Company Focus
Analysts aren't surprised to see the Danish diabetes giant stalking Global Blood Therapeutics (p5)

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Hemophilia patients are loyal to brand-name clotting factors but a shakeup may be coming (p8)

Changes to NICE Timelines
New rules will allow NHS England to delay some new drugs for up to three years (p15)

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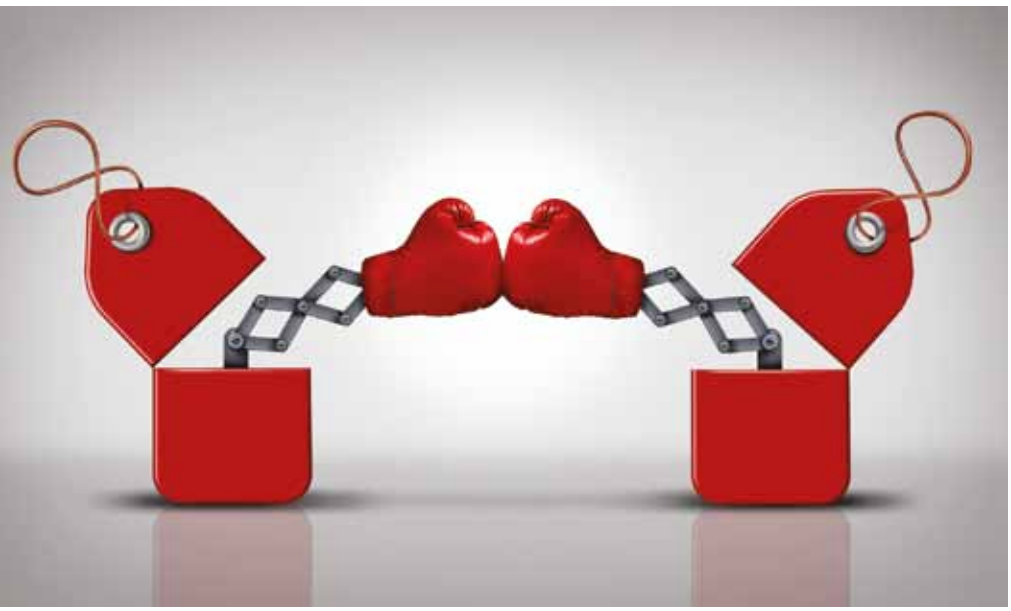
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Novartis Sets 'Flexible Pricing' For Kisqali To Compete Against Pfizer

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Novartis has packaged and priced Kisqali – the second CDK4/6 inhibitor approved in the US – to compete with Pfizer's Ibrance, which made the mechanism of action the standard of care in untreated metastatic HR+/HER2- breast cancer.

Novartis AG's *Kisqali* (ribociclib; LEE011) was approved on March 13 as the second drug of its kind in the first-line setting for certain breast cancer patients in the US – and it could have competition from a third next year – so the company has packaged and priced its product to compete with Pfizer Inc.'s first-to-market *Ibrance* (palbociclib).

Both drugs and Eli Lilly & Co.'s Phase III candidate abemaciclib are cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitors. The mechanism quickly became the front-line standard of care for post-menopausal women with hormone receptor (HR)-positive/human epidermal growth factor receptor-2 (HER2)-negative advanced or metastatic breast cancer – the populations for which Kisqali and Ibrance are approved. Similar profiles for the two drugs were seen in Phase III clinical trials that were stopped early for positive efficacy, so its appears that Novartis is looking to differentiate through its "flexible price structure."

Bill Hinshaw, head of Novartis US Oncology, revealed the price structure during a conference call with reporters on March 13, explaining that the wholesale acquisition cost (WAC) for a 28-day cycle (21 days on treatment followed by seven days off) is $10,950 for the 600 mg once-daily dose, $8,760 for the 400 mg dose and $4,380 for the 200 mg dose; a patient assistance program will be available for both insured and uninsured patients. The drug will be shipped to specialty and retail pharmacies as soon as March 14.

Hinshaw noted that Kisqali pricing responds to the need for prescribers to adjust dosing based on known cardiovascular, liver and hematologic side effects. Some cases of QT prolongation, AST and/or ALT elevation and high-grade neutropenia were reported in the Phase III MONALEESA-2 trial, which was the basis for the US FDA approval.

Novartis has formulated Kisqali in 200 mg capsules, making it easier for oncologists to lower dosing to the required 400 mg or 200 mg doses as needed to manage the CDK4/6 inhibitor's effects on heart rhythm, liver function and neutropenia – three items that prescribers must measure at certain points before and during treatment.

Hinshaw noted that Kisqali dosing can be reduced without treatment interruption – a luxury that oncologists don't have with Pfizer's Ibrance, which is formulated in 125 mg, 100 mg and 75 mg capsules and was launched in early 2015 with a WAC price per cycle of $9,850. Ibrance pricing in ex-US markets has come under pressure, particularly in the UK where its cost may limit access. The drug is under review in Japan.

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from the editor

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The term 'microbiome' has only really taken on any kind of currency since the early part of this century, but in the past few years it has become a regular feature of biopharma discussions. Referring to the totality of the micro-organisms (and their genetic material) in a particular environment, the human microbiome (and most commonly that of the gut) is increasingly the target of therapeutic R&D programs, and the raison d'être for a growing band of start-ups.

We have created an infographic (p14) on the industry's efforts in the field, which has attracted around $1bn in company funding since 2011. As with any hot topic, there are voices of caution and dissent; one panellist in a partnering function at a big pharma memorably declared at BIO last year that she might herself get *C. diff* if yet another microbiome proposition crossed her desk.

Scrip would like to hear the views of our readers: are you excited about the opportunity in this field? Or are you cautious about significant hurdles that you feel are being overlooked? Drop me an email.

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Is Amgen's FOURIER Enough For Physicians, Payers To Expand Repatha Use?
Detailed results presented at ACC show a reduction in risk of major adverse cardiovascular events, but perhaps not at the level hoped for by payers.
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Finance Watch: Two New VC Funds Raise $500m; One New US IPO; And Galena's 'Strategic Review'
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Deal Watch: Success Nets CytomX Another $200m From BMS, Up To $3.6bn For Milestones
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Mylan Clears Runway For US Herceptin Biosimilar Launch

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Mylan NV could be the first manufacturer to launch a biosimilar version of Roche's blockbuster breast cancer treatment Herceptin (trastuzumab) in the US. The company has an application for a version of trastuzumab pending at FDA with a user fee date of Sept. 3., and now the company has also cleared the crucial intellectual property hurdle.

Mylan announced March 13 that it has reached a patent settlement agreement and a licensing deal with Roche related to patents for Herceptin. The global license will provide a clear path for Mylan to commercialize trastuzumab globally (excluding Japan, Brazil and Mexico), the firm said. The catch is that the US launch timeline remains unknown. Mylan said the effective dates for launches in various markets under the agreement remain confidential, which means it is unclear how much, if any, delay Mylan and Roche might have negotiated beyond the FDA action date.

Mylan, meanwhile, agreed to withdraw its pending inter partes review (IPR) challenges against two US patents for Herceptin held by Roche's Genentech unit (patents 6,407,213 and 6,331,415).

Biosimilar sponsors face a tangled web of patent proceedings, which are one of the biggest hurdles to getting more biosimilars to market.

More clarity on the legal proceedings could come in 2017. The US Supreme Court agreed to hear a dispute between Amgen and Sandoz Inc. involving Sandoz's *Zarxio* (filgrastim) related to whether the Biologics Price Competition and Innovation Act's (BPCIA) "patent dance" is optional or mandatory and whether 351(k) sponsors must wait until licensure before providing 180-day notice of launch.

There has not been much legal precedent yet related to biosimilars in the US, so it remains to be seen how the IP issue will evolve.

There are many other versions of trastuzumab in development, and there is no guarantee that Mylan's product, developed with partner Biocon Ltd., will have a smooth regulatory review. Mylan updated investors on its pipeline during an investor overview March 1, highlighting biosimilars and complex small molecule drugs. The company said it has one of the broadest biosimilar pipelines in the industry, including a second product pending at FDA, a biosimilar to Amgen's *Neulasta* (pegfilgrastim), with an Oct. 9 action date.

There are as many as 19 different formulations of trastuzumab in development. Pfizer Inc. has completed Phase III testing of its formula and presented positive top-line results in December.

Approved in 1998, Herceptin is a backbone therapy for the treatment of women with HER2-positive breast cancer. Herceptin generated CHF6.78bn ($6.73bn) in 2016. The drug is one of Roche's top-sellers, behind *Rituxan* (rituximab) and *Avastin* (bevacizumab), which are also expected to face biosimilar competition, creating substantial headwinds for the Swiss pharma. Roche introduced an antibody-drug conjugate version, *Kadcyla* (ado-trastuzumab emtansine) in 2013.

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Blood Cancer Sector More Competitive After Keytruda Approval

The US FDA approval of Keytruda in its first hematologic cancer indication will put Merck & Co in a position to compete with Bristol-Myers Squibb, whose own checkpoint inhibitor Opdivo gained a similar, but not identical, marketing approval in classical Hodgkin lymphoma last year.

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Confirmation that checkpoint inhibitors are beneficial in the treatment of blood-borne cancers has come from the US approval of Merck & Co. Inc.'s anti-PD1 therapy *Keytruda* (pembrolizumab) for the treatment of patients with classical Hodgkin lymphoma refractory to other treatments, or who have relapsed after three or more prior lines of therapy. Previously the drug was only approved in solid tumors.

The approval, announced March 14, is the first for Keytruda in a hematologic malignancy, and Merck also highlighted that the additional indication is regardless of prior stem cell transplant or use of Seattle Genetics Inc.'s *Adcetris* (brentuximab vedotin). The approval comes nearly a year after Bristol-Myers Squibb Co.'s checkpoint inhibitor *Opdivo* (nivolumab) was approved in the US for a similar indication, although then the FDA specified that Opdivo therapy in relapsed and refractory classical Hodgkin lymphoma should follow treatment with autologous stem cell transplant and post-transplant brentuximab vedotin therapy.

In Europe, Opdivo was approved for the classical Hodgkin lymphoma additional indication in November 2016, while Keytruda is in Phase III studies for classical Hodgkin lymphoma.

Interestingly, Opdivo has just been knocked back by the UK's health technology assessment body, NICE, that asked in a preliminary assessment released March 13 for a revision of cost-effectiveness analyses versus standard of care, the use of UK data on standard of care, and data on the subsequent rate of allogeneic stem cell transplant. That could allow Keytruda to catch up some ground on the BMS drug, at least in the UK.

According to Datamonitor Healthcare senior analyst Dominique Fontanilla, the US approval is positive news for Keytruda, but is unlikely to have a major impact in terms of sales. Hodgkin lymphoma is relatively uncommon, with DMHC estimating there were 18,770 diagnosed cases in 2014 in the US, Japan, and the five major EU markets (France, Germany, Italy, Spain and the UK). Additionally, Keytruda's and Opdivo's approvals in the later line of treatments means the potential market size is even smaller.

However, Merck has started a large Phase III study (KEYNOTE-204) comparing Keytruda to the current standard of care Adcetris in patients with relapsed Hodgkin lymphoma, that could close any gap between Keytruda and Opdivo, Fontanilla commented.

Keytruda was cleared under the US's accelerated approval regulations for use in adult and pediatric patients with refractory classical Hodgkin lymphoma (cHL), or who have relapsed after three or more prior lines of therapy, based on the tumor response rate and the durability of that response in the KEYNOTE-087 study. In that study involving 210 patients, the overall response rate with Keytruda was 69% (95% CI: 62, 75) with a complete remission rate of 22% and a partial remission rate of 47%. Among the 145 responding patients, the median duration of response was 11.1 months (ranging from zero to 11.1 months).

Keytruda is administered intravenously every three weeks until disease progression or unacceptable toxicity, or up to 24 months in patients without disease progression. This compares with a dosing schedule of every two weeks for Opdivo.

Keytruda was discontinued due to adverse reactions in 5% of 210 patients in the KEYNOTE-087 study, and treatment was interrupted due to adverse reactions in 26% of patients. The most frequent serious adverse reactions (>1%) were pneumonia, pneumonitis, pyrexia, dyspnea, GvHD and herpes zoster.

> The additional indication is regardless of prior stem cell transplant or use of brentuximab vedotin

There are few other options for patients with classical Hodgkin lymphoma who do not respond to a stem cell transplant, or use of brentuximab vedotin. "Treating their disease becomes more challenging," commented Dr Craig Moskowitz, clinical director in the division of hematologic oncology at the Memorial Sloan Kettering Cancer Center, in a Merck statement.

