/HER2- breast cancer, but Ibrance is likely to remain the leader," Datamonitor analyst Zachary McLellan predicted.

Even Novartis Oncologyy CEO Liz Barrett acknowledged the challenge for Kisqali facing off against Ibrance.

"I really absolutely believe it will continue to be an important medicine for us," she said in an interview. "Do I think it's going to overtake Ibrance in the US? No, and I think we understand that."

All three drug makers are focused on expanding the market of treated patients, carving out unique niches for their products within the therapeutic area and moving CDK4/6 treatment up earlier in the course of the disease.

While the safety and efficacy profile of CDK4/6 inhibitors has come into focus with data from many large Phase III trials, there are still outstanding questions about how the category will develop. Whether CDK4/6 inhibitors should become the standard of care for the first-line treatment of advanced breast cancer or in pre-menopausal as well as postmenopausal women were topics of discussion at the American Society of Clinical Oncology meeting June 1-5.

Another looming question is if the impressive progression-free survival benefits that have been seen in clinical trials will translate to improvements in overall survival. No survival data from any of the Phase III studies of the three drugs has yet read out, as HR+/HER2- breast cancer is slow growing. Further, no biomarkers have been defined to help target treatment to the right patients, and perhaps more pressing, mechanisms of resistance are not well understood, and the search is on for what patients could move to next after progressing on CDK4/6 inhibitors.

MOVING UP IN FIRST-LINE SETTING

New data presented on the class of drugs at ASCO helped to color in the lines even more and flesh out the CDK4/6 portrait. Even though the three drugs are each approved for slightly different indications, based on differences in clinical trial patient populations, they appear to be viewed by physicians as similar.

As Penn Medicine Abramson Cancer Center's Angela DeMichele pointed out during a cross-comparison of Phase III data at ASCO, "We see very similar magnitude of effect and hazard ratios across these trials." The toxicity profile is also now well understood, she said, although Verzenio appears to have more gastrointestinal toxicity than Ibrance or Kisqali.

Consensus appears to be moving increasingly toward earlier treatment with CDK4/6 inhibitors for advanced breast cancer, as new data builds the case for earlier treatment rather than waiting until after patients progress on hormone therapy.

"It's simply an exercise in adding up what we know about PFS in first-line and second-line," DeMichele said. "In the absence of a CDK inhibitor, we see that total is about 24 months. Using updated data over the past year, we see that if we give the CDK4/6 inhibitor in the second line we extend that to about 30 months, and in the first line, we extend it to about 35 months."

"With maturation of the data, we are starting to see that perhaps we are giving more time if we give it in the first-line," she said. But, she added, "at this time, I think this is still an individual consideration, weighing the desire for time without treatment."

Dennis Slamon, director of clinical/translational research at UCLA's Jonsson Comprehensive Cancer Center, said he would recommend a CDK4/6 inhibitor in the first line-setting based on emerging data, and that a combination with fulvestrant would be his preferred choice. He said that decision was based on the results of the Phase III FALCON data evaluating AstraZeneca's Faslodex (fulvestrant) as monotherapy in HR+/HER2- breast cancer, as well as combination data of fulvestrant and CDK4/6 inhibitors. Slamon was the lead author on Novartis' MONALEESA-3 trial, presented at ASCO, studying the combination of fulvestrant and Kisqali in first-line advanced breast cancer.

In an interview, Lilly VP-Oncology, North America Eric Dozier agreed there is a movement toward CDK4/6 becoming standard of care in the first-line setting. "We would expect that marketplace to continue to grow," he said.

Ibrance, Kisqali and Verzenio each carry slightly different indications, based on the design of the supporting Phase III trials. Small differences could give one drug a possible advantage in certain patient populations.

Ibrance, approved in February 2015, is cleared for advanced or metastatic cancer in combination with an aromatase inhibitor as initial endocrine therapy in postmenopausal women; or with fulvestrant in women with disease progression following endocrine therapy. Kisqali, approved by FDA in March 2017, is indicated in combination with an aromatase inhibitor as an initial endocrine-based therapy in postmenopausal women. [A#SC098389] Novartis presented Phase III data at ASCO from MONALEESA-3 showing Kisqali in combination with fulvestrant demonstrated superior progression-free survival versus fulvestrant alone in first-line postmenopausal women, potentially a unique indication for Kisqali if it is approved by FDA.

Verzenio, meanwhile, approved in September 2017, is the only CDK4/6 inhibitor approved with a continuous dosing schedule. It has been approved in three settings: in combination with an aromatase inhibitor as initial endocrine-based therapy, in combination with fulvestrant for women with disease progression following endocrine therapy, and as monotherapy after disease progression following endocrine therapy and prior chemotherapy.

