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Sanofi/Regeneron Extend A Hand On Praluent, Express Scripts Takes It

JESSICA MERRILL jessica.merrill@informa.com

Sanofi and **Regeneron Pharmaceuticals Inc.** said in March they were willing to make a deal on the cost of the PCSK9 inhibitor *Praluent* (alirocumab) in exchange for improved access. Now, **Express Scripts Holding Co.** has taken them up on the offer.

The companies announced on May 1 that Express Scripts will grant Praluent preferred access on its national formulary over **Amgen Inc.**'s *Repatha* (evolocumab) and remove some of the burdensome access restrictions in exchange for a higher rebate on the wholesale acquisition cost (WAC) of Praluent. Express Scripts national formulary includes 20 million individuals. Repatha will now be available to patients on Express Scripts' national formulary only through a medical exception pathway.

Reducing the access restrictions for Praluent is an important win for Sanofi/Regeneron. Prescription rejection rates have been as high as 75% for PCSK9 drugs, according to Sanofi. Amgen has presented data showing as many as 80% of PSCK9 prescriptions initially are rejected. *(Also see "Will Physician Demand For Repatha Put Pressure On Payer Restrictions?" - Pink Sheet, 19 Mar, 2017.)*

"It takes [physicians] days and sometimes weeks to get approvals, and therefore, in the end, it is the patient that really suffers, waiting a month, or sometimes more, to get a prescription," Sanofi Senior VP and Global Head of CV Franchise Sheldon Koenig said in an interview, repeating a complaint the manufacturers have raised since the launch of the injectable high-cholesterol therapies. "This really simplifies the documentation necessary."

Express Scripts Chief Medical Officer Steve Miller said the negotiated price would be at the low end of the range recommended by the third-party Institute for Clinical and Economic Review (ICER) as being cost-effective. After reviewing positive outcomes data on Praluent earlier this year, ICER concluded the net price for Praluent for high-risk patients with cholesterol of at least 100 mg/dL despite intensive statin therapy should be $4,500 to $8,000 per year, depending on the risk to the patient.

"We are really excited because it puts this drug now within the affordable range of more patients," Miller said.

The WAC of Pralulent is $14,600 a year, though the companies have been offering rebates that some analysts estimate have reduced the costs to about $8,000 per year. After releasing the FOURIER cardiovascular outcomes trial for Repatha in 2017, Amgen concluded the benefit supported a net price in the range of $7,700 to $11,200 per year. *(Also see "Amgen Says Repatha Outcomes Trial Backs Up Its Pricing Math" - Pink Sheet, 19 Mar, 2017.)*

Sanofi/Regeneron announced they were willing to lower the price of Praluent in line with ICER's recommendations for insurers that removed access restrictions in March, at the same time the partners released positive outcomes data from the long-term ODYSSEY trial, showing a significant reduction in cardiac events and a benefit on mortality for patients taking Praluent. Sanofi/Regeneron's decision to

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Chinese Biogenerics
Limited uptake perplexes (p16)

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One big deal could do it, says PwC (p18)

Q1 Results
Sanofi, Roche, Amgen, Shire, Boehringer and Sun report (p4-6, 8-11)

from the editor

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Many of our readers will be aware of the annual Scrip Awards, which recognize outstanding achievements in the pharmaceutical, biotech and allied industries. It's my great pleasure to inform you that the 2018 Scrip Awards are now open for entries. I know from our daily reporting how much there is to celebrate in this industry, and I encourage all of you to get nominating.

With a new award for best use of real-world evidence having been added this year, there are now 16 trophies up for grabs, to be judged by our independent panel of 17 senior industry experts. For details of the individual award categories and how to enter, visit scripawards.com. Every year our prestigious ceremony gets bigger and better, and I look forward to welcoming even more of you when we gather to bestow the awards in the London Hilton on Park Lane, Mayfair, on November 28. Check out those entry criteria and good luck with your submissions. The entry deadline is June 1.

Back to the here and now, this issue's coverage is heavy on details gleaned from first-quarter big pharma financial reporting, from Roche's executives talking about their vision for their electronic health record specialist acquisition Flatiron Health (p8) to Boehringer Ingelheim's expectations for the impact of impending patent US patent expiries on its biggest revenue generator, Spiriva (p11). Sanofi, Amgen, Shire and GlaxoSmithKline are among the other major firms whose results we cover in the issue; go to our website for additional reporting on companies including Biogen and Gilead.

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Alnylam Set For Transformation As Patisiran Nears Market With Data Upgrade
https://bit.ly/2I3evRD
Alnylam has outlined further data and analyses from the Phase III APOLLO study supporting the use of its selective interfering RNA agent, patisiran, as it nears the market for the treatment of hATTR amyloidosis.

Brakes On Sanofi's Dengvaxia Prospects Amid WHO-SAGE Screening Advice?
https://bit.ly/2HJieQS
WHO's recommendation around a pre-vaccination screening strategy for Sanofi's Dengvaxia could potentially dull the prospects of the product further, especially in emerging markets with stretched healthcare resources. One industry expert suggests that governments should probably consider introducing the vaccine only after "better tests and tools" become available.

Biogen's Spinraza Sales Plateau; The Challenge Is Keeping Up With The Successful Launch
https://bit.ly/2HGqC7Z
Sales of Biogen's blockbuster rare disease drug moderated in the first quarter as the company worked through the bolus of urgent infant and pediatric patients awaiting treatment in the US.

HCV Sales Drive AbbVie's Great Quarter, But Gains Won't Last
https://bit.ly/2Ks8MTO
Q1 earnings far outpaced expectations due to the successful launch for new hepatitis C drug Mavyret, but with the HCV market overall in decline those gains won't last and won't make up for the looming loss of Humira revenue.

GW CEO: Cannabinoid Platform Is Growth Engine Beyond Epidiolex
https://bit.ly/2raBJM6
Aside from epilepsy in children, GW Pharma also looking to other therapeutic spaces for testing its cannabinoid product candidates, including autism and brain cancer.

Finance Watch: Former Alexion Execs Raise $37m To Launch Rare-Disease Focused RallyBio
https://bit.ly/2FwJqAs
Private Company Edition: Martin Mackay and two other former Alexion executives co-founded the rare disease start-up in January with a $37m Series A to kick things off. Also, Innovent raises $150m in venture cash, Tmunity adds $35m and Third Rock launches Cedilla.

inside:

Dupixent Dip Dogs Sanofi Efforts To Deal With Diabetes Decline

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Sanofi is hoping for a stronger second half of 2018 after posting a first-quarter sales decrease due to unfavorable exchange rates and weaker sales of the atopic dermatitis drug *Dupixent* (dupilumab), a drug the French group hopes will be instrumental in offsetting the decline of its diabetes franchise.

> Sanofi is hoping that Dupixent will help fill the gap in revenues that is growing with the continuing decline of its off-patent diabetes blockbuster *Lantus*

Dupixent sales came in at €107m (€95m in the US), some way off consensus estimates of €144m and down from €118m in the fourth quarter. The fall was due to inventory reductions in the US and to higher contributions to patient assistance programs, hitting revenues by €30m.

On a conference call, CEO Olivier Brandicourt claimed that the decline was not a major issue, saying that in the US, the total number of prescriptions for Dupixent remained strong, climbing 25% compared with last quarter, adding 500 new patients a week. Bill Sibold, head of Sanofi Genzyme, added that of the €30m reduction, two-thirds was an inventory issue and some inter-quarter variability was to be expected, but the higher contributions to patient assistance programs, a common phenomenon post-launch for specialty care products, are already diminishing.

He went on to say the launch of Dupixent was going well and while initially most use had been in severe eczema sufferers, now more moderate patients were also getting access to the drug as Sanofi expanded its educational efforts and a direct-to-consumer campaign in the US promoting disease awareness rolled out.

Brandicourt insisted that the lower Q1 sales of the interleukin-4 and -13 inhibitor were "not at all representative of the underlying dynamics of the launch," adding that it had the potential to be "a practice-changing therapy" both in atopic dermatitis and moderate-to-severe asthma. Filings for the latter indication have been made on both sides of the Atlantic and Japan.

Regarding the weaker sales for Dupixent, Deutsche Bank issued a note saying that it backed up **Novartis AG**'s claim that it had similar inventory issues in the first quarter for its skin drug, the psoriasis blockbuster *Cosentyx* (secukinumab). However, analysts at Jefferies called Dupixent "a significant miss," and although destocking and higher start of year contributions to patient assistance programs may have accounted for €30m of the shortfall, "even after adjusting for this, it is still 5% light of consensus expectations."

Sanofi is hoping that Dupixent will help fill the gap in revenues that is growing with the continuing decline of its off-patent diabetes blockbuster *Lantus* (insulin glargine). The latter brought in €911m, down 17.7%, while Lantus sales sank 31.1% to €413m in the US, battered by lower prices and the loss of Medicare Part D business.

Brandicourt highlighted that compared with the same quarter two years ago, US sales of Lantus have more than halved and now represent only 30% of global diabetes sales as compared with 50% of a much bigger franchise in the first quarter of 2016. The impact of the product's decline is waning and "we expect this headwind to diminish in the coming quarter."