There are also far fewer patients with classical lymphoma; there are around 8,500 new cases reported every year in the US, with around 1,120 deaths, with the condition affecting patients at a relatively young age, predominantly adolescents and young adults. Fortunately, nearly three-quarters of patients are cured with chemotherapy and/or radiation.

In the past, the use of checkpoint inhibitors has been primarily focused on solid tumors such as non-small cell lung cancer. However, their use in blood cancers is now an active field of research, with for example Celgene Corp. and AstraZeneca PLC partnering on the development of the PD-L1 inhibitor durvalumab in hematologic cancers, and BMS studying Opdivo in multiple myeloma.

Merck also reported March 14 a three-month extension, to June 9, 2017, to the FDA's target action date on its sBLA for Keytruda use in previously-treated patients with advanced microsatellite instability-high (MSI-H) cancer. MSI-H is seen in around 15% of patients with colorectal cancer, and Merck recently submitted additional data and analyses to the regulator, that was considered a major amendment necessitating a three-month extension to the review. Merck could become one of the first companies to gain an approval for a checkpoint inhibitor in colorectal cancer.

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Is Anemic Growth Sending Novo Nordisk After Global Blood Therapeutics?

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Once high-flying Novo Nordisk has been sending out M&A signals as it seeks a solution to weak growth, so analysts aren't surprised to see the Danish diabetes giant stalking US-based Global Blood Therapeutics.

Novo Nordisk AS's long and steady financial run on self-generated diabetes and obesity products is flagging – and the Danish group has acknowledged that it needs to revitalize its other product lines to generate fresh revenue growth – so reports it is interested in California-based Global Blood Therapeutics Inc. have not surprised observers.

Reuters and Bloomberg, quoting unnamed sources, reported the South San Francisco-based sickle cell drug developer has been approached by Novo Nordisk. Neither Global Blood nor Novo Nordisk would comment to *Scrip* on the reports, but analysts say it makes sense for the Danish group to actively look outside for a bolt on to help it diversify beyond its aging diabetes franchise.

DIVERSIFICATION NEEDED

"I'm sure it's a calculated risk; in this case since Novo Nordisk's diabetes business is suffering, so they need to focus elsewhere and this acquisition can help them strengthen their blood offerings. Novo has avoided acquisitions in the past so this is a change of direction for them," commented Steven Muntner of Medtrack.

Rising competition and pricing pressures in the US and elsewhere led Novo Nordisk last October to slash its growth expectations for 2017 and increase R&D efforts, announcing expansion into new therapy areas and seek external deals for early-stage assets to bulk up its pipeline.

Its outlook reduction last autumn sent Novo Nordisk shares south. Berenberg analysts Mar. 6 said, "Novo's shares have not recovered from the profit warnings issued by the group in 2016. It is clear from guidance that 2017 will be a slow year, and there is a risk of Roche's new hemophilia drug emicizumab (ACE910) eroding sales of *NovoSeven*, and thus acting as a drag on 2018 and 2019 earnings." NovoSeven is Novo Nordisk's aging hemophilia drug whose sales have been sliding; the company doesn't yet have strong commercial response after it decided in September 2012 to discontinue the development of vatreptacog alfa, a fast-acting recombinant Factor VIIa analogue for hemophilia patients with inhibitors which had been in Phase III trials and had been seen until then as a replacement for blockbuster NovoSeven.

GLOBAL BLOOD BOLT-ON?

So could Global Blood Therapeutics help the Danish group respond to its current commercial gloom?

The loss-making company was founded in 2012 by Third Rock Ventures and launched an IPO in Aug. 2014. Before media reports of Novo Nordisk's interest in it, Global Blood Therapeutics had a market value of around $1.2bn.

It is developing drugs for blood-based diseases including sickle cell disease (SCD) and idiopathic pulmonary fibrosis. Analysts say acquiring the young company would provide positive additions to Novo Nordisk's portfolio. Of immediate interest is its product candidate known as GBT440, a hemoglobin modifier that binds to hemoglobin molecules. The oral, once-daily therapy for sickle cell disease is in double-blind Phase I/II clinical trialing and will enter a pivotal Phase III study in SCD called HOPE by the end of 2017, according to BioMedTracker. Like hemophilia, SCD is an orphan disease.

Since oxygenated sickle hemoglobin does not polymerize, Global Blood Therapeutics thinks GBT440 blocks polymerization and the resultant sickling of red blood cells. "With the potential to restore normal hemoglobin function and improve oxygen delivery, GBT440 may be capable of modifying the progression of SCD," the company says. GBT440 has both fast track and orphan drug designation from the FDA for treating patients with SCD and orphan status in Europe.

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'Novo Nordisk has avoided acquisitions in the past, so this is a change of direction for them'

"It's an interesting approach, changing the affinity of hemoglobin for oxygen, but the data are still somewhat preliminary at this point," BioMedTracker analyst Peter Chang said, adding that the drug did increase hemoglobin appreciably "and could well impact symptoms, though the study was quite small and there is only limited side effect information so far."

Analysts said Novo Nordisk had alerted the investment community last year during its third quarterly earnings update that it was thinking about M&A.

"They were looking to do bolt-on acquisitions, which they said was more realistic than a large acquisition, and get slightly out of their core and add competencies, in addition to their growth in emerging markets for diversification. So it does look like this would fit into their strategy in that sense," Chang said.

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Ackman 'Throws In The Towel' – What's Next For Valeant?

Valeant's prospects were dim with or without Pershing Square's continued backing, but at least one analyst says Ackman's departure sends a signal that business won't rebound at the Canadian specialty pharma any time soon.

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The business outlook at Valeant Pharmaceuticals International Inc. is uncertain at best and the sell-off by Pershing Square Capital Management of its nearly 10% stake in the Canadian specialty pharma doesn't necessarily make the situation any worse – but only because Valeant's prospects are so bleak to begin with.

Pershing Square, led by billionaire activist investor Bill Ackman, had tied its fortunes to Valeant in the past two years, going so far as to increase its holdings in the firm as a combination of pricing pressure, accounting questions and a heavy debt load catalyzed an ongoing decimation of Valeant's share price. Ackman aligned himself with the troubled biopharma, even testifying alongside the embattled outgoing CEO Michael Pearson before the Senate Aging Committee about the company's practices last April.

All that changed March 13, as Pershing Square Holdings, the hedge fund's publicly traded security arm, revealed that it had sold off its entire interest in Valeant – more than 27m shares and options – incurring a loss estimated at between $3bn and $4bn. Investors reacted predictably by further punishing Valeant's stock, which dropped an additional 10.3% on March 14 to close at $10.86. All told, the Laval, Quebec-headquartered firm has seen its share price decline by approximately 95% since peaking at $257 in 2015.

Offering its rationale for selling the shares now at a loss rather than maintaining in hopes of a business rebound, Pershing Square said "the investment required a disproportionately large amount of time and resources. As a result, we elected to sell our investment and realize a large tax loss, which will enable us to dedicate more time to our other portfolio companies and new investment opportunities."

ATTEMPTED RECOVERY

Analyst Michael Waterhouse of Morningstar said Ackman's departure at this point likely won't have a major effect on Valeant's future prospects, which will be driven by getting out of debt, realizing solid returns by selling off assets and succeeding with the current portfolio, including recently approved psoriasis drug *Siliq* (brodalumab). Valeant CEO Joseph Papa expressed optimism about Siliq's potential to be a growth-driving product for the company during its most recent earnings call Feb. 28, but analysts aren't terribly bullish on the product.

"Unsurprisingly, Valeant's stock seems to be reacting to the loss of [Ackman's] vote of confidence, but the fundamentals of the business remain unchanged, from our perspective," Waterhouse told *Scrip*. "Restructuring the debt maturities is a slight positive, but management still has a lot of work to do with asset sales or returning to growth to climb out of the debt hole. Greater than expected performance from *Xifaxan* or from the launch of Siliq could offer some upside, but we're skeptical for the time being."

In a March 6 note on Valeant, Waterhouse had said the specialty firm faces an exacerbated debt problem with "no room for error." The gastrointestinal drug *Xifaxan* (rifaximin) faces near-term generic competition, as does *Jublia* (efinaconazole), a topical product for onychomycosis. Valeant earnings will continue to contract, the analyst wrote, "due to the firm's efforts to invest in new product launches combined with declining sales from higher customer rebates and new generic competition on several high-margin products. With ongoing performance below our expectations, we see few favorable options on the horizon."

One possible move Valeant could make, Waterhouse added, is to sell off the Bausch & Lomb Inc. eye care unit, whose legacy products continue to perform well. Theoretically, selling this business could bring Valeant a solid price, he said.

BMO Capital Markets' analyst Gary Nachman reads the Pershing Square decision to mean that it determined turning Valeant around would take longer than expected and face even more hurdles than initially anticipated. "The timing of this decision is particularly noteworthy since new management is just beginning to implement a number of its strategic initiatives, including asset sales to help pay down debt, pipeline approvals, and a primary care effort behind key product Xifaxan to accelerate that product," Nachman said.

In a March 14 note on Pershing Square Holdings, Jefferies analyst Matthew Hose suggested that with Valeant's stock having fallen 95% from its peak price, the hedge fund's investors "are likely to have attributed little or no value to the remaining position in Valeant." He expects the divestiture to play out positively for Pershing Square.

CHOPPY WATERS

It's been a stormy tenure at Valeant for Ackman, who stage-managed the departure of Pearson – the exec who had overseen a long string of acquisitions around already-on-market products or late-stage clinical candidates to build up the company's portfolio – and his replacement with Papa, former CEO of Perrigo Co. PLC. The Senate Aging Committee's review of Valeant's business practices unveiled a set of correspondence between Ackman and the company in which he urged the company to tell the full truth about its business relationship with the specialty pharmacy Philidor, adding that investors increasingly distrusted answers they were getting from Valeant management.

Using terms like "brink of catastrophe" and "death spiral," Ackman told Valeant execs in an October 2015 emails that their staged conference call to try to manage controversies around price increases and the Philidor relationship had worsened the situation.

Still, Ackman testified alongside Pearson before the Aging Committee in April 2016, to address reports that 30 of Valeant's top-selling drugs had increased in price by an average of 78%. At the time, Ackman said Pershing had been mistaken in taken a passive investment role in the company, but asserted that frequent price increases were only "a small part of the business" at the time his company evaluated investing in Valeant. Still, Ackman increased his initial stake from 5.6% to more than 9%, becoming second-largest holder of Valeant stock.

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CONTINUED FROM COVER

In addition to its flexible price structure, Novartis also believes it can compete with Pfizer in terms of convenience. Hinshaw pointed out that patients can take the drug whenever they like, since – unlike Ibrance – it does not have to be taken with food.

IBRANCE'S ADVANTAGE

Ibrance has a big and important advantage over Kisqali, of course, because it has been on the market for two years, rapidly becoming a blockbuster product. Pfizer reported $2.14bn in 2016 Ibrance sales versus $723m in 2015 and Leerink analyst Seamus Fernandez recently forecast $3.25bn in 2017 sales, rising to $6.83bn by 2021.

Novartis has its own blockbuster hopes for Kisqali – one of a dozen potential $1bn-plus sellers in its research and development pipeline – but Pfizer may very well maintain a strong lead in the market for CDK4/6 inhibitors. US oncologists have had two years to get acquainted with Ibrance, during which time it has become part of the standard of care in first-line treatment of metastatic HR+/HER- breast cancer.

Also, with remarkably similar data for the two drugs, it could be difficult for Novartis to switch prescribers from Ibrance to Kisqali, unless the Swiss pharma can win over both oncologists and payers with its flexible dosing and pricing strategy.

Kisqali plus the aromatase inhibitor/endocrine therapy letrozole reduced the risk of death by 44% versus letrozole alone at the first interim analysis for MONALEESA-2, when the Phase III trial was stopped for efficacy. The FDA relied on data from that interim analysis in its approval decision.

MONALEESA-2 results included in the drug's label show that median progression-free survival (PFS) hadn't been reached in the Kisqali/letrozole arm as of the first interim review, but the median PFS in the letrozole-only arm was 14.7 months ($p<0.0001$). PFS ranged from 13 to 16.5 months in the comparator arm of the study versus a minimum PFS of 19.3 months in the Kisqali group.