Dozier highlighted Verzenio's continuous daily dosing schedule as a differentiator and said Lilly believes the drug could offer an advantage among certain patients with a poor prognosis, where Verzenio has shown to perform well in sub-analyses.

At ASCO, Lilly presented data from MONARCH-2 in a subset of pre/peri-menopausal patients, who showed improvements in PFS and overall response rate when treated with abemaciclib plus fulvestrant and a GnRH agonist versus patients who received fulvestrant plus placebo. Despite the recent launches of Verzenio and Kisqali, Pfizer says it is not concerned that any new data will upend its solid lead in the marketplace. "There is no data that has emerged from ribociclib or abemaciclib that makes us concerned there may be an information gap or an efficacy gap with what we have with Ibrance," Pfizer's Oncology Chief Development Officer Mace Rothenberg said in an interview.

"All of these things are filling in knowledge gaps, providing an even greater level of evidence of the role of CDK inhibitors," he said. "How one group or one sponsor carves out a patient population may be different from what another company does, and that is expected."

EXPANDING USE

Novartis Oncology's Barrett credited the Swiss drug maker with under-taking a broad Phase III program, including studies like MONALEESA-3 in the first-line setting with fulvestrant and MONALEESA-7, a Phase III trial that read out positively in December, testing Kisqali in combination with tamoxifen and an aromatase inhibitor in pre- and peri-menopausal women who have not previously received endocrine therapy for advanced disease.

Barrett knows the category well, having built Ibrance into a blockbuster brand while leading Pfizer's oncology business. She moved to Novartis in February and is tasked with overseeing the launch of Kisqali.

In the US, she said Novartis is focused on expanding the category, since only 50% of first-line patients are treated with a CDK4/6 inhibitor currently. Outside the US, Novartis is on more equal footing with Pfizer.

"Physicians are still saying for my visceral patient, I want to use chemotherapy, I want to use an aromatase inhibitor, but in reality if you look at the clinical data, every patient population benefits," Barrett said. "So we still have a ways to go, and that's where we are focused." Data like MONALEESA-3 and -7 also build the case, she said, noting, "They also give physicians another reason to believe they should be using CDK4/6 in every patient."

Novartis has also developed a combination pack of Kisqali and *Femara* (letrozole), the Kisqali Femara Co-Pack, which it thinks offers added convenience for physicians prescribing that particular combination.

Despite the competitive dynamics with three similar drugs now on the market, payer push back in oncology remains minimal. It has been suggested that some categories like CDK4/6 and PARP inhibitors could be testing grounds for more payer management, but so far, that doesn't seem to be a big issue for drug makers.

"None of the payers are managing this category. I don't think they will," Barrett said. Still, she said Novartis is starting to rebate more in oncology when it comes to negotiations with group purchasing organizations or large community practices because competitors are. All three CDK4/6 inhibitors are priced roughly in line at a wholesale acquisition cost of just around $11,000 per month.

Another future area for growth could be the adjuvant setting. Pfizer is running the Phase III PALLAS trial, testing Ibrance as an adjuvant therapy in combination with endocrine therapy versus endocrine therapy alone in early breast cancer patients. Lilly is running the MonarchE trial, similarly testing Verzenio plus standard endocrine therapy in adjuvant breast cancer.

WHAT COMES NEXT?

Drug makers are thinking now about what comes next after patients progress following treatment with a CDK4/6 inhibitor and how to address what will eventually become the pool of patients that need another option.

"I want to see a biomarker that will tell me early enough that these patients are going to progress on ribociclib so I can give them the next best treatment as the progression in approaching," Novartis' Global Head of Oncology Development Samit Hirawat said in an interview ahead of ASCO.

One hope has been PI3K inhibitors targeting a common genetic abnormality in breast cancer known as PIK3CA mutations, which occur in about 40% of HR+/HER2- breast cancer. Roche presented only modestly positive data, however, from a Phase III SANDPIPER trial at ASCO testing the PI3K inhibitor taselisib in combination with fulvestrant in breast cancer, showing the combination slowed PFS by just two months versus hormone therapy alone. Roche said it doesn't plan to pursue a regulatory filing in breast cancer, based on the results, but said it is continuing to study the pathway.

Novartis, meanwhile, is also studying a PI3Kα inhibitor, alpelisib, in Phase III in HR+/HER2- advanced breast cancer. Barrett said she was reassured by the Roche data at ASCO because of the activity, and noted that taselisib and alpelisib have differences. "We still feel we have a good opportunity with our P13K," she said.