The CEO said that "I'm confident in delivering a return to growth in the second half," and much of that confidence comes from the performance of recently acquired Bioverativ, sales from which were only consolidated from March 9. Still, in just three weeks, *Eloctate* (recombinant Factor VIII) for hemophilia A and *Alprolix* (recombinant Factor IX) for hemophilia B contributed €43m (+27%) and €21m (+12%) respectively to Sanofi's coffers.

Brandicourt stressed that Sanofi had done extensive work to analyze the hemophilia market before buying Bioverativ and believes that factor replacement therapy will remain the standard of care for many years to come. Some observers have questioned that view, citing the arrival of **Roche**'s *Hemlibra* (emicizumab) to the market.

Speaking on the conference call, Bioverativ's CEO John Cox said that safety questions remained about Hemlibra, which is currently restricted to patients with factor VII inhibitors, and physicians will closely weigh up that risk relative to its benefit. However, Eloctate has an excellent safety profile with very low bleed rates, he added, saying that doctors could also adjust the treatment according to the patient's lifestyle.

Eyebrows have been raised over Bioverativ's $11.6bn price tag but Brandicourt said "we feel very confident that we are getting a very strong return" even factoring in the likelihood of Hemlibra getting some non-inhibitor market share.

The acquisition of Bioverativ and the soon-to-be completed deal to buy Belgium's **Ablynx NV** will see Sanofi focusing on integrating the two companies in the short term and "that's going to require a lot of attention," said Brandicourt. However, the shopping may not stop there.

When asked about the possibility of more M&A, he spoke about a "€20bn envelope we wanted to dedicate to inorganic growth [and] we basically have spent about €13bn of that." Therefore there is still €7bn to spend "if we find attractive bolt-on opportunities."

As for divesting assets, Brandicourt noted that following the €21.8bn business swap last year that saw Sanofi exchange its animal health division Merial for **Boehringer Ingelheim GMBH**'s consumer healthcare business, and the proposed €1.9bn sale of its European generics business to private equity group Advent International, no additional divestitures are planned.

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As Amgen Looks To Aimovig's Launch, It May Learn From Repatha's Past

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Since **Amgen Inc.** and **Novartis AG** are likely to have the first CGRP inhibitor on the market with *Aimovig* (erenumab), the partners will have an important opportunity to set the pricing and reimbursement tone for the class of migraine therapies, which ultimately will determine whether Aimovig lives up to the hype or becomes a PCSK9-like disappointment.

Amgen CEO Bob Bradway said on the company's April 24 first quarter earnings call that the company expects to launch Aimovig for the prevention of migraine headaches during the second quarter, assuming the drug wins US FDA approval by its May 17 user fee date.

Amgen and Novartis are poised to have the first-to-market advantage, but will be closely followed by **Eli Lilly & Co.**'s galcanezumab, which is likely to be the second CGRP inhibitor approved in the US after a setback for **Teva Pharmaceutical Industries Ltd.**'s fremanezumab. *(Also see "Bad News Teva Really Doesn't Need: A Potential Delay For Fremanezumab" - Scrip, 8 Feb, 2018.)* Setting the precedent for pricing and reimbursement will be a critical aspect for the drugs, which may be informed by the path to reimbursement for Amgen's *Repatha* (evolocumab).

LESSONS LEARNED FROM PCSK9

The PCSK9 inhibitors, including Repatha, were expected to become quick blockbusters due to their impressive LDL cholesterol-lowering abilities. However, with the availability of generic oral statins, the injectables Repatha and *Praluent* (alirocumab) from **Sanofi** and **Regeneron Pharmaceuticals Inc.** have struggled to find a price that convinces payers to reimburse the biologics' costs.

But Repatha finally is making significant headway after the FDA cleared a claim for reduction of cardiovascular risk in December. *(Also see "Outcomes Claim May Help Amgen Make Case For PCSK9 Inhibitor Repatha" - Scrip, 1 Dec, 2017.)* Sales jumped 151% year-over-year to $123m in the first quarter, including $84m in the US and $39m in the rest of the world.

"Over the past few months we've seen access to Repatha continue to improve and we remain committed to ensuring access and affordability for high-risk cardiovascular patients. We've been negotiating with several payers for months to expand patient access to Repatha and offering significant discounts with multiple offers pending," Executive Vice President-Global Commercial Operations Anthony Hooper said during the April 24 earnings call.

NEUROSCIENCE, NEGOTIATING EXPERTISE FOR AIMOVIG

Amgen carefully chose Novartis as its partner for the co-development of multiple neurology drug candidates and Aimovig will be the first product approved under that 2016 agreement. *(Also see "Amgen, Novartis Trade Rights For Migraine, Alzheimer's Drugs" - Scrip, 2 Sep, 2015.)*

In addition to its neuroscience expertise, Novartis also is one of the biopharma industry's most active negotiators of outcomes-based contracts that offer payers discounts or refunds when the company's drugs don't work. In fact, Novartis indicated last year that value-based contracts may be negotiated for Aimovig.

Being first to market will be a big win for Amgen and Novartis, since efficacy among CGRP inhibitors has been similar across clinical trials, often cutting the number of patients' days with migraine headaches in half.

Physicians and patients have been eagerly awaiting the first new migraine therapies in more than a decade, but pricing and reimbursement agreements that payers consider reasonable will help drug makers win market share for products that will cost thousands of dollars per year with millions of patients eligible for treatment.

But as with the PCSK9 inhibitors competing with less effective statins, payers may steer migraine patients away from brand-name, injectable CGRP inhibitors to oral, generic triptans to limit use of the new drugs.

PAYER NEGOTIATIONS REMAIN UNDER WRAPS

However, none of the companies developing CGRP inhibitors has given explicit guidance about planned pricing or payer negotiations, and Amgen executives offered few specifics during its earnings call.

"Novartis has a rich history of presence in the neuroscience market both in terms of the sales force and an outstanding medical organization. We are complementing it with both teams calling on specialists as well as some of the primary care physicians who have a propensity to look after patients with severe headaches or migraines," Hooper said.

"From a timing perspective, we clearly are in the lead; we look forward to launching first," he continued. "Unlike the PCSK9 situation where we had to follow, we will actually be setting the price ourselves. And this is clearly a market where patients have huge symptoms and actually know when they're not being properly treated, so we look forward to a large bolus of patients who want to come on this drug as quickly as possible."

Hooper took some issue with a recent Institute for Clinical and Economic Review (ICER) report assessing CGRP inhibitor pricing, because he said it didn't assess the absenteeism that occurs when migraine sufferers miss work. However, he indicated that the range of prices suggested by ICER ($8,500) and a separate Amgen-funded assessment by academic researchers published earlier this month ($14,238 to $23,998) are within the range of prices that are being considered for Aimovig.

Jefferies analyst Michael Yee said in an April 24 note that he estimates Aimovig's net price after discounts and rebates will be $5,000-$7,000. The drug will be "a key revenue upside driver, but over [the] longer-term since payers will likely try to restrict usage in [the] first year," Yee wrote.

Hooper was asked about a recent media report that **Express Scripts Holding Co.** wants to see outcomes-based contracts and other pricing concession for CGRP inhibitors. "We're delighted to hear

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that [Express Scripts] are looking at value-based prices and look forward to them opening up access in those situations to allow access to appropriate patients," he said.

"We will continue to come forward with prices that are responsible, that take into account the co-pay requirements as best we can. We have a number of risk-based contracts on the table with Repatha, and we're quite prepared to talk to payers about risk-based contracts with Aimovig," Hooper added.

SEARCHING FOR DIFFERENTIATION

Hooper asked Amgen Executive Vice President-Research and Development Sean Harper to discuss Aimovig's differentiating features, which include the fact that it targets the CGRP receptor rather than CGRP itself.

"We're the only receptor antagonist in the clinic, and we chose that path for a number of reasons, but one of them was potency," Harper said. "We seem to be the only product that doesn't require loading doses or intravenous administration, which can be quite an awkward thing for patients and providers, in general."

He also pointed out that new data in migraine patients who have failed as many as four prior prophylactic treatments appear to be different from results for other CGRP inhibitors, but Harper expected the novel CGRP receptor-targeting mechanism to be Aimovig's most distinguishing feature.

He noted that when physicians have to switch patients from a CGRP inhibitor due to adverse reactions or a lack of efficacy, they're more likely to choose a CGRP receptor-targeting product than another CGRP ligand-sequestering antibody.

NEW DRUGS MOST LIKELY AVENUE

While CEO Bradway noted that Amgen continues to invest in innovation that will drive growth, he stuck to previous assertions that the company would be conservative in terms of the price it will pay to acquire other biopharma firms. *(Also see "Amgen Invests In Deals, Share Buybacks And Manufacturing As Sales Dip" - Scrip, 1 Feb, 2018.)*

"Our priorities for the use of cash continue to be investment in innovation and supporting the launches of our growth products while continuing to build out our global presence," he said. "As for business development, we continue to look for innovative opportunities that are consistent with our areas of strategic focus while remaining disciplined about the path to earning a return for our shareholders."