Novartis reported that median PFS reached 25.3 months in the combination arm and 16 months in the letrozole-only arm after an additional 11 months of data were collected. Overall survival data are not mature, so the company expects to report those results at a later date. The data to date do not show a substantial difference from Ibrance efficacy, however, since median PFS for the Pfizer drug in combination with letrozole was 24.8 months in the Phase III PALOMA-2 study versus 14.5 months for letrozole alone. Ibrance is approved for treatment in combination with letrozole as well as in combination with the selective estrogen receptor degrader fulvestrant for postmenopausal women who fail treatment with letrozole or other endocrine therapies.

Safety also is not a major differentiator for the two drugs. Like Kisqali, Ibrance has warnings about cardiovascular and hematologic adverse events in its label – pulmonary embolism and neutropenia – with neutropenia specifically identified as a side effect that may require prescribers to reduce the Ibrance dose. The label has separate dose-lowering instructions for non-hematologic events.

ADDITIONAL TRIALS ONGOING

Outside of their approved labels, Pfizer's drug also has a lead over Novartis's product in the adjuvant setting where the Phase III PALLAS study began in August 2015 evaluating treatment with Ibrance plus an endocrine therapy for at least five years versus standard endocrine adjuvant therapy, such as letrozole. Novartis said on March 13 that it recently began its own adjuvant study, which will enroll 2,000 patients.

Ongoing Phase III trials for Kisqali include MONALEESA-3, which combines the CDK4/6 inhibitor with fulvestrant compared with fulvestrant alone in postmenopausal women with HR+/HER2- advanced breast cancer who have not been treated with or were treated only once with endocrine therapy. In MONALEESA-7, Kisqali plus endocrine therapy and goserelin are being compared to endocrine therapy and goserelin alone in premenopausal women with HR+/HER2- advanced breast cancer who have received no prior endocrine therapy. Data from both studies are expected around the end of 2017 or early 2018 and could support a supplemental filing with the FDA in 2018.

Lilly hopes that even with its third-to-market position, its CDK4/6 inhibitor abemaciclib will be able to grab market share from its predecessors based on potentially improved safety. The company thinks that its more selective drug could allow for continuous dosing without the need to interrupt therapy due to severe neutropenia.

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Threshold/ Molecular Templates: The Power Of Two

Although a vehicle for Molecular Templates to take its Engineered Toxin Bodies oncology platform public, the combined company also will seek a pathway to approval for Threshold's evofosfamide for pancreatic cancer in Japan.

A reverse merger between troubled Threshold Pharmaceuticals Inc. and privately held Molecular Templates Inc. will take the latter company, focused on new a class of cancer drugs with potential in immuno-oncology, public. However, the combined company remains committed to the former's evofosfamide, which was considered dead and buried after a pair of Phase III failures in late 2015.

The two firms announced their merger during an investor call on March 17, outlining an all-cash transaction approved by both boards of directors that will result in a new company called Molecular Templates Inc., headquartered in Austin, Texas. Current Molecular Templates CEO Eric Poma, a former ImClone Systems Inc. executive, will become CEO of the new company, while Threshold CEO Barry Selick will take one of Threshold's two seats on the board and serve as chairman.

Selick said the decision to merge with Molecular Templates was reached after a lengthy process of reviewing possible strategic directions for Threshold, which considered more than 100 alternatives.

Following the merger, expected to close during the second quarter, existing Molecular Templates' shareholders will own nearly 66% of the new company, with Threshold investors owning 34%.

joseph.haas@informa.com, 17 March 2017

Read about the next-generation potential in immunotherapy here: **http://bit.ly/2nidOsT**

Competition Coming For Hemophilia Franchises, But Will Patients And Payers Embrace New Drugs?

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Roche's emicizumab, Alnylam's fitusiran and multiple gene therapies may soon steal market share from established clotting factors sold by Shire, Novo Nordisk and others, but safety is a key consideration for physicians and patients.

Hemophilia patients are loyal to brand-name clotting factors that have enjoyed market dominance for many years, but a shakeup may be coming in the form of monoclonal antibodies, RNA-based treatments and gene therapies if safety factors and treatment durability don't get in the way.

Shire PLC has the world's largest hemophilia franchise following its acquisition of Baxalta Inc., generating more than twice the sales of its nearest competitor Novo Nordisk AS. Those companies' market dominance will be challenged, however, by novel therapies from the likes of Roche, Alnylam Pharmaceuticals Inc. and Spark Therapeutics Inc., which could eliminate the need for frequent clotting factor infusions.

However, hemophilia patients tend to be reluctant to give up therapies that have been safe and effective for many years, which could mean slow acceptance and growth for newer products.

Physicians and patients are interested in new therapeutic approaches, but they are reluctant to switch from approved clotting factors, according to a Feb. 28 report from Bernstein analysts Ronny Gal and Tim Anderson based on an interview with hemophilia key opinion leader (KOL) Christopher Walsh, a Mt. Sinai Hospital hematologist and an associate professor at the Icahn School of Medicine at Mt. Sinai.

"Within the [Factor VIII (FVIII)] market, Dr. Walsh sees little traction from the longer-acting FVIII products and sees many of his patients switching back to the older products as they do not feel 'protected.' Discussions with peers suggest at least some other physicians have noted the same," the Bernstein report says. "Within the FIX market, Dr. Walsh is seeing similar switch back with [Biogen spinout Bioverativ Inc.'s recombinant Factor IX product] *Alprolix*."

Top Hemophilia Franchises By 2016 Sales*

Shire (Baxalta): $3.7bn
Novo Nordisk: $1.5bn
Pfizer: $1.3bn
Bayer: $1.2bn
CSL Behring: $1bn
Bioverativ: $847m

*Grifols and Octapharma do not report product-level sales or hemophilia franchise totals, but they are major players in the market.

Walsh was more optimistic about new biologic approaches, since subcutaneous administration every one or two weeks would be a big convenience and compliance benefit compared with weekly or more frequent clotting factor infusions. The doctor was less enthusiastic about gene therapies, however, based on the early-stage data presented to date.

Shire's group vice president and head of US hematology Jeffrey Schaffnit said in an interview with *Scrip* during the American Society of Hematology (ASH) Annual Meeting in December that the safety of new therapies is key for hemophilia patients, who've relied on products like Shire's anti-inhibitor activated prothrombin coagulant complex *Feiba* for decades.

"We fully support the innovation of these products, but they shouldn't have any additive risks," Schaffnit said. "We think further study is warranted."

EMICIZUMAB QUESTIONS

The most advanced of the new treatment modalities is Roche's monoclonal antibody emicizumab (ACE910), which was given prophylactically in the Phase III HAVEN 1trial to patients with hemophilia A, including individuals who have developed antibodies – also known as inhibitors – to clotting factors. The bispecific monoclonal antibody mimics the production of clotting Factor VIII to bring together Factors IXa and X to help the blood coagulate.

A once-weekly injection of emicizumab was an effective prophylactic therapy for hemophilia A patients enrolled in HAVEN 1, including individuals with inhibitors to Factor VIII. Roche also is testing the therapy dosed every other week and every four weeks.

"Patients on standard of care bypass therapy are still bleeding quite a bit; there's definitely an unmet need," Roche subsidiary Genentech Inc.'s Gallia Levy, associate group medical director, told *Scrip* during the ASH meeting.

Levy noted that many hemophilia A patients aren't adhering to treatment regimens, because of the burden of infusions three and four times per week, so emicizumab's once-weekly – or even less frequent – injections could be a significant differentiating factor in the market.

However, a recently reported patient death in HAVEN 1 raised new questions about which patients are the best candidates for treatment with emicizumab and how they should be treated when they experience a breakthrough bleeding event.

Shire contends that emicizumab may not be safe enough for patients that require frequent and life-long therapy. The company generated in vitro data last year for Feiba dosed concomitantly with an emicizumab biosimilar, which showed that thrombin levels jumped four to 10 times above pre-treatment levels, increasing the risk for serious adverse events. The preclinical findings were published in the journal Blood just before the ASH meeting.

A Suntrust Robinson Humphrey analysis of the in vitro data on Dec. 2 noted that thromboembolic events and thrombotic microangiopathy (TMA) – the serious adverse events reported in HAVEN 1 – appear to be a result of co-administration of emicizumab with a bypassing agent, because the severe side effects are not known to occur among hemophilia patients treated with Feiba or Novo Nordisk's *NovoSeven* and they occurred only in patients who had a breakthrough bleeding event in the Roche study.

Bernstein noted in its KOL report that Mt. Sinai's Walsh expects broad adoption of emicizumab for hemophilia patients with inhibitors if the final data expected later this year show an 80% or greater reduction in bleeding events versus 50% to 60% reductions for existing clotting factors. If so, physicians are likely to use the monoclonal antibody in the inhibitor population even without a deeper understanding of the safety risks.

But for broader used in hemophilia A and B, the risks associated with the combination of emicizumab and Feiba – and potentially with NovoSeven – would have to be better understood, the Bernstein report notes. That suggests that it could take a while for emicizumab to have an impact on Shire's portfolio beyond Feiba if the product is approved in the US in the next year or so.

Shutterstock: Jarun Ontakrai

Shire certainly has a lot at stake with around a 50% share of the hemophilia market after closing its acquisition of Baxalta last year, making hemophilia the company's largest franchise. Baxalta's hematology franchise generated $3.7bn in 2016 sales, which was 3% more than in 2015 on a non-GAAP basis, but Shire recognized only $2.2bn in post-acquisition hemophilia sales, or 20.6% of the company's $10.7bn in product sales last year.

Novo Nordisk reported DKK10.5bn ($1.5bn) in hemophilia sales for 2016, which accounted for 9.4% of the Danish company's DKK111.8bn ($15.9bn) in product sales. Novo said in its annual report that its hemophilia sales declined by 2% from 2015 levels, because of "lower NovoSeven sales in the USA due to increased competition and patients participating in clinical trials with competing drugs, partly offset by the roll-out of *NovoEight* in Europe and the USA, and by sales growth for NovoSeven in [Asia] Pacific."

NovoSeven has been on the market since 1996 and, like FEIBA, treats patients with inhibitors. Novo also has long-acting clotting factors in late-stage development and under regulatory review as well as a Phase I monoclonal antibody called concizumab. However, the company is looking for ways to diversify its revenue beyond diabetes and hemophilia and may expand in hematology, since it is rumored to be considering an acquisition of the sickle cell drug developer Global Blood Therapeutics Inc.

FITUSIRAN NEARING PHASE III

Another closely-watched novel hemophilia treatment in clinical development is the RNA interference (RNAi) therapeutic fitusiran from Alnylam and partner Sanofi/Genzyme Corp. The companies are co-developing and will co-commercialize the drug in the US, Canada and Western Europe, while Sanofi has rights to fitusiran in the rest of the world.

The drug is designed to reduce antithrombin (AT), thereby increasing thrombin, which should improve clotting in people with all types of hemophilia, including patients with inhibitors, and other bleeding disorders. It is being tested in a four-part Phase I/II study ahead of Phase III studies that are expected to begin during the first half of this year.

Alnylam presented interim Phase I data for fitusiran at ASH that showed reduced levels of AT, increased thrombin and a median annualized bleeding rate (ABR) of zero in 16 patients with hemophilia A or B with inhibitors who were treated with a once-monthly subcutaneous injection of fitusiran versus a pre-study median ABR of 31. The median ABR in the company's Phase II extension study was 1 as of the data cutoff for the ASH presentations.

All side effects in the Phase I study were characterized as mild or moderate with no thromboembolic events reported, including among patients who experienced breakthrough bleeds that were managed with bypassing agents – recombinant Factor VIIa and/or activated prothrombin complex concentrate (Shire's Feiba and Novo Nordisk's NovoSeven).

"Patients are very excited about something with such a different approach," Alnylam chief medical officer Pushkal Garg said in an interview with *Scrip* during ASH. Garg said the ongoing early-stage studies are looking at health care utilization costs as will the forthcoming Phase III program, since infusion costs are a big expense for payers in terms of reimbursing current hemophilia therapies.

"The inhibitor population has a high unmet need and some require treatment that cost $1m-plus per year," he noted. "It's very expensive, so if you can obviate the need for bypassing agents – which have a high burden, cost and risk – you can benefit patients and society."

Garg also pointed out the potential quality of life improvement for hemophilia patients, many of whom avoid sports or other activities and plan their lives around when they are due to get their next clotting factor infusion.

"Factor doesn't have a consistent effect over time," he said. "We have a clear and consistent effect; it's freeing for patients. Seeing the bleeding rates we're seeing is really quite positive and encouraging."