Pfizer's Rothenberg had another view on it. "Even though biologically it makes sense, and it is such an attractive pathway to hit, are the clinical data pointing toward or away from it," he questioned. Pfizer is studying a dual inhibitor of PI3K and mTOR, gedatolisib, in solid tumors instead, including in combination with Ibrance and hormonal therapy. Lilly is also studying a dual PI3K/mTOR inhibitor.

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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

Selected clinical trial developments for the week 15–21 June 2018

LEAD COMPANY/PARTNER	COMPOUND	INDICATION	COMMENTS
PHASE III SUSPENDED			
Teva Pharmaceutical Industries Ltd.	fremanezumab	migraine	ENFORCE; endpoints unlikely to be met for chronic cluster headache.
PHASE III RESULTS PUBLISHED			
Fennec Pharmaceuticals Inc.	sodium thiosulfate	hearing loss - chemotherapy-induced	PEDMARK study in the *NEJM*.
Gilead Sciences Inc.	*Biktarvy* (bictegravir/ emtricitabine/tenofovir alafenamide)	HIV/AIDS	GS-US-380-1844 non-inferiority trial in *The Lancet*.
Gilead Sciences	*Biktarvy* (bictegravir/ emtricitabine/tenofovir alafenamide)	HIV/AIDS	GS-US-380-1878 non-inferiority trial published in *The Lancet HIV*.
PHASE III INTERIM/TOP-LINE RESULTS			
Nanobiotix SA	NBTXR3	sarcoma	Act.In.Sarc trial; positive results for soft tissue sarcoma.
Shire PLC	*Cinryze* (IV) (C1 esterase inhibitor [human])	hereditary angioedema (HAE)	Study 0624-301 pediatric study. Lessened the severity of attacks.
Novo Nordisk AS	oral semaglutide	Type 2 diabetes	PIONEER 4 and PIONEER 7; positive results.
Bristol-Myers Squibb Co.	*Orencia* (abatacept)	lupus nephritis	Failed to meet its primary endpoint.
UPDATED PHASE III RESULTS			
Rigel Pharmaceuticals Inc..	*Tavalisse* (fostamatinib)	immune thrombocyto-penic purpura (ITP)	Study 049; represents a treatment option for adult ITP.
Alexion Pharmaceuticals Inc.	ravulizumab (ALXN1210)	paroxysmal nocturnal hemoglobinuria (PNH)	Noninferiority to eculizumab on primary and key secondary endpoints.
Geron Corp.	imetelstat	myelodysplastic syndrome	IMerge study; encouraging results.
Johnson & Johnson	esketamine	major depressive disorder	SUSTAIN-1 AND -2, TRANSFORM-2 AND -3; updates at ECNP.
Alnylam Pharmaceuticals Inc.	patisiran	transthyretin-related hereditary amyloidosis	APOLLO; positive results for primary endpoint.
Celgene Corp.	*Pomalyst* (pomalidomide)	multiple myeloma	OPTIMISMM: significant and clinically meaningful PFS improvement.
CSL Ltd.	*Privigen* (immune globulin)	chronic inflammatory demyelinating polyneuropathy	PATH; significantly reduced relapse rate.
Daiichi Sankyo Co. Ltd.	quizartinib	acute myelogenous leukemia	QuANTUM-R; significantly prolonged OS.
Novartis AG	*Cosentyx* (secukinumab)	axial spondyloarthritis	MEASURE 1 and 2; sustained improvement.
Novartis AG	*Kymriah* (tisagenlecleucel)	diffuse large B-cell lymphoma	JULIET study; strong efficacy with durable responses.
Seattle Genetics Inc.	*Adcetris* (brentuximab)	Hodgkin's lymphoma	ECHELON; improved outcomes for advanced patients.
UCB SA	*Cimzia* (certolizumab pegol)	psoriatic arthritis	RAPID-PsA; long-term positive results.

AbbVie Inc.	*Venclexta* (venetoclax)	multiple myeloma	MURANO trial; encouraging findings.
Amgen Inc.	*Evenity* (romosozumab)	osteoporosis	FRAME Study; substantially higher BMD T-score increases after one year.
Celgene Corporation	*Revlimid* (lenalidomide)	indolent non-Hodgkin's lymphoma	RELEVANCE; lenalidomide plus rituximab vs rituximab + chemotherapy not superior but different toxicity profile.
Novartis	*Jakavi* (ruxolitinib)	myelofibrosis	JUMP; may lead to greater benefits.
Novartis	*Cosentyx* (secukinumab) sc	psoriatic arthritis	FUTURE 5 study.
Novartis	biosimilar *Erelzi* (etanercept), GP2015	rheumatoid arthritis (RA)	EQUIRA; positive switching data in moderate-to-severe RA.
Novartis	biosimilar *Zessly* (infliximab).	rheumatoid arthritis	REFLECTIONS B537-02 study; positive switching data.
Verastem Inc.	duvelisib	chronic lymphocytic leukemia/small cell lymphocytic Lymphoma	DUO Extension study; further support oral duvelisib monotherapy as an effective oral treatment option.