Bradway's comments suggested that Amgen is more comfortable investing in its current assets than in overpaying to add products to its portfolio, although he said biopharma company valuations are beginning to come down.

Amgen's 2% year-over-year revenue growth in the first quarter, including a 3% rise in product sales to $5.34bn, was driven by double-digit gains for newer products, reinforcing the company's ongoing investments in its pipeline.

Repatha's 151% jump was by far the biggest gainer, but the bispecific T-cell engager (BiTE) *Blincyto* (blinatumomab) for certain leukemia patients saw a 44% spike to $49m; *Sensipar/Mimpara* (cinacalcet) for secondary hyperparathyroidism rose 18% to $497m; and the multiple myeloma drug *Kyprolis* (carfilzomib) grew 17% to $222m.

However, several of the company's legacy products had significant declines due to competition and pricing pressures, including a 6% drop for the blockbuster TNF inhibitor *Enbrel* for inflammatory diseases (etanercept) to $1.1bn; a 5% decline for the neutropenia therapy *Neulasta* (pegfilgrastim) to $1.16bn; a 10% fall for the anemia drug *Epogen* (epoetin alfa) to $244m; and a 30% plunge for the shorter-acting neutropenia treatment *Neupogen* (filgrastim) to $103m.

Neupogen and Epogen already are facing biosimilar competition, but Amgen has so far delayed biosimilars for Neulasta, Enbrel and Sensipar.

"Amgen beat on total product sales of $5.3bn versus consensus of $5.2bn, but the majority of this was from Sensipar at $497m versus consensus of $405m," Yee wrote. "Good news is other products like Repatha … was a slight beat (and a notable 'pick up' in acceleration from Q4, which could be a good sign if this continues) and Enbrel was in line (always a sensitive spot of focus for investors)."

Amgen revised its earnings guidance slightly from a range of $21.8bn-$22.8bn in 2018 revenue to a new range of $21.9bn to $22.8bn. Earnings per share (EPS) guidance changed from $12.60-$13.70 to a new range of $12.80-$13.70.

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Zerhouni Retires, Sanofi Hires John Reed

Sanofi is bringing in an outsider to spark the company's R&D engines: the former Global Head of Pharma Research & Early Development (pRED) at **Roche**. Sanofi announced April 24 that John Reed will join Sanofi as the head of global R&D effective July 1, succeeding the company's long-time R&D Chief Elias Zerhouni.

Zerhouni joined Sanofi in 2009 as a scientific officer to the CEO, a consultant of sorts, and was appointed to head R&D in January 2011. The passing of the torch appears to come at an appropriate turning point for Sanofi, as the company looks to redefine its R&D strategy in an increasingly innovative drug industry.

Sanofi is building a new hematology specialty, powered by the recent acquisitions of the blood products specialist **Bioverativ Inc.** and the nanobody platform company **Ablynx NV**, and the company's long-stand antibody development agreement with **Regeneron Pharmaceuticals Inc.** is winding down.

Reed has led the research and early development activities at Roche Pharmaceuticals for the last five years, responsible for activities through Phase IIb proof-of concept across all therapeutic areas, including oncology, immunology, rare diseases, neuroscience, ophthalmology and infectious disease. He joined Roche after a long career in academia at the prestigious Burnham Institute, where he was eventually appointed president and CEO of the Sanford-Burnham Medical Research Institute.

Roche already announced in March that Reed would be leaving the company for personal reasons and be succeeded by William Pao, the global head of the oncology discovery and translational area for pRED. At Sanofi, Reed will report directly to CEO Olivier Brandicourt and will join the executive committee. He will join Sanofi on April 30 to help ensure a smooth transition.

Zerhouni has been a steady hand at Sanofi amid some tumultuous leadership transitions, notably when Christopher Viehbacher was pushed out

of the company in 2014 and eventually replaced by Brandicourt in 2015. Zerhouni's focus was on revamping Sanofi's R&D machine as the company's top-selling revenue generator – the insulin *Lantus* – came under pressure.

He focused on pruning Sanofi's pipeline and improving R&D productivity. In an interview with *Scrip* last year, Zerhouni talked about his track record at the company, pointing to 13 drug launches between 2012 and 2017 versus three drug lunches between 2008 and 2012. He steered the company's portfolio toward biologics, with the help of Regeneron, a partnership that resulted in drugs like *Praluent* (alirocumab) for high cholesterol, *Kevzara* (sarilumab) for rheumatoid arthritis and *Dupixent* (dupilumab) for atopic dermatitis.

Although the antibody development deal with Regeneron is winding down, the two companies are continuing to collaborate in an immuno-oncology alliance that was signed in 2015.

Despite some R&D successes during Zerhouni's tenure at Sanofi, the company has also experienced R&D disappointments and misses. Even some clinical and regulatory wins like Praluent and Kevzara have failed to become commercial wins. Sanofi's attempts to extend the life of its insulin glargine franchise with the launch of *Toujeo* only made up some of the ground lost to competition.

Most notable perhaps were the company's missteps in cancer, as Sanofi failed to transition its portfolio from chemotherapy to targeted cancer drugs and then missed out altogether on the early push into immuno-oncology. The company experienced two high-profile late stage failures in cancer R&D in 2013 in areas where others have had success: the PARP inhibitor iniparib for breast and lung cancer and the JAK2 inhibitor fedratinib for myelofibrosis. There was also the downright dismal launch of *Zaltrap* (aflibercept) for metastatic colorectal cancer in 2012.

Whether Sanofi can compete in increasingly innovative areas of drug development like immuno-oncology and gene therapy – where some of its rivals are finding success – will now fall to the next R&D leader.

jessica.merrill@informa.com, 24 April 2018

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work with ICER on the review and willingness to publicly accept the outcome was a first for the industry, representing an interesting turning point with a drug maker agreeing to lower the price of a drug despite positive new data.

It also highlighted how the PCSK9 manufacturers miscalculated when they initially set the price of the drugs. Sanofi acknowledged that the company had learned some valuable lessons through the process. "I would hope that others will learn from what Sanofi/Regeneron have done, to be very public with this," Koenig said. "We want to show that we are really committed to improving access."

Whether or not payers would take the manufacturers up on the offer remained a big question, since payers have been quite effective blocking access to the expensive biologics. Praluent generated only €49m ($59m) in the first quarter, €26m ($31m) of which came from the US, well below the blockbuster level sales the drug was expected to generate when it launched in 2015. The situation has been similar for the rival drug Repatha, but the addition of an outcomes claim in labeling has helped. ((Also see "Outcomes Claim May Help Amgen Make Case For PCSK9 Inhibitor Repatha" - Scrip, 1 Dec, 2017.)) Repatha sales jumped 151% year-over-year to $123m in the first quarter, including $84m in the US and $39m in the rest of the world.

Miller said the decision by Sanofi/Regeneron to work closely with ICER on the value assessment for Praluent was notable and put the onus on payers to respond. Express Scripts has been a proponent of ICER and other similar third-party organizations, he said.

"With that combination of great clinical data, a company willing to voluntarily look at fair price and bring it down to a level of affordability, it gave us the opportunity to do something special with Praluent that we think will be a trend in the marketplace," Miller said.

Beginning on July 1, physicians will only need to submit an attestation form confirming Praluent is appropriate for patients based on the FDA-approved indication and patient history versus more burdensome requirements. The form is more of a check box physicians can use to assert patients have met certain requirements for treatment, rather than having to provide layers of documentation, like laboratory results, patient histories and proof of prior statin failure.

REBATES AT POINT OF SALE

Another important element of the contract is that Express Scripts will pass a portion of the rebate for Praluent onto eligible patients. The decision could reduce out-of-pocket costs for patients and thus improve the affordability of Praluent. Miller said about one-third of the rebate would be passed onto patients.

While Express Scripts has distributed some rebates at the point of sale before, Miller said it is the first time they have done point-of-sale rebates for a specific drug.

"That's going to be a game-changer that we hope we can take forward with other drugs in the future," he said.

The move is part of a broader debate in the industry over how rebates should be distributed to patients. The drug offsets traditionally have gone directly to insurance plans, which say they are distributed indirectly to patients through lower premiums. But affordability has become a growing issue for patients as high-deductible health plans have grown. **UnitedHealthCare**, for example, announced in March that it would launch a point-of-sale rebate program in its fully-insured commercial group plans in 2019. Aetna Inc. followed with a similar announcement.

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'Watch This Space' Roche Execs Say, Outlining RWE Rationale For Flatiron Buy

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Grilled by journalists and analysts during **Roche**'s quarterly sales update about the purchase of **Flatiron Health Inc.**, the Swiss group's CEO and pharma chief explained in detail how acquiring the oncology-focused electronic health record company will give valuable access to real-world evidence (RWE) data that Roche aims to use to better design clinical trials and outcomes, improve chances for drug reimbursement, and thus reinforce its place as a leader in oncology therapeutics.