Both fitusiran and emicizumab are compelling for payers, which are looking for cost savings from new subcutaneous therapies, which could prevent bleeds without frequent and costly infusions of clotting factors. The novel medicines also don't cause patients to develop inhibitors, which leads to treatment with more expensive bypassing agents, like Feiba and NovoSeven.

Gene therapies are not as compelling in the eyes of payers, however, because they have not yet determined how to pay for what could be once-in-a-lifetime treatments, according to a recent report from Datamonitor Healthcare.

GENE THERAPY CLAMOR

Six gene therapies and a gene-editing treatment for hemophilia are in Phase I/II testing, although BioMarin Pharmaceutical Inc. plans to move its BMN 270 for hemophilia A into a potentially registrational Phase IIb clinical trial in the third quarter of 2017, and uniQure NV intends to begin a pivotal trial for its hemophilia B candidate AMT-060 later this year as well.

Spark and Dimension Therapeutics Inc. continue to report data from ongoing Phase I/II clinical trials for their hemophilia gene therapies, but Sangamo BioSciences Inc. only recently started trials for its hemophilia A gene therapy SB-525 and its hemophilia B gene-editing therapy SB-FIX and

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expects its first data from those studies in late 2017 or early 2018. Spark and uniQure reported interim results during the ASH conference in December. Spark and its partner Pfizer Inc. presented data from seven out of nine adult patients with hemophilia B who were at least 12 weeks past infusion with the gene therapy SPK-9001 as of the Nov. 30 data cutoff. Those individuals were able to produce Factor IX (FIX) at sufficient levels after a single infusion.

Baseline FIX levels were less than 2% of normal, but increased to a range of 12% to 46% of normal with a mean steady-state level of 28%; that's more than twice the 12% level deemed sufficient to prevent minor, chronic bleeding in the joints – a common cause of disability in hemophilia. "Most people are not going to bleed at that level," Spark co-founder, president and chief scientific officer Katherine High said in an interview at ASH.

Six patients reported increased physical activity and improved quality of life, because they did not have to continue with once- or twice-weekly clotting factor infusions. Patients have indicated that the benefit for gene therapy is "the freedom from worrying about when you're going to bleed and when was your last infusion," High said.

"The goal of all drug development is to give patients choice in how they manage their disease," she added. "Patients find this life-changing."

However, Spark reported that two patients had elevated liver enzymes associated with an immune response to the viral vector capsid that's used to deliver FIX DNA to the liver. They were treated with tapering courses of corticosteroids and their FIX levels dropped, but the two patients did not have any breakthrough bleeding events or require FIX infusions.

High said the immune response seems to occur between four and eight weeks after infusion with SPK-9001, so Spark will look for signs of an immune response during that period going forward and treat it with steroids before FIX levels fall too far.

No patients treated with SPK-9001 developed FIX inhibitors and none experienced thrombotic events or other series side effects. More data from the 10-patient Phase I/II study and an update on Phase III plans are expected around the Hemostasis and Thrombosis Research Society (HTRS) Scientific Symposium Apr. 6 to 8 in Scottsdale, Arizona. Discussions with the FDA are ongoing about the design of a Phase III study, which would be run by Pfizer.

Spark's wholly-owned hemophilia A gene therapy SPK-8011, which delivers Factor VIII, is about a year behind SPK-9001, so the first set of data from an ongoing Phase I/II study are expected in mid-2017.

"We continue to see a reasonable chance to show clinically meaningful improvement in [the] initial cohort … based on preclinical data," Leerink analyst Gena Wang said in regard to SPK-8011 in a Feb. 22 report on Spark's pipeline.

UNIQURE GENE THERAPY

UniQure will report additional data from its Phase I/II study for AMT-060 for hemophilia B in 2017 as it prepares to initiate a pivotal study this year, but at the ASH meeting the company presented results from ongoing earlier-stage study for patients in the low-dose cohort treated for up to 52 weeks and in the higher-dose cohort for up to 31 weeks. Three patients across both cohorts were given tapering doses of corticosteroids to treat mild increases in liver enzymes.

Four out of five patients in the second cohort required chronic FIX infusions prior to the clinical trial (the fifth had less severe disease and used FIX therapy only as on-demand treatment) and were able to discontinue prophylactic FIX therapy after receiving AMT-060. Only one spontaneous bleed was reported at the data cutoff after the hemophilia B patients stopped prophylactic FIX therapy.

All five patients in the first cohort had uncontrolled bleeding episodes despite prophylactic FIX therapy prior to treatment with AMT-060. They maintained "robust, constant and clinically meaningful levels of FIX activity" for up to 52 weeks, according to uniQure, with a mean FIX expression level of 5.2%.

None of the 10 hemophilia B patients across both cohorts of the study developed inhibitors. The safety and efficacy data supported uniQure's decision to test the higher dose in its forthcoming pivotal trial.

Jefferies analyst Eun Yang said in a report issued on Dec. 5 in response to the data presented at ASH that "we continue to see little value in AMT-060 given 1) competition, 2) small market size and 3) adequacy of existing therapeutics. Given the competition from SPK-9001 and availability of long-acting recombinant FIX replacement therapeutics (yielding about 20% FIX expression with weekly prophylactic dosing), we see little commercial opportunity for AMT-060."

Even so, Yang said uniQure has about a 75% chance of winning FDA approval for AMT-060 based on available data. She forecast cumulative sales of $785m between 2020 and 2032 – an average of $60.4m per year – based on the gene therapy's potential to penetrate a market of about 7,000 hemophilia B patients in the US and EU.

"Dr. Walsh believes gene therapy works in principle, but its adoption is gated by high variability of results," the Bernstein KOL report said. "He expects gradual adoption as the technology gets better, but this would require multiple generations of products (it would not be first-to-market wins)."

That may be good news for Shire after all, since the company has gene therapies in preclinical development for hemophilia A and B – SHP654 for hemophilia A and SHP648 in hemophilia B, which were acquired by Baxter International Inc. before it spun out Baxalta as a separate company. Both assets were initially developed by Chatham Therapeutics LLC.

"The biggest thing to overcome [in gene therapy] is the immune response … but there's a lot of technology looking at what can be done to minimize that, looking at new capsids and vectors. It's as close as it's ever been in terms of commercialization," Schaffnit said.

"We want to maintain our leadership; we're looking to expand our breadth," he added, noting Shire's investments in gene therapies, treatments for ultra-rare disorders, like Von Willebrand disease, and the company's Phase I long-acting recombinant Factor VIII candidate SHP656, which is being developed with technology from Xenetic Biosciences Inc.

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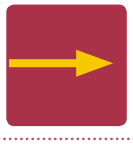

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Fortress Adds Rare Disease-Focused Subsidiary

Fortress Biotech Inc. unveiled a new subsidiary March 14, Cyprium Therapeutics, Inc. focused on treatments for the rare pediatric genetic disease Menkes disease and related copper metabolism disorders. Fortress now has nine companies under its umbrella, a few of which are developing drugs for rare diseases. Fortress, which finances each subsidiary company separately and through various means, while retaining an economic stake, has a goal of bringing in one or two new portfolio companies quarterly. The firm's 20-person business development team is hard at work scouring the life sciences sector for assets, CEO Lindsay Rosenwald said in an interview at the company's New York City headquarters March 8. Days later, Fortress followed through on its company-building ambitions by announcing the formation of Cyprium. The new company will be focused on the development of the Phase III candidate CUTX-101 for the treatment of Menkes disease, a rare pediatric disease caused by genetic mutation of copper transporter ATP7A that affects one in 100,000 newborns each year. Menkes patients often have low levels of copper in their blood and brain, and clinical features of the disease include connective tissue disorders and severe neurological symptoms such as seizures. Many patients die before the age of three. Milder versions of ATP7A mutations are associated with other diseases, including Occipital Horn syndrome and ATP7A-related distal motor neuropathy. There are no FDA-approved treatments for Menkes disease and its variants, according to Fortress. CUTX-101 is a subcutaneous injectable formulation of copper histidinate. Cyprium will develop the drug under a Cooperative Research and Development Agreement (CRADA) with the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), part of the National Institutes of Health. Cyprium and NICHD have also entered into an exclusive license agreement to develop and commercialize an adeno-associated virus (AAV)-based gene therapy, AAV-ATP7A, to deliver copies of the copper transporter that is defective in Menkes patient and be used in combination with CUTX-101. The gene therapy is in preclinical development at NICHD.

jessica.merrill@informa.com, 15 March 2017

Cell Medica Targeting Next CAR-T Wave

The next generation of chimeric antigen receptor T-cell (CAR-T) therapies to be developed, where most companies are at around the same (preclinical) stage, is expected to be aimed at treating solid tumors, and the Anglo-American biotech, Cell Medica Ltd., believes it will be advancing its first potential products in this sector into clinical studies sometime in 2018. Kite Pharma Inc., Novartis AG and others may be nearing the market for the treatment of blood cancers with their CD19-targeted CAR-T products, but there is a "whole new category of therapies, an unexplored continent," out there relating to cell immunotherapies, says Cell Medica's CEO Gregg Sando. The UK-headquartered biotech has just raised a hefty £60m ($73m) in a Series C financing round partly to support development of its lead product, a Phase II Epstein-Barr virus-associated anticancer, baltaleucel-T (CMD-003), but also to support its work on its next generation of cell immunotherapies. Since raising £50m at the end of 2014 in a Series B round, Cell Medica has expanded its chimeric antigen receptor (CAR) technology with two large research collaborations (with Baylor College of Medicine and with University College London) and the acquisition of Delenex Therapeutics AG. The company will now execute on its plans to develop new products with the Series C funding, Sando said. Cell Medica's cell-based technologies involve the use of natural killer T-cells that traffic naturally to the periphery of the human body where most solid tumors are located; other T-cells, such as those used as the basis of the first generation of T-cell based immunotherapies, tend to circulate around the blood and lymphatic systems, Sando noted.

john.davis@informa.com, 16 March 2017

Glenmark Wins 'Milestone' US Nod For COPD

In the face of increasingly cut throat generic competition, Glenmark Pharmaceuticals Ltd. is betting on its specialty and innovative drugs pipeline, and the development of niche and complex generics and new dosage forms, to power future sales in a strategy focusing on three therapeutic areas – respiratory, oncology and dermatology. Now, in what the Indian firm sees as an important development for its respiratory and broader ambitions, the US FDA has approved an IND for a Phase II study of GSP 304 (tiotropium bromide) for the treatment of chronic obstructive pulmonary disease (COPD). The added-value generic is being developed as a maintenance therapy for bronchospasm associated with COPD, administered once-daily using an oral nebulizer. Mumbai-based Glenmark characterized the FDA nod as a "milestone" in its drive to be a more innovation-focused company. "Moving GSP 304 into Phase II is a great example of that focus and, if approved, will be the first nebulized form of tiotropium bromide," noted Fred Grossman, president and chief medical officer of Glenmark Pharmaceuticals Inc. in the US. Currently, tiotropium bromide is marketed in the US by Boehringer Ingelheim GMBH in powder form under the brand name Spiriva and as a spray under the Spiriva Respimat label.

Penelope MacRae,16 March 2017

AstraZeneca's Lynparza Looks To Hang On To Lead

Tesaro's niraparib has an advantage over other PARP inhibitors in that it has been tested successfully in ovarian cancer patients with and without BRCA mutations, but AstraZeneca thinks it may have a case for broad labeling in this population.

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AstraZeneca PLC's strong results for *Lynparza* in maintenance treatment of ovarian cancer could help the PARP inhibitor retain its leadership position in the class, particularly if the company persuades the US FDA to approve the drug in this indication for all comers, regardless of mutation status.

Lynparza (olaparib) was the first poly ADP-ribose polymerase (PARP) inhibitor to reach the market, in 2014, but Clovis Oncology Inc.'s *Rubraca* (rucaparib) was approved in December 2016 and Tesaro Inc.'s niraparib is under review at FDA with a June 30 user fee date. Studies on all three drugs were presented at the Society for Gynecologic Oncology (SGO) Annual Meeting on Women's Cancer from March 12-15 in National Harbor, Maryland.

AstraZeneca presented impressive data for Lynparza in the SOLO-2 study, which tested the drug against placebo as a maintenance treatment for patients with BRCA mutations, after two lines of therapy, on March 14 at the SGO meeting. This followed a top-line release from the trial in October.

Tesaro has been hoping to reach the market with niraparib as the first PARP inhibitor approved to treat women regardless of mutation status and as a maintenance therapy.