Source: Biomedtracker

Johnson & Johnson group worldwide chairman ***Sandra Peterson*** is leaving the business, effective Oct. 1, after more than five years with the company. Peterson, who reports to CEO ***Alex Gorsky***, was hired in 2012, primarily with the task of turning around J&J's Consumer business, and addressing IT and supply-chain issues. Before that she was chairman & CEO of Bayer CropScience AG in Germany, and previously served as CEO of Bayer Medical Care and president of Bayer HealthCare AG's Diabetes Care Division. To help with the transition, J&J is making a series of additional leadership changes, all effective from July 2: ***Joaquin Duato***, executive vice president, worldwide chairman, pharmaceuticals, and ***Paul Stoffels***, executive vice president, chief scientific officer of Johnson & Johnson, have been appointed to the position of vice chairman of the executive committee. Duato will be responsible for the pharmaceuticals and consumer sectors, as well as supply chain, IT, global services, and the health and wellness businesses. Stoffels will be responsible for pharmaceutical esearch & development, global public health, the office of the chief medical officer, external innovation, pharmaceuticals business development and healthcare technology. Other promotions are: ***Ashley McEvoy*** to executive vice president, worldwide chairman, medical devices; ***Jennifer Taubert*** as executive vice president, worldwide chairman, pharmaceuticals; ***Kathy Wengel*** as executive vice president, chief global supply chain officer; and ***Michael Sneed*** as executive vice president, global corporate affairs and chief communication officer.

Following the announcement of the planned departure of ***Sophie Kornowski-Bonnet*** as **Roche**'s head of Roche Partnering on 31 July, ***James Sabry***, currently head of partnering for Genentech Research and Early Development (gRED), has been appointed global head of partnering. This is a new role that combines the partnering functions for the two R&D units. Sabry will be based in Basel and assume his new role on 1 August 2018. Before joining Genentech in his current role in 2010, Sabry was CEO of a start-up biotech company and was founder and CEO of Cytokinetics, a biopharmaceutical company in the San Francisco Bay Area. Kornowski-Bonnet is leaving to pursue other opportunities.

Eric Ducournau will assume the position of chief executive officer of the **Pierre Fabre Group** on July 2, taking over from ***Bertrand Parmentier*** who is retiring. Ducournau has been CEO of Pierre Fabre Dermo-Cosmetics since his appointment by Mr. Pierre Fabre in October 2012. He joined the company in 2000 since when he has held positions of increasing responsibility, and was one of the co-founders of G5 Santé, an association of the biggest French pharmaceutical companies, and a member of the LEEM executive committee.

Eduardo Bravo has been appointed CEO of **Nordic Nanovector ASA**. He will take up the position on July 2 and be based in London, UK. Bravo brings more than 25 years' experience in the biopharmaceutical industry and was previously CEO of TiGenix, which is being acquired by Takeda Pharmaceutical Co. Ltd. Prior to joining TiGenix' predecessor, Cellerix, in 2005, Bravo held several senior management positions at Sanofi-Aventis and SmithKline Beecham. He is currently chairman of Vivet Therapeutics

Inthera Bioscience AG, a preclinical stage oncology company, has announced that three senior management team hires. ***Bernd Hentsch*** joins the company as chief development officer, ***Ralph Lindemann*** as chief scientific officer and ***Monique Schiersing*** as chief operating officer. Hentsch has held various senior positions in the European Biotech industry, most recently as chief development officer at 4SC AG, and TopoTarget. Lindemann joins from Merck KGaA and has 15 years of experience in translational research and drug discovery. Schiersing was previously investment director at the Roche Venture Fund, F. Hoffmann–La Roche AG's corporate venture fund.

The ***Dementia Discovery Fund*** (DDF) is has appointed ***Angus Grant*** as its CEO with effect from July 9. Dr Grant has more than 20 years' international experience in the regulation and development of pharmaceuticals. Most recently he served as Corporate Vice President, Business Development at Celgene, and before that, he held business development and regulatory affairs at Novartis, Merck KGaA/EMD, RPR/Gencell and SmithKline Beecham.

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