Answering questions on April 26 while outlining its first-quarter sales performance – which saw revenue from new drugs offset erosion of sales from generic and biosimilar competition - Severin Schwan, Roche's Austrian CEO said buying Flatiron Health offered the world's biggest developer of cancer drugs research-quality electronic medical records (EMR) data that will be used to leverage and increase oncology synergies and help accelerate funding.

FLATIRON'S INDEPENDENCE 'KEY'

Roche also stressed that it will not block competitors from using Flatiron Health. Rather, Roche will encourage rival pharma companies and other life sciences groups to use the digital record generator's services, activating firewalls to preserve client relationships, and thereby encourage success.

"There's a new space opening up here. Our industry probably has been a bit behind in terms of this digitization compared to other industries such as the media or retail industries – but now increasingly healthcare data is getting digitized and as such there's a new space of innovation opening up for us that we are very interested and very active in," Schwan told *Scrip* during a media call on the day. Success would depend on Flatiron remaining an independent operator, he added.

"We normally work through partnerships. In the case of Flatiron, however, we felt we could drive the synergies of the market leader in oncology on the one hand and the market leader in oncology EMR [electronic medical records] data with Flatiron on the other even better, and make even faster progress – including funding – and this benefit is also available to competitors because we've put a lot of emphasis on keeping the Flatiron operations separate."

Doing that is the only way Flatiron could remain credible as a neutral partner for other stakeholders, including competitors of Roche, Schwan said .

"The acquisition is not about blocking out competitors at all – on the contrary, we want to make the offering, by leveraging our synergies, even more attractive for other stakeholders, including other pharma companies, and as the market leader in oncology medicines Roche has a special interest in being at the very forefront of this," Schwan told analysts on an afternoon conference call.

"We have a lot of partnerships in this space but from time to time it makes sense to either build up internal know-how and expertise to start with or strengthen that by means of acquisition. That's what we have done with Flatiron," Schwan said. Roche's pharmaceuticals head, Daniel O'Day noted that Roche had had a long relationship with Flatiron before deciding in February to buy it. Roche already held a 12.6% stake in Flatiron before announcing that month that it was paying $1.9bn for the remainder. The deal is to close during the first half of 2018.

"Flatiron as an independent company was already on track as being successful. We only want to encourage and accelerate that, as a standalone company that provides services to oncology customers, providers and life sciences companies, " O'Day told the analyst call.

> 'Increasingly, healthcare data is getting digitized and as such there's a new space of innovation opening up for us that we are very interested and very active in'

CHANGING TIMES

"What we get out of it and what the industry gets out of it is a world-leading, real-world database that allows us to do things very differently than the way we do them today in oncology; everything from looking at different treatment regimens to get reimbursement approval and markets," O'Day said.

"You can't possibly, in a Phase III clinical trial, have every different treatment regimen that might be appropriate for a reimbursement authority around the world," he explained. "By using the robustness of this data, we've been able to get reimbursement faster and I think some of the real benefit will also be in accelerating clinical trial hypotheses, clinical trial design by bringing the clinical trial to the patient or in the community oncology setting, and also potentially supplementing or replacing or speeding up clinical trials by using a real-world data control arm," said O'Day, adding that regulators were also keen to see what can be done with the approach.

"Every time a sponsor company has a new medicine, they have to replicate a standard-of-care control arm. We, and the FDA to a large extent, believe there's a better way to do things out there."

He added: "The only way that we can be successful leveraging this is if all companies are successful by leveraging this, because you have an unbiased and a standard created out there with the regulatory authorities."

As a result, Roche needs to keep Flatiron at arm's length and independent. "So we are doing the contrary to blocking companies' [access to Flatiron]; we are creating firewalls so that providers and other life science companies can be very confident in the primacy of their data and to make sure that this business model continues. We know that this business model can work overall," O'Day concluded.

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Keeping Mum On Takeda, Shire Outlines Two-Division Performance

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The possible acquisition by **Takeda Pharmaceutical Co. Ltd.** was top of mind for everyone involved in **Shire PLC**'s first quarter 2018 earnings call April 26, but under UK takeover law the company could not discuss the situation, although that didn't stop one analyst from asking CEO Flemming Ornskov how shareholders feel about the possible buyout.

Since first publicly disclosing its interest in acquiring Shire on March 28, Takeda has made five offers, increasing incrementally from £44 to £49 per share (about $64.3bn in aggregate) as of April 24, which Shire said it would take to its shareholders. This outcome extended the deadline for the transaction from an original date of April 25 to May 8, although investors on both sides of the deal reportedly oppose the merger.

Overall, Shire reported a solid first quarter with 7% year-over-year sales growth, led by 10% growth within its rare disease franchise. The specialty pharma said in January that it would begin presenting its financial performance as two separate business units – rare diseases and neuroscience – with a decision to come later in the year on whether it would seek to spin out the neuroscience unit in some manner.

The neuroscience business – comprised of ADHD drugs *Vyvanse* (lisdexamfetamine dimesylate), *Adderall XR* (amphetamine, dextroamphetamine mixed salts) and *Mydayis* (mixed salts of single-entity amphetamine product) as well as ulcerative colitis products *Lialda* and *Pentasa* (different formulations of mesalamine) – brought in $918m during the quarter.

That represents a 2% decline year-over-year, but Chief Financial Officer Thomas Dittrich noted that the unit saw a 14% increase if the sharp decline in Lialda, which has faced generic competition since mid-2017, was excluded. Worldwide Lialda sales totaled $62m for the quarter, down 65% from the first quarter of 2017. Non-Lialda growth could be attributed mainly to Vyvanse and also international sales growth, Dittrich added.

NEUROSCIENCE OFFERS HIGH-MARGIN BUSINESS

Two analysts noted that despite its sales decline, the neuroscience unit could offer a potential acquirer high profitability, as it produced a segment contribution margin of 84%, compared to 48% for rare diseases. Shire defines segment contribution margin as total revenue minus cost of sales, direct R&D expenses, and direct sales and marketing expense.

Calling neuroscience "a highly profitable division" in an April 26 note, Jefferies analyst Peter Wellford ascribed a $13bn net present value to the unit with potential for $4bn in peak worldwide sales, prior to Vyvanse losing patent protection in 2022.

Despite statements at the start of the call that Shire could not comment on the pending transaction with Takeda, one market analyst thought perhaps he'd found a clever way around this limitation, asking Ornskov how he interacts with Shire shareholders and what feedback he is getting about the potential deal.

Ornskov replied that he, his executive team and the board all make efforts to hear out the shareholders. He also implied that the negative feedback on the Takeda/Shire merger is coming mainly from analyst and media coverage.

"I think a lot of that feedback has also siphoned into the public domain through analyst reports and other people that had commented, so I'm not going to comment more on that," Ornskov said. "But getting the right feedback, hearing that feedback, making sure that's an important part of any decision-making, I can assure you I have a board of directors that puts significant emphasis on that and have an independent channel through our brokers to get that information."

PAIR OF OUTLIERS

Shire's apparent goal on the call was to refocus attention on solid earnings performance and success in its efforts to position itself as mainly a rare disease company. Ornskov noted that about 70% of Shire's revenue comes from rare disease therapies, which mostly are biologics. The pipeline, likewise, is increasingly focused on rare diseases, with approximately 70% of the 40-odd clinical candidates addressing such indications.

Ornskov pointed to lanadelumab, a monoclonal antibody for the prevention of hereditary angioedema (HAE) now being reviewed for potential approval in the US, Canada and Europe, as one of Shire's more promising rare disease assets. The drug could shake up the treatment paradigm in HAE, he asserted. Shire's existing three-product HAE portfolio brought in $369m in first quarter sales, up 1% year-over-year.

Firazyr (icatibant) – for the acute treatment of HAE attacks – posted solid growth, bringing in $206m globally, compared with $119m a year earlier. However, prophylactic agent *Cinryze* (C1 esterase inhibitor) fell off sharply, from $226m globally in first quarter 2017 to $147m in the recent quarter. Shire attributed this decline both to inventory and stocking issues, as well competition from **CSL Ltd.**'s *Haegarda*, a self-administered, subcutaneous formulation of C1 esterase inhibitor.

Shire is counting on lanadelumab, which has an Aug. 26 PDUFA date at US FDA, to change that dynamic. The company noted that lanadelumab 300 mg dosed every two weeks reduced the incidence of HAE attacks by 83%-93% across patient subtypes in its Phase III program. These subgroups differentiated based on how frequently patients experienced attacks and whether they used preventative therapy previously.

"If lanadelumab is approved in the US and outside the US, that's, of course, going to be the key product for us with this franchise," Ornskov said, noting efficacy and quality-of-life data for the candidate and its less-frequent dosing.

"We feel very confident that this will be a potential paradigm shift in the way hereditary angioedema patients are being treated and their attacks are being prevented," he added. He said it was too early to speculate about price, but indicated that Shire expects lanadelumab, as an antibody, to be a higher-margin product compared to the company's existing HAE therapies.

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Sun Rises For GSK's Trelegy And Shingrix, Sets For Advair

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GlaxoSmithKline PLC is investing behind several important drug launches as it builds a new generation of blockbusters to make up for lost sales from its aging stalwart, *Advair*. Management tried to keep investors' attention on the potential of new drugs during the company's first quarter sales and earnings call on April 25, even while sales of Advair (fluticasone proprionate/salmeterol) fell 25%.