Niraparib is under review at FDA as a once-daily maintenance treatment for patients with platinum-sensitive, recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer who have responded to platinum-based chemotherapy, supported by progression-free survival (PFS) data from the Phase III ENGOT-OV16/NOVA study. Positive secondary endpoint data from the trial were presented at the SGO meeting on March 13.

The Tesaro drug's advantage might be a short-lived, however, if AstraZeneca can leverage its latest Lynparza data for a broader approval.

AstraZeneca presented new data from SOLO-2 study that promise to expand the role of Lynparza, which is cleared in the US for use as a monotherapy for germline BRCA (gBRCA)-mutated advanced ovarian cancer after three or more prior lines of therapy. SOLO-2 will serve as a confirmatory trial to convert the drug's accelerated approval to full approval in the US and the data support a maintenance therapy indication.

The SOLO-2 study tested a new dosing regimen – 300 mg twice daily – as a maintenance treatment for germline BRCA-mutated platinum-sensitive relapsed ovarian cancer. The current approved dose is 400 mg twice daily and the new regimen promises to reduce the pill burden from 16 to four tablets daily.

AstraZeneca reported a statistically significant improvement in PFS compared to placebo: 19.1 months versus 5.5 months – a 70% improvement, per investigator review. It also reported significant improvements on a range of secondary endpoints, including a 50% reduction in time to second progression or death. Safety was in line with prior trial results.

Biomedtracker analyst David Dahan said the results were impressive. Cross-trial comparisons suggest it is equal to niraparib in gBRCA patients with a better safety profile; for example, lower rates of Grade 3 or higher thrombocytopenia, neutropenia and anemia.

"Niraparib, however, has the advantage of having demonstrated efficacy in patients who had tumors with homologous recombination deficiency (HRD) as well as in non-gBRCA patients, which may translate to a wider label," he noted.

AstraZeneca will discuss the data with the FDA in pursuit of expanded labeling beyond fourth-line treatment. While SOLO-2 enrolled patients with BRCA mutations, Lynparza was tested in a broader population in the Phase II Study 19, a maintenance trial. AstraZeneca believes the drug has prospects for approval in all comers, regardless of mutation status, based on the totality of the data, though it needs to discuss this with regulators, Mika Sovak, executive director and Lynparza global development lead, told *Scrip*.

AstraZeneca initially sought accelerated approval in the US for Lynparza as a maintenance therapy based on Study 19, but the agency asked the company to go back and study the drug as a later line therapy for heavily pretreated patients. Sovak explained that more is known about the PARP class now and suggested that Study 19 may now be viewed in a different light.

Although Study 19 included platinum-sensitive ovarian cancer patients regardless of BRCA mutation status, the current data in the overall population doesn't seem sufficient for approval in the wider patient subset, Datamonitor Healthcare analyst Zachary McLellan said.

In a five-year follow-up for Study 19 published last year, median survival for patients treated with Lynparza was longer compared to placebo – by 4.7 months in gBRCA-mutation-positive patients and two months in the overall trial population – but the overall survival results were not statistically significant, the analyst observed.

"Additionally, any survival increase in the overall trial population is likely driven by the gBRCAm+ cohort. AstraZeneca announced further analysis into the patients without BRCA mutations who were positive for other homologous recombination deficiencies is ongoing. That data would likely need to be significant and be included in any regulatory submission for Lynparza's approval beyond BRCAm+ patients," McLellan said.

NIRAPARIB'S SECONDARY GOALS

Activity in the market suggests investors think AstraZeneca's gain is Tesaro's loss. Tesaro stock fell 10.6% on March 14 to $153.65 per share.

Yet Tesaro presented additional positive data for niraparib in the NOVA study at the SGO meeting that support the drug's approval as a maintenance therapy in recurrent ovarian cancer, ahead of the drug's user fee date on June 30. No FDA advisory committee is needed for the review and Tesaro has advised it expects rapid approval and plans to launch in the first half.

In the study, the chemotherapy-free interval was significantly improved for patients who were BRCA-mutation positive as well as those without germline BRCA mutations compared to the placebo control arm – the hazard ratios were 0.26 and 0.50 respectively.

The time to first subsequent treatment was significantly improved for those with and without BRCA mutations. Tesaro also reported a 52% improvement in time to second progression for those with mutations and a 31% improvement in those without mutations, plus a trend toward improved overall survival.

The company had reported in December 2016 that the drug met the primary endpoint of the trial, with significantly increased PFS in patients with germline BRCA mutations (73%) or without (55%) versus control.

Combined with previously released PFS data from the NOVA trial, the evidence reaffirms that niraparib could become the leading PARP inhibitor in treating ovarian cancer, McLellan said.

"The Tesaro update at SGO showed niraparib treatment significantly improved the chemotherapy-free interval and time to first subsequent treatment over placebo in both germline BRCA-mutated patients and patients without these mutations. This bodes well for niraparib's regulatory submissions as a maintenance regimen for recurrent platinum-sensitive ovarian cancer patients regardless of mutation status," the analyst commented.

CLOVIS'S COMPETITIVE ORR DATA

Clovis Oncology Inc. reported additional subgroup results for BRCA-mutated patients taking Rubraca in the Phase II ARIEL2 study of 493 patients with relapsed platinum-sensitive ovarian cancer at the SGO meeting. Rubraca is a relative newcomer on the market, having been approved in December 2016 for patients with BRCA mutation (germline and/or somatic) associated advanced ovarian cancer, after treatment with two or more chemotherapies.

"These data demonstrate that the objective response rate (ORR), disease control rate (DCR) and median progression-free survival (PFS) in patients with a BRCA mutation were greatest in platinum-sensitive patients," Clovis said in a statement.

Among the platinum-sensitive patients enrolled in the trial, the objective response rate (ORR) was 70% overall, 83% in those who had one prior therapy and 52% who had three or more prior treatments. Credit Suisse analyst Kennen MacKay said in a March 13 note that the ORR data for Rubraca in pretreated patients with germline BRCA mutations looked competitive with Lynparza. PFS and duration of treatment data favored Rubraca, though the data for Lynparza reflected patients who had more prior therapy, the analyst noted. There were no new safety signals in the data at the SGO meeting.

McLellan noted that the ARIEL2 trial data were positive for Clovis, but only pertain to patients with BRCA mutations.

"Efficacy beyond BRCA-mutated cancers will be important as more PARP inhibitors reach the market and companies attempt to differentiate their respective therapies and increase available patient populations," McLellan said.

Rubraca is in Phase III for use as a maintenance treatment in ovarian cancer and data are expected in the middle of this year. The study is enrolling patients with and without BRCA mutations, but the primary endpoint is progression-free survival in molecularly defined subgroups.

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Editas Deal Opens Allergan's Eyes To CRISPR

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Editas' stock shot up 11% by mid-morning on March 14, after the gene therapy company announced a deal with Allergan worth $90m up front for "cool" CRISPR programs in ocular indications. However, the lead therapy included in the deal offers potentially limited profitability in a small orphan space.

Allergan PLC has entered a strategic alliance with Editas Medicine Inc. for exclusive access and the option to license up to five of the latter firm's genome-editing ophthalmic programs – including its lead program for Leber congenital amaurosis (LCA), a rare, inherited retinal degenerative disease that appears in childhood and leads to blindness. This lead therapy is due to enter Phase I trials later in 2017.

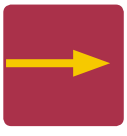
Editas will receive a $90m upfront fee from Allergan as well as potential milestone payments and royalties from any approved products. Allergan can license anything Editas develops over the next seven years in the ophthalmic space, but has already expressed interest in three programs, including the LCA candidate, one targeting usher syndrome – a form of retinitis pigmentosa – and another for ocular disease manifestations of herpes simplex virus (HSV).

Evercore ISI senior analyst Umer Raffat described Editas's CRISPR platform as "cool technology" and said in a March 14 research note that the lead LCA program is a "super orphan indication" for Allergan. The LCA program involves editing of the CEP290 gene, a protein that plays an important role in centrosome and cilia development. Mutations in CEP290 can cause the frequent form of LCA called LCA10.

Editas's therapy uses Cas9 endonuclease to remove the mutation, repairing the gene, with all components of the process delivered via a single adeno-associated virus (AAV) injected into the eye. The company has not disclosed which vector it is using as the AAV, but has said it is one that has been administered to the human eye before.

Raffat also noted, however, that Editas' CRISPR programs are yet to be tested in humans and that the LCA10 population being targeted by the company represents a small market. He estimates the cumulative market for the LCA10 gene-editing therapy to be worth $1.6bn, amortized over several years. Unusually, Europe is expected to be the more valuable market for this treatment, as the estimated prevalence of the condition is approximately 1,700 cases compared to only 300 in the US.

Published online 14 March 2017



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THE MICROBIOME

The Industry's Efforts In Targeting The Microbiome. Why It Is Important

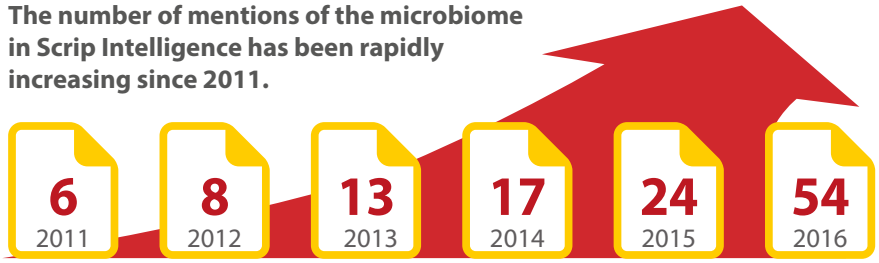
100 trillion

The number of bacteria, fungi, protozoa and viruses residing in or on our bodies, known collectively as the microbiome.

Some roles of the microbiome:
Digesting food
Producing vitamins
Regulating the immune system.

Changing the composition of the microbiome, or the way it interacts with the human body, **could have therapeutic effects** in inflammatory bowel disorders, Clostridia-associated diarrhea, diabetes and obesity.

The number of mentions of the microbiome in Scrip Intelligence has been rapidly increasing since 2011.



$4.8 billion

Estimated annual US acute care costs of C. difficile infection, one microbiome-related disorder.

>30

New biotech companies are focused on developing drugs to modify the microbiome.

Just under $1 bn in public and private funding has been invested since 2011 to support companies that are researching therapeutic approaches targeting the microbiome.

RESEARCH ACTIVITY IN THE MICROBIOME AREA BY STAGE OF DEVELOPMENT

DISCOVERY

Enterome/J&J/EB110
Crohn's disease

Enterome/Takeda/EB420
ulcerative colitis, irritable bowel disease

PRECLINICAL

Allergan/Assembly Biosciences/ABI-M201
ulcerative colitis

Allergan/Assembly Biosciences Inc./ABI-M301
Crohn's disease

Da Volterra/DAV121
C difficile-associated diarrhea

Seres Therapeutics/SER-301
ulcerative colitis

Synthetic Biologics Inc/SYN-020
GI disorders

Synlogic/SYNB1020
urea cycle disorders

Synlogic/SYNB2010
phenylketonuria

Vedanta Biosciences/J&J/VE202
inflammatory bowel disease

C3J Therapeutics/CD17-DL
C difficile infection

Symbiotic Health/SHP-01
C difficile infection

PHASE I

Seres Therapeutics Inc./SER-262
C difficile-associated diarrhea

Seres Therapeutics Inc./SER-287
ulcerative colitis

Second Genome Inc./SGM-1019
Crohn's disease

Enterome Bioscience SA/EB88018
Crohn's disease

Microbiome Therapeutics/NM-505 (metformin, prebiotic fibers)
diabetes type 2

PHASE II

Seres Therapeutics Inc./SER-109
C difficile-associated diarrhea

Shire/VP20621
C difficile-associated diarrhea

C3J Therapeutic/C16G2
dental caries prevention

DAV132/Da Volterra
C difficile infection

Synthetic Biologics/SYN-010
constipation associated with irritable bowel disease

PHASE IIB

Rebiotix Inc./RBX2660
C difficile-associated diarrhea

Summit Therapeutics PLC/ridinilazole
C difficile infection

Synthetic Biologics/SYN-004 (ribaxamase)
Microbiome disruption by antibiotics

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NICE Appraisal Changes: A New Pricing Hurdle

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New NICE and NHS England appraisal rules regarding timelines and price thresholds – labeled stark and contradictory – could fast-track new cost-effective drugs but then subject the same products to significant delays of multiple years.

New rules set to come into force next month that will allow NHS England to press the pause button on the use of around 20% of new drugs, even after they have been deemed cost effective by NICE (National Institute for Health and Clinical Excellence), look set to heap further pricing pressure on companies hoping to access the major UK market.

Currently once NICE, which is responsible for deciding whether new drugs show enough benefit versus their cost for use on the National Health Service, has granted a recommendation, NHS England must provide the product to patients within 90 days. However, under new rules agreed on March 15 and which will be put into action within weeks, NHS England will be able to play for more time before providing the drugs, delaying their use despite their being considered cost effective.

Instead of 90 days, NHS England will be able to request up to 1,096 days (a maximum three years) to try to negotiate a new price with manufacturers of drugs that are expected to cost more that £20m a year to the NHS – a method NICE is calling a "budget impact test." It is anticipated that this cost cap will affect one in five new drugs in England. Previously, assessments for novel therapeutics were only assessed on cost versus benefit for individual patients – not by the total cost it may incur to the NHS.

The £20m budget impact assessment is being seen as a second pricing hurdle for companies looking to get drugs to market in England and it also represents a shift in power from NICE to NHS England when it comes to drug pricing decisions. During an extended valuation period, in which time NHS England will invite drug developers to negotiate on pricing for products, NICE will offer phased funding of recommended treatments to patients in England – but this is not a long-term solution and has raised concerns that companies will face pressure to maintain the reduced price after that phase-in time has expired.

If a company decides to hold out, and by the time the extension period ends no commercial agreement has confirmed, then NHS England must provide the product to patients at the price originally agreed by NICE. However, this could be as much as three years later, delaying both access to the medicine for patients and revenues to the company significantly.

NICE, which first announced potential changes to assessment timelines and pricing caps in October 2016, will reassess the new rules in three years' time to see what impact it has had on access to new drugs. Last year £16.8bn was spent on drugs by the NHS, only a small segment of the healthcare provider's total budget for 2016 of £102bn.

Sir Andrew Dillon, chief executive of NICE, said the changes would "enhance our ability to optimize access to innovative treatments in the light of the significant financial challenge facing the NHS."

FAST-TRACK PLANS

In parallel to the introduction of a budget impact test, NICE will next month introduce a scheme for fast-tracking new drugs that have a likely cost per extra year of quality-adjusted life (QALY) of under £10,000. New drugs that come in under this threshold will be considered "exceptional value for money," the committee noted. Under the fast-track option, NHS England would be required to offer the new medicine to patients within 30 days instead of the traditional 90-day deadline.

This is a positive new guidance that could speed up market access in England for drug developers of products with lower per-patient costs.

However, in a contradictory move, fast-tracked drugs will also be submitted to the new budget impact ruling. Meaning a product could be granted fast-track status by NICE only to be held up by NHS England if the product is likely to create a cumulative bill of more than £20m to the NHS per year due to the number of patients to be treated.

Adela Williams, partner at law firm Arnold & Porter Kaye Scholer, told *Scrip* this was an irrational move by NICE and NHS England. "If you have a medicine that is so cost effective it has a price of less that £10,000 per QALY, then simply because there is a large population eligible for it you shouldn't be able to defer implementation," she said.

MULTIPLE COST ASSESSMENTS

"These proposals emasculate NICE to some extent and represent a shift in power towards NHS England that wants to carry out its own determinations for prioritizing treatments," said Williams, who specializes in advising companies on UK reimbursement systemts.

Rare disease drug developer Alexion, which has experienced arguing for access to the NHS for its highly specialized drugs, told *Scrip* that these changes to the system were a "serious setback for patients in England suffering from rare and ultra-rare diseases, and for the life-sciences industry in England." The company said it called into question whether England remains a viable country in which to invest and launch new therapies.

"Alexion questions the government's commitment to its patients and its pledge to support the life-sciences industry," a spokesperson for the company said. "This decision also puts the UK's Industrial Strategy at risk, which highlighted the life sciences sector as a primary source of innovation for the UK economy going forward."

Industry body the ABPI added that the new plans would "prevent patients from receiving NICE approved, cost-effective medicines, undermining their basic rights under the NHS constitution."

Industry has raised concerns over how the £20m threshold has been calculated by NICE and NHS England. After consultation, this query remains unanswered.

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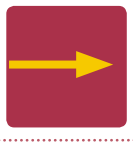

Why £20m?
Read more here:
http://bit.ly/2nKeqW0

Celltrion Healthcare's Biosimilar Successes

For investors in Celltrion Healthcare, the long wait seems to have been worth it. After originally planning an initial public offering a few years ago, Celltrion Healthcare, the exclusive marketing, distribution and partnering arm of South Korea's Celltrion Inc., has picked the perfect timing to launch an IPO amid the glow surrounding its parent from a series of biosimilar approvals in the US and Europe. Earlier this week, Celltrion Healthcare received the green light from the Korea Exchange (KRX) to launch a float on the second-tier Kosdaq market, where Celltrion is already traded. The IPO, estimated to be worth KRW819.3bn ($714.9m) to KRW1.01tn, is set to be one of the largest ever on the Kosdaq bourse. Although details of the IPO will be determined later, Celltrion Healthcare plans to price at KRW33,300 to KRW41,000 per share, the KRX said in a statement, and the offering is likely to take place in April. As of the end of 2015, Celltrion's chair Jung-Jin Seo, who is also chair and CEO of Celltrion Healthcare, held the largest (46.47%) stake in Celltrion Healthcare, while JP Morgan Chase's private investment arm One Equity Partners owned a 22.44% stake, and Singapore's Temasek Holdings' Ion Investment a 15.62% holding. Celltrion Healthcare's IPO filing and approval come several years after it first unveiled plans in 2015 to launch an IPO in South Korea or overseas. Under an agreement reached when its overseas investors made investments in Celltrion Healthcare several years ago, the company had agreed to launch an IPO in 2014, but this timing was delayed.

jungwon.shin@informa.com, 16 March 2017

Circassia Builds US Respiratory Presence with AstraZeneca Deal

Shares in UK biotech firm Circassia Pharmaceuticals PLC jumped by as much as 30% to 114 pence on the LSE on Mar. 17 on news that it had entered into a deal with AstraZeneca PLC to secure certain US commercial rights to two chronic obstructive pulmonary disease products (COPD), *Tudorza* (aclidinium bromide) and *Duaklir* (aclidinium bromide plus formoterol), for up $230m. Circassia said the deal would "transform its product portfolio and commercial presence". It already markets the airway inflammation test *Niox* for use in asthma management in the US, EU, Japan and China, and this will immediately provide it with another marketed product, as well as giving it another in the wings. In addition to the strategic fit with Circassia's renewed focus on respiratory medicines, the deal would leverage Circassia's commercial infrastructure – it plans to double its US sales force as a priority – and put it in a better position for future production licensing and acquisitions. CEO Steve Harris said the way the deal is structured was "highly attractive" as it allows Circassia "to fund the consideration without further investment anticipated from shareholders, while at the same time welcoming AstraZeneca to our share register". The company has been concentrating on its respiratory franchise all the more since its cat allergy product Cat-SPIRE failed in a high-profile Phase III study last June, wiping more than 60% off its share price. This was Circassia's lead development drug product and attention had been particularly focused on it following a highly successful IPO and funding round by the company. Just prior to the failure, Circassia shares had been trading at around 270 pence.

alex.shimmings@informa.com, 17 March 2017

Fosun/Shanghai Deny Interest In Stada

In response to reports of their interest in acquiring Germen generic and over-the-counter firm Stada Arzneimittel AG, Shanghai Fosun Pharmaceutical Group Co. Ltd. and Shanghai Pharmaceuticals Holding Co. Ltd. have both issued public statements denying the speculation reported. Even so, the two Chinese companies are continuing to seek potential overseas targets as part of their internationalization strategies. News reports quoting sources with knowledge of the matter emerged on March 9 that Fosun Pharma and Shanghai Pharma shared an interest in bidding for Stada in a possible €3.6bn ($3.8bn) takeover battle. Reuters reported that Fosun Pharma was in talks with funds including CVC Capital Partners for a possible joint bid, while Bloomberg stated that CVC was teaming up with Shanghai Pharma to compete against other investor groups. Both reports noted that the pharma companies may consider making an initial offer alone. Both Fosun Pharma and Shanghai Pharma responded by releasing official statements a day after the reports, with Fosun Pharma stating that "there is no such plan or arrangement as the media reports; the content of the report does not match the actual situation." Shanghai Pharma acknowledged that it has a continuous focus on identifying overseas acquisition opportunities as part of its internationalization strategy during China's 13th Five-Year Economic Plan. The company has had preliminary contacts with several pharmaceutical companies in Europe and the US, but no formal statement of intent has been made to any including Stada, it said. Shanghai Pharma stressed that its business operations are continuing as normal and that it has not hidden any information required to be disclosed.

ying.huang@informa.com, 14 March 2017

Lilly Eyes Top 10 Japan Ranking Built On Launches

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Lilly says it remains on track to enter the pharma industry top 10 in Japan by sales by 2020, driven by planned launches of a raft of new products and despite some major recent losses of exclusivity.

While there has been recent speculation from some observers that a flat overall pharma market outlook and the specter of fundamental reimbursement pricing reform may negatively affect multinationals' business and R&D commitment to Japan, Eli Lilly & Co. remains strongly bullish on its growth prospects in this key Asia-Pacific market.

Country president Patrik Jonsson said that the US major still considers Japan - already home to its largest ex-US single-country business - "by far the number one priority" outside of its home market.

Alluding to the importance of policy stability, Jonsson told a Tokyo media briefing that part of the reason for this confidence is that, along with top-class healthcare and a reliable social security system, has been that the "overall environment in Japan has offered predictability."

Consistent product pricing and the "innovation premium" system that rewards innovation by maintaining reimbursement levels for new drugs during their patent life have led to continuous investment, he stressed, implying that this could be affected if such policies change.

However, the executive stopped short of wading too deeply into the deepening drug pricing reform debate now getting underway within the government in Japan, perhaps cognizant that compatriot company Pfizer Japan Inc. was not so reticent in its recent business briefing, when it called strongly for wider industry participation in the process.

ZYPREXA IMPACT CONTAINED

Focusing on commercial performance and innovation in what was a challenging year for Lilly in Japan due to the advent last June of the first local direct generic competition for long-time top seller *Zyprexa* (olanzapine), Jonsson said the subsidiary's overall sales nevertheless increased by around 3% to JPY243.2bn ($2.15bn) in the calendar year.

The increase also came despite a roughly 5% average price cut for the business in the April 2016 general biennial reimbursement price cut in the country (which averaged around 6% across the industry).

Reimbursement level sales of Zyprexa, an atypical antipsychotic, slipped 22% to JPY47.7bn, but Zydis oral-dissolving 2.5mg formulations were launched in 2015 for both schizophrenia and bipolar disorder to try and provide differentiation from the 119 generic presentations launched last year.

Osteoporosis drug *Evista* (raloxifene) also suffered from generics, falling by 35% to JPY13.1bn.

Even so, "Our sales in Japan have tripled in 10 years, and we remained among the top three growth companies for the eighth consecutive year last year after Gilead Sciences Inc. and Ono Pharmaceutical Co. Ltd.," both of which were boosted by big-selling individual drugs, Jonsson said.

Lilly's Japan pharma sales ranking as of December was 12, up from 19 in 2011, but it has released no specific sales targets for achieving its targeted top 10 position.

NEWER PRODUCTS SHINE

The growth in 2016 came mainly from newer major products, with big increases for antidepressant *Cymbalta* (duloxetine; +37% to JPY41.6bn (including sales by Shionogi & Co. Ltd.)), helped by new pain indications, and cancer drug *Cyramza* (ramucirumab; +314% to JPY28.9bn). *Cyramza* was launched for gastric cancer and also approved for colorectal and non-small cell lung cancer during the year.

Biologic *Taltz* (ixekizumab) was also approved in Japan for second-line plaque, pustular, and erythrodermic psoriasis, and psoriatic arthritis - the last indication ahead of any other country - and Jonsson said the company is looking to differentiate it from competitors by highlighting strong clinical results showing potential full clearance of disease, an easy to use autoinjector, and patient support programs. The diabetes franchise was also strong, with drugs launched in 2015 including once-weekly GLP-1 agonist *Trulicity* (dulaglutide), and SGLT2 inhibitor *Jardiance* (empagliflozin), logging good increases along with biosimilar insulin glargine, which managed to carve out share in the basal insulin market.