As for any big strategy updates coming from the new leadership team of CEO Emma Walmsley and President-R&D Hal Barron, that will have to wait. Walmsley said Barron will be ready to deliver an update on R&D priorities during the second quarter conference call.

The company announced the appointment of **Genentech Inc.**'s oncology business development head Kevin Sin to lead worldwide business development on April 18, suggesting big changes could be coming on the business development front as the company looks to ramp up in cancer. But Barron was tight-lipped about what the appointment could mean for GSK during the call.

"Kevin has got a lot of business development experience in oncology, although he's got a lot of experience in other areas, including technology," Barron said when pressed by an analyst.

In the near-term GSK is in the midst of launching several new drugs, including the shingles vaccine *Shingrix* (zoster vaccine recombinant, adjuvanted), the first triple combination therapy for chronic obstructive pulmonary disease *Trelegy* (fluticasone furoate/umeclidinium/vilanterol), and a new dual regimen for HIV, *Juluca* (dolutegravir and rilpivirine).

All three launches are just getting off the ground, with the first quarter representing the first full quarter on the market for each. Already, Shingrix appears to be on a solid launch trajectory, generating revenue of £110m ($153.2m) in the first quarter.Trelegy and Juluca generated £11m ($15m) and £10m ($14m), respectively.

Last year, Shingrix cleared a big hurdle in the US, when the Centers for Disease Control and Prevention's Advisory Committee on Immunization Practices (ACIP) recommended Shingrix over a rival shingles vaccine, *Zostavax*, from **Merck & Co. Inc.**, based on the efficacy. Now, GSK appears poised to take over the big market for a shingles vaccines, a target population of about 100m patients, according to the company.

In fact, Pharmaceuticals President Luke Miels said the latest market share data shows Shingrix holds a 99% share of the pharmacy market. He pointed out that the early sales were driven by filling the pipeline, and that only about one-third of the doses sold have been used to vaccinate patients.

DATA HAVE A BIG IMPACT

New respiratory launches, including Trelegy and the biologic therapy *Nucala* (mepolizumab) for patients with severe eosinophilic asthma, could face more challenges getting off the ground, particularly when it comes to convincing payers to reimburse the medicines. Trelegy is made up of the inhaled corticosteroid fluticasone, the long-acting muscarinic antagonist (LAMA) umeclidinium and the long-acting beta2-adrenergic agonist (LABA) vilanterol, dosed once-daily in the Ellipta dry powder inhaler.

GSK has been working to build a case that the triple combination provides a synergistic effect that improves outcomes for patients, including a lower rate of exacerbations and hospitalizations versus dual therapy. Positive data from the IMPACT study were published April 19 in the *New England Journal of Medicine*, showing that Trelegy was superior to two of GSK's dual therapies, *Breo* Ellipta (fluticasone/vilanterol) and *Anoro* Ellipta (umeclidinium/vilanterol).

The data supported FDA approval of an expanded indication for Trelegy that opens the door to a broader patient population with COPD. The new indication is for the long-term, once-daily maintenance treatment of airflow obstruction in patients with COPD. It is also indicated to reduce exacerbations in COPD patients with a history of exacerbations. The original approval last September was for maintenance treatment of COPD patients who are receiving Breo and require additional bronchodilation.

Not everyone has been sure about what the data will mean for clinical practices; an accompanying editorial in the NEJM questioned the robustness of the data and wondered if the evidence was strong enough to support stepping up to a single triple therapy in clinical practice.

But GSK is confident the data support broader commercialization of Trelegy. "This data, which is answering for the first time important questions in COPD management, supports the expanded label that was approved by the FDA, and will now enable us to ramp up our promotional activities and expand our reach beyond the initial target universe to the primary care physician base," Miels said. "This really is the key to the longer-term success for Trelegy."

GSK was initially targeting 8,500 pulmonologists in the US with its promotional strategy, but plans to expand outreach to primary care physicians as well. Miels said the company is now shifting commercial spending away from Advair to drugs like Trelegy, Breo and *Nucala* (mepolizumab).

Nucala was the first in a wave of new biologics for a severe eosinophilic asthma when it was approved in 2015, but **AstraZeneca PLC** launched a new rival *Fasenra* (benralizumab) last year, which could put pressure on the launch. GSK said it is focusing on the consistent efficacy seen with Nucala as it competes against a new entry. The company has filed a supplemental biologic license application (sBLA) for an expanded indication in COPD and is awaiting action from the FDA later this year. Nucala generated £104m ($144.8m) in the first quarter.

Nucala, Trelegy and other respiratory medicines like Breo and Anoro are expected to fill the gap from lost sales of Advair, which has come under increased pricing pressure in the US and is facing generic competition in Europe. The first generic version of Advair in the US could launch later this year from **Mylan NV**, which has an ANDA pending at the FDA with a June action date.

Pricing pressure on Advair in the US was worse than expected in the first quarter, Miels said. Sales of Advair declined 25% to £566m ($788.3m) worldwide. In the US, sales fell 32% to £229m ($318.9m). Sales of products delivered on the Ellipta inhaler, meanwhile, nearly eclipsed Advair in the US with £207m ($288.3m) in revenues, growth of 16%.

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Boehringer Breathes Easy Over Spiriva Patent Expiry In US

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Reports of the death of **Boehringer Ingelheim GMBH**'s *Spiriva* (tiotropium) are greatly exaggerated, and even though its US patents start to expire in the summer, the German group does not expect to see any competition across the Atlantic to its chronic obstructive pulmonary disease (COPD) blockbuster for quite a while yet.

Boehringer's financials for 2017 show that Spiriva was once again comfortably the family-owned firm's biggest earner, with sales reaching €2.83bn. That represents a decrease of 3.9% (currency adjusted) due to the increased level of generic competition in Europe and while the decline in the latter market is significant, CEO Hubertus Von Baumbach told *Scrip* at Boehringer's annual press conference in Ingelheim that physicians were still preferring to use the original in some countries.

Allan Hillgrove, head of Boehringer's human pharma business, echoed that point, saying that penetration of generic Spiriva varies from country to country in Europe but the impact on sales was not very strong. The reality is that the copies will take a greater share over time in Europe, "due to a combination of a price impact and a value issue," he acknowledged, and "we are not forecasting it to grow; it would be a bit crazy if we did, quite frankly," but as for the US, the picture is still a rosy one.

The first of the patents on Spiriva in the US will start to run out from July this year but Hillgrove told *Scrip* that "we have got a few more years to go" and generics are not expected in the short term. His confidence is based on the case of **GlaxoSmithKline PLC**'s rival COPD blockbuster *Advair* (fluticasone propionate/salmeterol).

Although the US patents on Advair ran out a while ago, there are still no approved generics as the FDA has rejected a number of copycat versions that have been submitted, due in part to concerns about the inhalers used to deliver the drug. Hillgrove sees similarities in the case of Spiriva and Boehringer has been shifting patients to its *Respimat* inhaler from the older *Handihaler* device. He added that tiotropium "is not an easy compound for one thing," plus he doubts very much if generics companies will come up with a soft mist inhaler like Respimat, making the pathway to US approval for copies even more difficult.

> 'We are not forecasting it to grow; it would be a bit crazy if we did, quite frankly'

He noted that the combination product *Spiolto* (tiotropium/olodaterol) was making good progress from a market share point of view as well for sales and confirmed that Boehringer was not looking at a triple combo such as GSK's *Trelegy Ellipta* (fluticasone furoate/umeclidinium/vilanterol). Hillgrove said that the company looked at the possibility of a triple a number of years ago, but decided to put its resources elsewhere, believing that a triple combo would only be used as an end-stage rather than regular therapy. *(Also see "Experts Challenge GSK Triple Inhaled COPD Therapy Claims" - Scrip, 19 Apr, 2018.)* Some of the aforementioned resources will be going on expanding indications of *Ofev* (nintedanib). The drug, which is approved for idiopathic pulmonary fibrosis, has become market leader in the US and had 2017 sales of €915m (+52.3%); Boehringer is conducting two Phase III trials which are exploring Ofev in systemic sclerosis and progressive fibrosing interstitial lung disease.

JARDIANCE BOOSTED BY CV LABEL CHANGE

Away from respiratory, Hillgrove told *Scrip* he was particularly pleased with the performance of its **Eli Lilly & Co.**-partnered type 2 diabetes blockbuster *Jardiance* (empagliflozin). The drug had sales of €1.01bn (+135.7%) in 2017 and in many countries it is the number one SGLT-2 inhibitor not in the market as a whole – it competes with **AstraZeneca PLC**'s *Farxiga/Forxiga* (dapagliflozin) and **Johnson & Johnson**'s *Invokana* (canagliflozin) – but in terms of new-to-brand prescriptions.

The company is reaping the benefits of a label update based on the 7,000-patient EMPA-REG cardiovascular trial, in which empagliflozin demonstrated a 38% reduced risk of CV death, a 35% reduction in the risk of hospitalization for chronic heart failure and cut the risk of incidence or worsening nephropathy by 39%. Hillgrove noted that about half of diabetic patients die of CV disease so having "a 38% risk reduction is pretty significant" and has impressed physicians and regulators.

Boehringer is now looking at whether a similar reduction in the risk of heart failure (HF) and kidney disease would be seen in the general population, ie patients with and without diabetes. It began the EMPEROR clinical trial program for HF last year and earlier this month launched EMPA-KIDNEY in partnership with Lilly, Oxford University, Duke University and others to study the drug in patients with chronic kidney disease. The trials are expected to read out between 2019 and 2020.

Hillgrove said "the potential for Jardiance is very large," noting that more cardiologists are increasingly interested in SGLT-2 inhibitors. He added that "we are very bullish about the class," saying he will be looking out with interest for the forthcoming data from the PIONEER 2 trial pitting **Novo Nordisk AS**'s investigational oral version of its GLP-1 agonist *Ozempic* (semaglutide) head-to-head with Jardiance. *(Also see "Novo Nordisk Already Plans A 'Next Generation' Oral Semaglutide - CEO" - Scrip, 8 Mar, 2018.)*

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Boehringer Bigs Up US and China As Europe Sales Slip: **https://bit.ly/2jleeL0**

Lilly May Need To Reassess Baricitinib Market After FDA Advisory Committee

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Eli Lilly & Co. is seeking US FDA approval for baricitinib to treat adults with moderate to severe rheumatoid arthritis (RA) who have inadequately responded to or cannot tolerate methotrexate, but members of the agency's Arthritis Advisory Committee suggested on April 23 that the JAK1/2 inhibitor's risk-benefit profile could limit the drug's market.

Multiple advisory committee panelists recommended baricitinib's indication be limited to moderate to severe RA patients who have failed or can't tolerate treatment with methotrexate and other disease-modifying anti-rheumatic drugs (DMARDs), including biologics – which would give Lilly's drug a narrower label than the only other approved JAK inhibitor, **Pfizer Inc.**'s *Xeljanz* (tofacitinib). But since the potential for thrombosis risk can't be ruled out without larger studies of baricitinib, the committee was more inclined to limit use to later lines of treatment or approving only the lower dose than to support Lilly's proposed indication and dual dosing.

Lilly is developing baricitinib under a licensing agreement with **Incyte Corp.** dating back to 2009. The drug is approved with a once-daily dose of 2 mg or 4 mg in more than 40 countries and is marketed as Olumiant in the EU, where it's approved for moderate to severe RA in patients who don't respond to or can't tolerate methotrexate.

Lilly is seeking approval for 2 mg as the recommended baricitinib dose with 4 mg reserved for patients whose RA has progressed after treatment with more than one DMARD.

FDA's Arthritis Advisory Committee voted 14-1 that the data show efficacy for the 2 mg once-daily baricitinib dose and 15-0 in support of the 4 mg once-daily dose's efficacy. But when it came to the question of safety data being adequate to support baricitinib's approval, the committee voted 9-6 for the 2 mg dose and 10-5 against the 4 mg dose (one committee member changed their vote to "no" after voting "yes" by mistake, bringing the 4 mg dose tally to 11-4).

Asked whether the benefit-risk profile was adequate to support approval, the vote was 10-5 in favor of the 2 mg dose but 10-5 against the 4 mg dose, because committee members did not believe there were enough data to rule out a thrombosis risk.

"Bulls may argue that at least the 2 mg has likely made it through," Bernstein analyst Timothy Anderson noted in a report issued after the advisory committee meeting, while "bears may argue that without the 4 mg dose, the perception and commercial profile of baricitinib is wounded (in the US)."

Lilly closed up 1.4% at $80.20 per share on April 23, but fell 1.2% in after-hours trading to $79.28. Lilly issued a statement that although it was "disappointed" in the panel's assessment of the 4 mg dose, it is "confident in the positive benefit-risk profile of both the 2 mg and the 4 mg doses" and will continue working with the FDA.

Anderson noted that "nothing is final until FDA weighs in with its decision, but history shows FDA usually follows the advice of the panels it convenes. Recall that with competitor product Xeljanz, the lower dose was the only one approved, too, a decision [that] came as a surprise to most investors."

Xeljanz is approved for RA in the US at a dose of 5 mg twice-daily with an extended-release formulation, *Xeljanz XR*, dosed at 11 mg once-daily. However, Xeljanz is limited to 5 mg daily for patients with moderate to severe renal impairment and moderate hepatic impairment, but Xeljanz XR is not recommended at any dose for those patients.

THROMBOSIS SAFETY IS TOP BARICITINIB CONCERN

The FDA was particularly concerned in its review of the baricitinib new drug application (NDA) about thrombotic events, which occurred more frequently in Lilly's trials than in Pfizer's studies for Xeljanz, including post-marketing studies. The agency's reviewers concluded that there was not enough data on the 2 mg dose to determine it was sufficiently safe and effective to merit approval, and said that a 1 mg dose tested in an early dose-finding study may have been effective enough to treat patients and a safer alternative to the 2 mg and 4 mg doses.

Lilly cited findings from the Sentinel safety database to show that the rate of venous thromboembolism (VTE) in its studies was consistent with the general population of DMARD-treated moderate to severe RA patients, but the agency did not agree that the Sentinel data reduced concerns about VTE risks for baricitinib.

Donald Miller, a pharmacy professor at North Dakota State University, said he voted "yes" in favor of the safety data supporting the 2 mg dose, because he believes the population for which Lilly is seeking approval are "patients who will tolerate a little higher risk."

Patient representative Diane Aronson voted the opposite, however, noting that the safety profile of the 2 mg dose represented too high a risk for RA patients who have failed or can't tolerate methotrexate.

However, patient advocate Jennifer Horonjeff voted in favor of the 2 mg dose's safety profile, but said she was a little uncomfortable with the vote because the indication Lilly is seeking is for patients who've failed methotrexate, not methotrexate as well as DMARDs. Horonjeff is a founder and patient advocate at the Savvy Cooperative as well as a patient outcomes and quality consultant in the rheumatology division at Columbia University Medical Center in Sunnyside, NY.

NOT ENOUGH DATA TO SATISFY

Beth Jonas, rheumatology division chief at University of North Carolina School of Medicine in Chapel Hill, NC, said she came to the difficult decision of determining that safety data does not support the 2 mg dose because "we just don't have enough data to say we have enough data."

University of Pennsylvania biostatistician Warren Bilker voted in favor of the 2 mg dose's safety, noting that the completed studies were not sized to prove baricitinib does not carry a thrombosis risk, but that data could be collected in post-marketing studies.

As to safety for the 4 mg baricitinib dose, Alyce Oliver of the rheumatology division at

the Medical College of Georgia at August University voted in favor of the drug's safety to be consistent with her "yes" vote on the 2 mg dose. However, Oliver said she hopes that baricitinib will be used to treat patients with multiple failures of methotrexate and DMARDs.

Many of the panelists unconvinced by the 4 mg dose's safety commented that there wasn't enough data available, but Jon Russell, medical director of fibrosis and consulting at the Arthritis and Osteoporosis Center of South Texas, voted in favor of the higher dose regardless of any safety risk.

Russell said Lilly's studies showed the 4 mg baricitinib dose's efficacy against RA and noted that "it's war" when treating the debilitating disease, so potent medicines are needed.

On the questions about baricitinib's benefit-risk profile, Miller voted in favor of the 2 mg dose, because, he said, "if I was going to be a patient on this drug, I am going to take the 2 mg dose."

Horonjeff also voted in favor of both the 2 mg and the 4 mg dose's benefit-risk being sufficient for approval, but repeated her previous caveat that she wished the requested indication was for failure after DMARDs, including biologics.

Soko Setoguchi of the Institute for Health, Health Care Policy and Aging Research at Rutgers University also voted in favor of the lower dose's benefit-risk profile, but said post-marketing studies should be required to confirm baricitinib's safety. Her vote was the opposite for the 4 mg dose, however, noting that the thrombosis risk should be more certain before baricitinib is approved at the higher dose.

Thomas Ortell, Duke University Medical Center, also voted against approval of the 4 mg dose, saying that additional data are needed to show whether thrombotic events seen in the baricitinib studies was due to the drug or other factors.

The advisory committee's votes were based on a global development program that included four completed Phase III studies enrolling 3,492 patients. Baricitinib stumbled on its way to a committee hearing with the FDA initially rejecting Lilly's NDA. An FDA approval decision is expected in June.

The baricitinib advisory committee's reluctance to endorse the drug's higher dose and the member's questions about safety do not bode well for a competing drug from AbbVie Inc. The company plans to submit it JAK1 inhibitor upadacitinib for FDA approval in the second half of 2018, but along with positive efficacy in RA, AbbVie's candidate has raised similar questions about cardiovascular safety. *(Also see "AbbVie's Upadacitinib Safety Appears Improved In Largest, Longest RA Study" - Scrip, 9 Apr, 2018.)*

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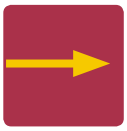

Lilly Rides To Solid First Quarter On Diabetes, Newer Products: https://bit.ly/2HEH3BH

Bayer Exercises Option To Up Stake In JV With Zydus

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Partners **Bayer** and **Cadila Healthcare Ltd.** are tweaking the holding structure of Bayer Zydus Pharma Private Limited, their long-running 50:50 sales and marketing joint venture for pharmaceutical products in India.