R&D PLANS

Head of medicines development unit Dr. Toshio Fujimoto stated that the growth over the next few years will continue to be driven by Lilly's global pipeline, noting that fully 90% of the R&D projects in Japan are progressing under global simultaneous development programs.

"Our aim is to get approvals for 20 innovative products over the 2014-23 period - of which five [including Cyramza and Taltz] have already been launched - in five main target therapeutic areas: oncology, diabetes, neurodegenerative disorders, autoimmune disorders, and pain," he said.

In terms of key mid-term products, Fujimoto highlighted in particular the oral JAK1/2 inhibitor baricitinib (*Olumiant*), which has now been filed for rheumatoid arthritis in Japan in line with global timings.

Other Phase III projects include new indications for ramucirumab and ixekizumab, and abemaciclib for breast and non-small cell lung cancer.

Another area where Lilly Japan says it has been innovating is in the customer space, specifically its interactions with physicians.

Jonsson pointed to a new dedicated website for medical information, and "e-medical rep" channels that allow the delivery of scientific and product information to physicians via video calls with specialized reps, as well as text chats and screen sharing. Such systems are also being used to shorten the time needed to make scheduled face-to-face appointments.

Lilly now has around 1,900 sales reps in Japan, among the highest in the industry but a number that Jonsson sees as appropriate given the launch plans over the next few years.

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From the editors of *PharmAsia News*.

FDA Moves On Endo's Opana ER Unlikely To Sweep Up Other Opioids

Shift toward intravenous abuse with the reformulated long-acting opioid, coupled with reports of a serious bleeding disorder and HIV transmission, spurred an US FDA advisory committee to recommend regulatory action, which could include new labeling, strict risk management measures or market withdrawal.

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Endo Pharmaceuticals Inc. faces the prospect that the US FDA will request withdrawal of, or require new labeling and a restrictive Risk Evaluation and Mitigation Strategy (REMS) for, *Opana ER* (oxymorphone extended-release) due to issues with intravenous abuse.

However, given the unique circumstances surrounding the re-evaluation of Opana ER's safety, there is no indication that other long-acting opioids on the market are necessarily headed for the same fate.

On March 14, 18 of 27 members of the Drug Safety and Risk Management and the Anesthetic and Analgesic Drug Products advisory committees voted that the benefits of the currently marketed version of Opana ER do not outweigh the drug's risks.

Some panelists believed the drug should be removed from the market due to a lack of unique benefit and data suggesting an increased incidence of intravenous abuse since it was reformulated in 2011 with physicochemical properties that make it more difficult to crush, thereby discouraging intranasal abuse.

However, other committee members, including some who voted that the drug still had a positive risk/benefit profile, called for less drastic regulatory action. Their recommendations included new labeling limiting prescribing to second-line use, warnings about the serious risks of intravenous abuse, and a restrictive REMS limiting who could prescribe the drug.

Despite the potentially dire circumstances for Opana ER from a regulatory standpoint, analysts do not think FDA's action will have any broad sweeping implications for opioids in general even though the agency still faces intense political pressure to stem the epidemic of opioid-related overdoses and deaths in the US.

"We don't see widespread recalls or withdrawal of opioid products following the committees' discussion this week," Canaccord Genuity analyst Dewey Steadman said in a March 14 note. However, products that use formulations similar to Opana ER may face additional scrutiny, he cautioned.

Analysts also do not think FDA's ultimate regulatory action will have much of a financial impact on Endo, which has increasingly de-emphasized its branded pain portfolio in favor of other therapeutic areas.

In a March 15 note, JMP Securities analysts Donald Ellis and Nazibur Rahman said Opana ER accounted for only 4% of their 2017 revenue estimate for Endo and is not a growth driver. "We do not view this advisory committee as a meaningful event for Endo," the analysts said.

In a press release issued after the two-day meeting, Endo said it believes that Opana ER remains an important clinical choice for appropriate patients, and the company "will evaluate the range of available options for maintaining access for legitimate use."

"Endo remains confident that the body of evidence established through clinical research demonstrates that Opana ER has a favorable risk/benefit profile when used as intended in appropriate patients," said Matthew Davis, senior vice president of R&D for Endo's Branded Pharmaceuticals division. "We plan to work collaboratively with the FDA as the agency completes its evaluation of Opana ER, while advocating to preserve the important benefits of the medicine for patients."

ABUSE-DETERRENT LABELING

FDA's safety concerns over Opana ER stem from abuse patterns that have evolved since the product was reformulated several years ago.

The currently marketed formulation includes a polyethylene oxide (PEO) matrix that is intended to make tablets more difficult to crush and abuse by the intranasal or injection routes. However, FDA's December 2011 approval of the new formulation did not include labeling language on abuse deterrence.

In February 2012, Endo began replacing distribution of original Opana ER with the new formulation. In 2013, FDA issued a complete response letter to the company's supplemental new drug application (sNDA) requesting labeling that describes the product's abuse-deterrent properties. The agency also denied Endo's citizen petition requesting a determination that original Opana ER had been removed from the market for safety reasons. Had FDA granted the petition, it would have blocked generics of the older formulation.

The FDA concluded there was insufficient evidence to establish that the original formulation had a higher abuse potential than the reformulated product. The agency noted certain data suggested the reformulation is more easily prepared for injection and the "troubling possibility" that more intravenous use was occurring compared to the original version.

Endo resubmitted the sNDA in January 2016 with results from an intranasal abuse study requested by FDA and interim epidemiologic study data on the abuse patterns. However, the company withdrew the supplement in August in anticipation of more complete epidemiological data becoming available in late 2016.

Although Endo said it is not currently seeking abuse-deterrent labeling claims, FDA nevertheless brought the product to its advisory committee due to concerns that epidemiological data suggest the reformulation has led to a shift in the preferred pattern of abuse from intranasal to intravenous.

DATA ON PATTERNS OF ABUSE

At the advisory committee meeting, Endo and its experts defended Opana ER's safety.

Harris Rotman, vice president of US regulatory affairs, asserted that two key events confound the interpretation of epidemiology data on Opana ER abuse patterns: the introduction of an abuse-deterrent formulation of Purdue Pharma LP's *OxyContin* (oxycodone

extended-release) in 2010, which led to an increase in Opana ER abuse, and the launch of generic oxymorphone extended-release products immediately before and after the introduction of reformulated Opana ER.

Endo pointed to evidence of decreased intranasal abuse with the reformulation and asserted that epidemiologic data suggesting a sharp jump in intravenous abuse of the drug in Tennessee was an anomaly.

"Endo believes the totality of the evidence demonstrates a favorable benefit/risk profile in the intended population," Rotman said. "Coincident with the introduction of reformulated Opana ER, intranasal abuse was lower. I.V. abuse initially increased in Tennessee but has stabilized, and was stable or decreasing in other states."

However, Jana McAninch, an FDA medical officer and epidemiologist, said the data are compelling that the reformulation has caused a shift from intranasal to injection route of abuse, although it's unclear if the increase is greater than if the product had not been reformulated. In addition, limited geographic areas, including Tennessee and other Appalachian states, appeared to be driving the increases. In addition to high incidence of injection abuse reported in Tennessee, FDA presented data showing that the state accounts for the highest number of dispensed prescriptions for branded and generic oxymorphone extended-release per 1,000 residents (18.5), followed by North Carolina (9.9).

Puzzled by the high amount of oxymorphone use and Opana ER intravenous abuse reported in Tennessee, advisory committee member Raeford Brown, a pediatric anesthesiologist at the University of Kentucky, asked Endo whether there is any difference in the way it markets drugs in different areas of the country.

"There is not, and actually at the current time we're not prospectively marketing with sales representatives," Rotman said. "But there's no state-by-state difference."

INTRAVENOUS RISKS

The advisory committee also was presented with FDA research implicating high molecular weight PEO as a potential cause of the cases of thrombotic thrombocytopenic purpura (TTP), a potentially fatal bleeding disorder, associated with Opana ER intravenous abuse.

PEO is found in other long-acting opioid formulations, including OxyContin, Egalet Corp.'s *Arymo ER* (morphine sulfate extended-release) and Purdue's *Hysingla ER* (hydrocodone extended-release). However, there have been more than 60 cases of TTP reported with Opana ER, compared to just a few with OxyContin.

Advisory committee members generally concluded that the epidemiologic data show a shift in abuse patterns from intranasal to intravenous and saw a biologically plausible pathway between Opana ER's PEO component and TTP. When injected, Opana ER has a short duration of action. It needs to be dosed repeatedly and frequently, in a large injection volume, which could allow for PEO to accumulate in a person's body, panelists said.

A 2015 HIV outbreak in rural Indiana likely resulted from the high injection volume and the drug's high price, which make sharing Opana ER for injection more efficient, thereby increasing the risk of bloodborne disease transmission, panelists said.

Advisory committee members acknowledged that removing Opana ER from the market likely would shift misuse to other more readily abusable drugs, including the generic extended-release and immediate-release forms of oxymorphone.

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PTC Gambles On Success With Emflaza

PTC Therapeutics Inc., already at cross purposes with the US FDA over its re-filing of *Translarna* (ataluren) for non-sense-mutation Duchenne muscular dystrophy (DMD), apparently decided to take a chance on the drug-pricing controversy as well, paying $140m up front on March 16 to acquire all rights for Marathon Pharmaceuticals LLC's DMD drug *Emflaza* (deflazacort), the launch of which has been delayed by pricing pushback. PTC execs said during a same-day investor call to outline the transaction and report fourth quarter earnings that the company plans to revise Marathon's initial Emflaza pricing of $89,000 per year, but they offered few specifics. Marathon attracted significant unwanted attention from Congress and the media with its planned pricing of the DMD drug, which has been available for decades overseas as a generic corticosteroid therapy. US patients able to re-import the drug have been paying roughly $1,000 per year. CEO Stuart Peltz said during the PTC conference call's question-and-answer period, "We appreciate that [Emflaza's] pricing is receiving a lot of attention and we believe that a change needs to be made." PTC's investors already were concerned about the South Plainfield, New Jersey-based firm's decision to go against the FDA and use the "file over protest" pathway to re-file the new drug application (NDA) for Translarna after receiving a refuse-to-file letter for the drug in 2016.
joseph.haas@informa.com, 16 March 2017

US Insulin Pricing Probe Clouds Prospects for Novo Nordisk

While insulin makers are facing US government investigations of their pricing and relationships with pharmacy benefit managers, Novo Nordisk AS is also dealing with a flurry of lawsuits alleging the Danish diabetes fighter colluded with other insulin manufacturers to increase prices, artificially inflate its financial results and mislead investors. Consumer class actions also have been filed against Novo, Sanofi and Eli Lilly & Co. alleging their discount prices with pharmacy benefit managers were anti-competitive. The lawsuits arose after the US Attorney's Office for the Southern District of New York issued civil investigative demands (CIDs) to Novo and Sanofi in March 2016 for documents relating to their contracts and relationships with pharmacy benefit managers involving insulin products. Lilly also received a CID regarding unspecified products. Senator Bernie Sanders, I-Vt., and Representative Elijah Cummings, D-Md., subsequently sent a letter to the Department of Justice and Federal Trade Commission in November asking them to investigate whether insulin manufacturers have colluded or engaged in anticompetitive behavior in setting their drug prices. The Minnesota Attorney General jumped in and launched an investigation. Novo and Sanofi reported in February 10-K SEC filings that in January this year they received civil investigative demands from the Minnesota AG's office requesting documents and information "relating to pricing and trade practices" for Novo's long-acting insulin products, including *Levemir* (insulin glargine) and *Tresiba* (insulin degludec), and Sanofi's insulin glargine products Lantus and Toujeo. The potential impact of the investigations can't be gauged at this early stage. "It depends on what the specific allegations are and if there is any substance to them," a former Department of Justice prosecutor said. sIt is also unclear whether the probes will have any effect on the price of insulin.
brenda.sandburg@informa.com, 17 Mar 2017

Gottlieb Nomination: Changes To Generic Approval Process?