Cadila Healthcare, the flagship company of the Zydus Cadila group, said that it was divesting 12,500,001 equity shares "at a value determined in terms of their joint venture agreement" to Bayer.

The transaction would take Bayer's holding in the JV up to 75%, leaving the Zydus group with a 25% stake – a move that has led to speculation that a definitive transitioning of the venture was underway. Both Cadila Healthcare and Bayer held 25 million shares each in Bayer Zydus Pharma Private Limited.

Zydus Cadila, however, told *Scrip* that the current divestment of "25% of the joint venture's shareholding plus one share is exactly as per the terms of the joint venture agreement", which gives an option to Bayer to buy 25% plus one share at the end of seven years of forming the JV as per the agreement. "The joint venture company, Bayer Zydus Pharma Pvt. Ltd (BZPPL) continues to exist and Zydus has not moved out of the JV," Zydus emphasized.

In response to specific queries from *Scrip*, Zydus also maintained that the joint venture company independently markets products and so products such as *Xarelto*, *Yaz*, *Yasmin* and *Nexavar* will continue to be marketed by the JV. "Zydus' women's healthcare products, diagnostic imaging business would also continue to remain the products of BZPPL and are not being transferred back to Zydus," it added.

Bayer did not respond to specific queries from *Scrip* on the reasons for realigning its holding in the Indian joint venture. The German multinational said: "We can confirm the transaction with Cadila Healthcare, which was executed as per our joint venture agreement for Bayer Zydus Pharma."

The Bayer-Zydus JV operates in the female healthcare, metabolic disorders, diagnostics, CVS, anti-diabetics and oncology segments in India; it essentially leverages the strengths of Bayer's optimized product portfolio and Zydus' marketing and distribution capabilities.

TRANSITIONING ALLIANCE?

While it's not immediately clear if there's more to the seemingly "transitioning" venture, some industry watchers say that **Bayer AG** may be keen to have a bigger say in the alliance as it builds on its play in the Asia Pacific - a region where senior Bayer executives have, in the past, underscored an intent to give "special attention".

The changing alliance contours perhaps also need to be seen in the backdrop of Zydus Cadila's own growing global ambitions.

"But with just 25% in an alliance, it could certainly limit the interest of the minority partner (Zydus)," an industry expert told *Scrip*. Staid numbers – Cadila's annual report for 2016-17 attributes a loss of INR117m to the JV - won't have helped either though the latest earnings/revenues position of the alliance could not be immediately ascertained.

Zydus is the fourth-largest drug firm in India with market share of 4.2%, while it's the ninth largest US generics player based on prescriptions, details in a company presentation in March indicated.

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Glenmark Eyes First In-House Biologic Blockbuster

PENELOPE MACRAE

Indian drug firm **Glenmark Pharmaceuticals Ltd.** says GBR 830, a novel investigational drug candidate to treat moderate-to-severe atopic dermatitis, could be a "blockbuster." The drug is the first biologic that Glenmark has developed in-house and is part of the company's quest to be more innovation-led and shift from away producing plain-vanilla generics.

The company completed a Phase IIa trial last year of GBR 830 that indicated "clinically meaningful and sustained" improvement in patients with moderate-to-severe atopic dermatitis, also known as atopic eczema. Atopic dermatitis is a skin inflammation often associated with other atopic disorders like allergic rhinitis and asthma and represents a multi-billion-dollar treatment market globally.

Now, Glenmark has said it is beginning a Phase IIb clinical trial of the medicine, marking what company president Fred Grossman called an "exciting step." GBR 830 is "Glenmark's first new biologic entity developed in-house," he said, adding the company is moving "to rapidly advance the GBR 830 development program."

Company chairman Glenn Saldanha, whose father founded the company in 1977 and named it after his two sons, has said the global market size for atopic dermatitis "is estimated at being $8-$9bn." He told India's CNBC TV18 network last year following the successful Phase 2a trial he believed GBR 830 "could be a blockbuster" drug. He said the company would seek an out-licensing deal with a "significant upfront payment" and "milestones as the drug progresses."

The Mumbai-headquartered company expects it will take at least till fiscal year 2022 to get GBR 830 to market because of "multiple studies" required, he said.

APAC SHOWING HIGHEST DERMATITIS GROWTH

Anti-inflammatory agents are viewed as a major revenue-generating segment as they're normally used as a first-line therapy after failure of moisturizers. Analysts expect Asia Pacific to show the highest rate of market growth, eclipsing North America, as atopic dermatitis treatment awareness in the region grows. But the atopic dermatitis treatment market also is fiercely competitive with a multitude of players including **AbbVie Inc**, **F Hoffmann-La Roche AG**, **Glaxosmithkline plc.**, **Novartis AG**, **Pfizer Inc.** and **Sanofi SA**.

Glenmark aims to start enrolling volunteers in the trial in two months on GBR 830 which is designed to inhibit OX40, a costimulatory immune checkpoint receptor expressed on activated T-cells and memory T-cells. Inhibiting OX40 potentially reduces inflammation linked with atopic dermatitis symptoms. Costimulatory signals are essential for T-cell activity, and binding between OX40 and OX40L is a biomarker for severity of autoimmune diseases.

The Phase 2b, double-blind, placebo-controlled multicenter trial will randomize some 392 patients across four dosing arms of GBR 830 and a placebo. The launch of the trial is a "meaningful milestone," said Kurt Stoeckli, Glenmark's chief scientific officer.

In the 12-week Phase 2a study which involved 64 patients with moderate-to-severe atopic dermatitis, data showed GBR 830 had an effect on AD-related disease biomarkers and there was clinical improvement in the Eczema Area and Severity Index (EASI) scores in 17 out of 23 patients. "We observed consistency between molecular signals of disease activity, measurable changes in skin thickening and clinical improvement in AD symptoms," said dermatologist Emma Guttman-Yassky, who teaches at Mount Sinai's Icahn School of Medicine in New York.

In addition to dermatitis, Glenmark is evaluating possibilities for conducting studies with GBR 830 for treating other inflammatory autoimmune conditions where dysregulation of OX40 overexpression is implicated in disease activity. Preparations for a clinical trial assessing GBR 830 for treating systemic lupus erythematosus (SLE) are underway.

GLENMARK MAKING STRATEGIC TRANSITION

Development of the biologic drug is part of Glenmark's game-plan to remake itself from being a pure generics-driven company to being an organization built on three pillars -- global generics, specialty products and innovative products. Saldanha, who took over Glenmark nearly two decades ago from his father, was one of the early movers in India in the drug-discovery business but the company has so far met with limited success.

Now Glenmark's making a concerted strategic transition in the face of increased buyer consolidation and a more crowded generics space in the US. Other Indian drug firms, like market leader Sun Pharmaceutical, are making the same strategy pivot to come up with more complex drugs that offer bigger margins and face less competition even though these medicines are also more costly, time-consuming and risky to develop.

On the novel biologics side, Glenmark added it's making progress on GBR 1342, a bi-specific antibody targeting multiple myeloma by initiating phase 1 trials. In addition, the company plans to submit an NDA for its first specialty product, a nasal spray called *Ryaltris* to treat seasonal allergic rhinitis, with the US FDA by the end of June.

The company has completed Phase III clinical trials in the US for the nasal spray, containing a fixed-dose combination of 25 mcg mometasone furoate and 665 mcg olopatadine hydrochloride.

Even though it has operations in over 50 countries, Glenmark is a small drug player -- it's ranked just 13th in India's fragmented market with annual sales of INR28bn ($421.4m). But the company has big aspirations and it's working to discover new molecules -- both new chemical entities (NCEs) and new biological entities (NBEs). As part of its strategy, the company is also looking at a bigger presence in complex generics.

By 2025, Glenmark expects specialty and innovative drugs to contribute 30% to total sales. "Our pipeline of speciality products, to be rolled out over the next three to four years, is expected to act as a defence against generics price erosion and increase in competition, and boost profitable growth," Saldanha said in the company's annual report. The OTC segment will be another growth lever.

SHARES RALLY ON MORE POSITIVE NEWS FLOW

The company got a sharp reminder of the need to generate new revenue streams when third-quarter-to-December net profit plunged 78% to INR1.04bn ($15.6m) from a year earlier on the back of a 40.2%

slide in US revenues. Performance was hit by loss of exclusivity in the US market for its generic version of anti-cholesterol drug Zetia and falling generics prices. The company has said it believes the fourth-quarter should be better, even though it expects the US market business "to remain very challenging."