President Donald Trump's choice of Scott Gottlieb to head the US FDA could signal efforts to bring reforms among a variety of fronts, perhaps none more notable than how the agency approves generic drugs. Gottlieb, returning for what would be his third stint at the agency, has been a staunch proponent for flexible approval pathways, and despite some ominous tweets, the Trump Administration has made speeding ANDA clearance (rather than direct government intervention) the central focus of its drug pricing policy efforts. The president's selection of Gottlieb underscores that point, but the effort could require a considerable shift by FDA to make a politically meaning impact on drug prices. Gottlieb wrote in an August 2016 Wall Street Journal op-ed that a series of "costly requirements" imposed by the FDA under the Obama administration are responsible for keeping generic competitors off the market, and recommended that FDA "prioritize applications for generic categories where competitors are exiting." In testimony before a Senate pricing hearing in October, Gottlieb also suggested that companies who pursue applications for these abandoned generics receive a voucher, which would provide the sponsor with an expedited review of another generic application. "The value of this voucher would give firms more incentive to market copies of low-volume generics," Gottlieb wrote. The voucher system proposed by Gottlieb runs somewhat parallel to the one proposed in the Lower Drug Costs Through Competition Act (H.R. 749), sponsored by Rep. Kurt Schrader, D-Ore., and Gus Bilirakis, R-Fla. The bill would create a six-month priority review pathway for ANDAs for drugs with only one sponsor marketing them already, products on FDA's drug shortage list or possibly first generics. The sponsors could then receive a priority review voucher once the drug is approved.
michael.cipriano@informa.com, 13 March 2017

iTeos: IO Therapies For Hot And Cold Tumors

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With the immuno-oncology space a battleground for large pharmaceutical companies, surely there isn't much a small biotech can offer? iTeos Therapeutics, a 2011 spin off from Ludwig Cancer Research, believes otherwise, CEO and founder Michel Detheux told Scrip.

iTeos is targeting hot and cold tumors. "This concept in targeting the tumor microenvironment is becoming more and more important in the field of oncology," said Detheux.

Tumors can be labelled as 'hot' or 'cold' or somewhere in between, depending on how densely they are infiltrated by lymphocytes, according to Detheux. Typically, hot tumors are associated with a better prognosis, because the presence of lymphocytes suggests that the immune system has recognized that the tumor is 'foreign' on some level, despite not being able to clear it effectively. 'Cold' tumors are characterized by little or no infiltration of immune cells, and these patients usually have a poorer prognosis.

"Most current therapeutic programs are targeting hot tumors, trying to activate the immune cells that have infiltrated the tumor. If you are targeting a cold tumor, you are trying to create an immune response – that was the purpose of the entire effort behind cancer vaccines."

iTeos' later stage programs – one licensed to Pfizer Inc. and two which it hopes to take into the clinic next year (a small molecule A2A receptor antagonist and a TIGIT antibody) – are focused on 'hot' tumors, with the aim of activating the lymphocytes already inside the tumor to do their job of clearing up the 'foreign' cells. However, an earlier STING agonist project is looking at the 'cold' tumor environment, with the aim of creating immunogenicity.

iTeos was founded as a spinoff from Ludwig Cancer Research as a new initiative. "They agreed to try a dedicated company that would take some of the Ludwig's know-how – the IDO1 and TD02 programs – and be the champion of these programs."

The two enzymes IDO1 (indoleamine-2,3-dioxygenase) and TDO2 (tryptophan-2,3-dioxygenase) break down the essential amino acid tryptophan, and have emerged

Michel Detheux

as key targets in the cancer immunotherapy field. iTeos was the first spin-off created by the Ludwig in which it invested cash, noted Detheux. Two years later, the programs were out-licensed to Pfizer at the lead stage.

Compared to the competition, which includes Incyte Corp., NewLink Genetics Corp. (partnered with Roche's Genentech Inc.), Bristol-Myers Squibb Co. (through its Flexus acquisition) and Merck & Co. Inc. (through its IOmet Pharma acquisition), "our IDO1 compound is differentiated by a very favorable PK profile with a long half-life but also penetration to the brain which could be very useful to control brain metastases," explained Detheux.

"When iTeos was founded, there was only the knowhow: no IP and nothing to out-license." iTeos conducted classical high throughput screening, hit-to-lead assays, lead optimization, and characterization of a preclinical candidate, which went on to be selected by Pfizer.

Pfizer took the IDO1 program into Phase I testing in patients with brain cancer (malignant gliomas) in September 2016. The candidate, PF-06840003, has been tested in combination with PD-L1 antibodies and other immune-oncology compounds and appears to boost anti-tumor immune response.

Since signing the deal with Pfizer, iTeos has worked hard to build a sustainable pipeline, entering an antibody platform access deal with Adimab in the US and a targeted delivery platform access deal with Cristal Therapeutics in The Netherlands.

A2A AND TIGIT

This year iTeos is aiming to raise a €40m series C; it plans to bring in €15-20m from existing investors. This money will be used to push iTeos earlier programs: A2A and TIGIT, into Phase I in 2018. If successful, iTeos could be ready for an IPO in 2019, believes Detheux.

The A2A receptor antagonist program is based on the fact that adenosine inhibits the immune response through A2A receptors. However, A2A receptor antagonists in the tumor microenvironment can prove problematic as the concentration of adenosine in tumors is 10 to 15 fold higher than in the brain, meaning the introduction of A2A receptor antagonists affects the brain more than the tumor. Many A2A receptor antagonists in development for oncology applications were initially developed for the treatment of Parkinson's disease – not the ideal starting point in this setting, Detheux pointed out.

iTeos has developed compounds with limited CNS penetration and has some promising preclinical data from cancer models. It plans to select a candidate in the coming months to take into clinical testing in 2018.

iTeos also has a TIGIT antibody program that could be ready for the clinic in 2018. The diversity of small molecules and antibodies is important to the company, emphasized Detheux.

TIGIT is a co-inhibitory receptor expressed on the surface on T lymphocytes. The binding of an antibody to it blocks a negative signal to immune cells via one mechanism, and stimulates immune cells via another. Genentech has a TIGIT program in Phase I.

STING AGONIST

Further back in development is iTeos' STING agonist program. The addition of these compounds to 'cold' tumor cells can transform them into 'hot' tumors. This is thought to be a key factor in making these tumors more susceptible to IO treatment. Aduro and Novartis are collaborating on a STING agonist in Phase I.

STING agonists require tumor-specific delivery, and iTeos signed a nanoparticle delivery partnership with Cristal Therapeutics last year. The program, along with a galectin-3 antibody program, are at the lead identification stage.

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Scrip's weekly **Pipeline Watch** tabulates the most recently reported late-stage, Phase III clinical trial developments for the more than 10,000 drug candidates under active research worldwide. To see changes to the progress of product candidates further back in the development pipeline, and a table of the week's product approvals, please visit our Pipeline Watch webpage at scrip.pharmamedtechbi.com.

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Visit the Pipeline Watch webpage at scrip.pharmamedtechbi.com for all the week's changes to the industry's R&D pipeline

Selected clinical trial developments for the week 10–16 March 2017

LEAD COMPANY/PARTNER	COMPOUND	INDICATION	COMMENTS
Updated Phase III Results			
AstraZeneca PLC	*Lynparza* (olaparib)	ovarian cancer, BRCA mutation, relapsed	SOLO 2; progression-free survival benefit confirmed .
Tesaro Inc.	niraparib	recurrent ovarian cancer	NOVA; results of secondary endpoints presented .
Biofrontera AG	*Ameluz* (5-aminolevulinic acid)	actinic keratosis	Photodynamic therapy, effective and well tolerated.
Phase III Interim/Top-line Results			
Amgen Inc.	*Repatha* (evolocumab)	dyslipidemia	Reduced the need for LDL-C apheresis.
Indivior PLC	RBP-7000 (risperidone monthly depot)	schizophrenia	Clinically effective and durable responses.
Phase III Initiated			
Alkermes PLC	ALKS8700 (monomethyl fumarate)	multiple sclerosis	Study will evaluate gut tolerability versus *Tecfidera*.
Jazz Pharmaceuticals PLC	JZP-258	narcolepsy, cataplexy	In 60 centers in the US and EU.
Pharnext SAS	PXT3003	Charcot-Marie-Tooth disease	PLEO-CMT-FU; a Phase III extension study.
LSK BioPartners Inc.	apatinib	gastric cancer	ANGEL; in advanced or metastatic disease.
Phase III Announced			
AstraZeneca PLC	PT010	chronic obstructive pulmonary disease	To be compared with PT009.
Novartis AG/Otsuka Holdings Co. Ltd.	*Kisqali* (ribociclib)	breast cancer	EarLEE-2; with endocrine therapy.
Amgen Inc.	*Repatha* (evolocumab)	dyslipidemia	FOURIER OLE; long term safety study in patients with CV disease.
Updated Phase II Results			
Genkyotex SA	GKT137831	diabetic nephropathy	Mixed results, improved secondary endpoints.
TiGenix NV	AlloCSC-01	acute myocardial infarction	CAREMI; well tolerated.
Clovis Oncology Inc.	*Rubraca* (rucaparib)	advanced ovarian cancer	ARIEL2; new analyses of patient subsets .
Phase II Completed			
Advaxis Inc.	axalimogene filolisbac	cervical cancer	Improved 12-month survival rate, Phase III planned.
Phase II Interim/Top-line Results			
Karyopharm Therapeutics Inc.	selinexor	diffuse large B-cell lymphoma	SADAL; response rates strong, amended to a single arm study.
Shionogi & Co. Ltd.	S-237648	obesity	A neuropeptide Y5 antagonist, induced weight loss but not clinically meaningful.
Catalyst Pharmaceuticals Inc.	*Firdapse* (amifampridine phospate)	myasthenia gravis	Significant effects on co-primary endpoints.
Galectin Therapeutics Inc.	GR-MD-02	severe refractory atopic dermatitis	Clinical responses seen, well tolerated.

Source: Biomedtracker

Smart Matrix Limited (SMLC)., a company focused on wound healing, has appointed ***Andy Hill*** CEO. Meanwhile, board member ***Leonor Stjepic*** has stepped down to focus on other responsibilities. Hill has more than 30 years of experience in the medical technology industry and previously, he was CEO of Deltex Medical plc.

IRX Therapeutics Inc. has appointed biotech industry veterans ***Mark Leuchtenberger*** and ***Monil Shah*** to president, CEO and director and chief operating officer, respectively. IRX's founder and prior CEO, ***John W. Hadden***, will continue on at the the company as a director. With over 20 years' experience, Leuchtenberger was president, CEO and member of the board at Chiasma, Acusphere Inc. and Rib-X Pharmaceuticals Inc. (now Melinta Therapeutics Inc.). He has also been president and CEO of Targanta Therapeutics Corporation and Therion Biologics Corporation. Shah brings more than 17 years of pharma and biotech experience in oncology to IRX and most recently, he was medical affairs lead for immuno-oncology at Bristol Myers Squibb. He started his career at Novartis, in the oncology early development group and later co-founded Ventrus Biosciences as head of clinical operations and development.

Rare genetic diseases focused **Therachon AG.** has appointed ***Maarten Kraan***, AstraZeneca's former vice president, head of innovative medicines and respiratory and inflammation, chief medical officer. Before AstraZeneca, Kraan was vice president, head of clinical research and experimental development inflammation at Hoffman La Roche. Prior to this, he was vice president, immunosciences at Bristol Myers Squibb and began his pharma career at Schering Plough.

Mission Therapeutics, a company focused on cancer and neurodegenerative diseases, has appointed ***Anne Phelan*** as senior vice president, head of discovery research. Phelan joins Mission from BenevolentAI (formerly Stratified Medical), where she was VP, drug discovery. Before this, she held various positions within Pfizer including chief operating officer and head of pharmacology at Pfizer Neusentis in Cambridge, UK.

Derek Adams has joined **bluebird bio Inc.** as chief technology and manufacturing officer; and ***Joanne Smith-Farrell*** has also been appointed as bluebird's senior vice president, corporate development and strategy. Adams joins bluebird from Evelo Biosciences, where he was senior vice president of CMC and before this he was vice president of technical strategic product development at Alexion Pharmaceuticals. Previously, Smith-Farrell was vice president business development transactions at Merck Inc. and before this she was vice president of strategic transactions at Pfizer Inc.

ASIT Biotech, a Belgian clinical stage biopharmaceutical company focused on the treatment of allergies, has appointed ***Gerd Zettlmeissl*** chair of its board. Since 2011, Zettlmeissl was an independent director of ASIT and previously, he was CEO of Intercell AG, an Austrian vaccine company that merged with the French company Vivalis, to create Valneva.

Kiadis Pharma, a biopharma company developing immunotherapy treatments for blood cancers and blood disorders, has appointed ***Jan Feijen*** chief operating officer – effective April 1, 2017. Most recently, Feijen was vice president manufacturing and technical operations, platform lead vaccines and advanced therapies at Janssen (a Johnson & Johnson company).

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