Glenmark's shares have gained around 10% in the past month on positive news that has included US regulatory clearance for its Baddi plant, which produces oral solids and liquid doses, and makes up about 10% of company sales to the US market. The plant was hit by a Form 483 last November. Glenmark's stock was up nearly 2% at INR581.80 on April 23, but that was still less than half its peak of INR1,226.80 reached in mid-2015.

Glenmark's pipeline contains oncology, respiratory disease and dermatology compounds in various stages of clinical development along with molecules primarily focused on inflammation -- asthma and COPD, rheumatoid arthritis, neuropathic pain and inflammatory pain and metabolic disorders like diabetes and obesity. The company has said it will continue with its approach of out-licensing its molecules, a business model that involves licensing original molecules to foreign drug companies which conduct clinical trials, especially Phase III trials.

Even Indian drug companies with the big balance sheets find it difficult to finance expensive large-scale drug development programs.

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Toujeo, Perjeta Biosimilars On Biocon-Mylan Menu But Humira Version Iffy

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Biocon Ltd. and **Mylan NV** are expanding their long-running biosimilars collaboration to include two new next-generation biosimilar programs - insulin glargine 300 units/mL (**Sanofi**'s *Toujeo*) and pertuzumab (**Roche**'s *Perjeta*) – but the Indian firm's management was non-committal on the outlook for the duo's own partnered *Humira* (adalimumab) biosimilar.

Biocon said that the new programs would bolster their existing global biosimilars portfolio comprising antibodies and insulin analogs, though no specifics on plans around the programs were provided. The duo have, so far, had a fairly effective collaboration that cross-leverages development and commercialization capabilities in a risk and reward share model.

Last month Biocon and Mylan's *Semglee* (insulin glargine) was approved by the European Commission (EC), following a positive recommendation earlier by the EMA's Committee for Medicinal Products for Human Use (CHMP). In the US, the duo's insulin glargine under the NDA pathway is under review by the FDA; their biosimilar version of Roche's breast cancer drug *Herceptin* (trastuzumab) was approved by the FDA in December last year.

EARNINGS CALL

Semglee is expected to be launched by Mylan in Australia and Europe in the second half of 2018, Biocon chair, Kiran Mazumdar-Shaw said on the company's fourth-quarter earnings call April 27. The product is also expected to be commercialized by Biocon's local partner in South Korea later this year.

Near-term opportunities are currently being addressed by "our very successful" global partnership with Mylan, Mazumdar-Shaw noted. This, in the backdrop that Biocon is straddling another biosimilars collaboration – with **Sandoz International GMBH** – for developing a set of next-generation biosimilar products, opportunities for which are expected to open up in the next decade.

But the Biocon management were less forthcoming on how commercialization priorities could pan out for its partnered Humira biosimilar with Mylan currently in phase III, in the backdrop of Mylan's recent in-licensing deal with **Fujifilm Kyowa Kirin Biologics Co. Ltd.** (FKB) for its biosimilar adalimumab. FKB's biosimilar Humira could potentially obtain approval in Europe in the second half of 2018.

To an analyst's query on Biocon's plans with its own Mylan-partnered adalimumab in markets such as the US and Europe, Biocon CEO and Joint MD, Dr Arun Chandavarkar, said that while the arrangement with FKB is currently for Europe, there are "options to extend that to the US or other jurisdictions."

"At this stage, based on what we have seen and you are aware of the potential launch timelines/market formation timelines in the US, we feel that there is time to take a decision on which option to pursue in the US and other markets. We have not ruled in or ruled out any option, outside of Europe at this stage."

MARKET COMES FIRST

Mylan president Rajiv Malik had at the time of the FKB deal maintained that "nothing is wrong with the Biocon partnership" but that the market comes first. *(Also see "Mylan Looks To Expedite Biosimilar Humira in EU Through Kyowa Deal" - Scrip, 12 Apr, 2018.)*

"And when we realized that we will not be in time for Europe for market formation with our biosimilar to Humira, we had to make the call in favour of the FKB product. If we don't have a product and market needs it, we'll go and find it," Malik had explained.

Biocon had, at the time, said that it retained "its economic interest" in the FKB arrangement vis-a-vis Mylan "in line with its existing global collaboration with Mylan for monoclonal antibodies."

"We participate in whatever costs and profits Mylan has as part of the deal [with FKB]; we participate in our share of that as per our global arrangement," Chandavarkar explained on the earnings call.

Biocon reported a growth of 27% in revenues to INR12.37bn ($186m) in the fourth quarter ended March 2018 led by the biologics and research services businesses, which grew 47% and 45%, respectively. Its traditional small molecules and branded formulations businesses also turned in a positive performance in the quarter. Net profits for the quarter grew 2% to INR1.30bn.

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Biologics Kill Biosimilars? Limited Originator Uptake Perplexes China Biogenerics Market

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Armed with four biosimilars that are poised to gain regulatory approvals, China's most prominent biosimilar developer **Henlius Biotech Co. Ltd** still finds it difficult to develop such products alone, and sees it necessary to have an innovative biologics pipeline.

The Shanghai-based firm, which is majority controlled by **Fosun International Ltd.**, has high hopes to launch its first biosimilar product to China soon. But it seems not to be holding its breath for a spectacular market debut.

Founded in 2009, Henlius has managed to enter four biosimilars into Phase III development, among which HLX01 (rituximab) is pending approval at the new China State Drug Administration (CSDA) after an NDA filed last October.

The follow-on product to Roche's anticancer *MabThera* could be the first biosimilar to be launched in China under a new regulatory pathway for these products issued in 2015. The company is going through manufacturing inspections by the regulatory agency, and an approval is expected within 2018.

Aside from rituximab, Henlius also has HLX02 (trastuzumab), HLX03 (adalimumab) and HLX04 (bevacizumab) in late-stage development.

Biosimilars are expected to grow rapidly in China given the latest strong policy bush; the country now has only a very low market penetration of biologics, below 5%, partially due to the high costs associated with them.

But there are many hurdles facing biosimilars in China, said industry experts attending the BioCon China conference, held on April 23-24 in Shanghai. These include: a lack of awareness among physicians and patients; no reimbursement; head-on competition with established multinational originator companies such as **Roche** and **AbbVie**; uncertain pricing; and China's feverish activity to develop innovative biologic therapies from gene-editing to immuno-oncology drugs to CAR-T treatments.

Biosimilar and conventional generic drugs are expected to play a bigger role in the country, where the government has recently voiced its strongest-ever support for generics in a bid to greatly enhance access to some life-saving but costly drugs, many in the cancer area.

HOW AFFORDABLE?

Affordable innovation is exactly what Henlius is banking on to grab biologic market share in China, and the company's motto is literally "affordable innovation".

The company has yet to disclose its pricing for biosimilar rituximab, however, this may not be as low as some hope, cautioned Scott Liu, CEO and co-founder of the Shanghai-based company.

"The pricing must let physicians and patients feel the difference compared to the originator product," Liu told participants at the conference. "However, the price can't be that low, because we must consider the pricing of the originator product, and leave enough room for further [downward] adjustment." Liu emphasized that marketing efforts centered on academic promotion – similar to what biologics companies have been doing – will be necessary but will also add cost. "We must inform physicians about our products similar to originators' products so they fully understand the clinical data, which are obtained under international standards," Liu stressed.

A premium associated with being the first anticancer biologic to be launched in China could also mean the price won't be low. Furthermore, China in the past has resorted to negotiations to lower costly cancer drug prices, and the last round of such reductions was over 50% for some targeted therapies.

Outside China, biosimilars are priced at a discount of roughly 30% to originator biologics. In China, biologics are deemed to be high-priced treatments, partially because there is no reimbursement.

LIMITED ORIGINATOR UPTAKE

Interchangeability is another key issue. Although China has a regulatory approval pathway, there are no formal rules on whether originators can be substituted with biosimilars, and no rules on indication extrapolation and how biosimilars will be named.

In 2015, China issued its first regulatory pathway for biosimilars, largely adopted from the regulations of the European Medicines Agency. Many believe the naming of biosimilars and interchangeability will be similar to what the EU has in place.

Meanwhile, cancer drug makers including Roche have puts much effort on market access programs in China, providing patient assistance including free product after certain treatment cycles.

Still, the lack of insurance coverage has led to the limited uptake of original biologics in China, where Roche's global bestselling anticancer *Avastin* (bevacizumab) sales are merely 16% of their sales in Japan, despite China having a much larger population.

Despite the high hopes for biosimilars in China, several developers are aggressively looking at overseas markets, or developing their own other innovative biologic therapies given the general environment.

Just three years ago, biosimilars seemed to be a sure area for biotech investment in China, but now many companies are switching to immuno-oncology and cell therapies, fueled by the deep pockets of venture funds that are eager to leap into the foray and grab a share of a potentially huge market.

One of these, **Innovent Biologics Inc.**, founded by US returnee Michael Yu and which started as a developer of biosimilars, is now is steaming ahead as an immuno-oncology developer. Billed as China's largest biotech unicorn, Innovent recently received a fast-track review designation from the CSDA for its PD-1 checkpoint inhibitor to treat cancer.

But Innovent suffered a setback for its anti-PD-1 agent, IBI308, developed jointly with Eli Lilly, after the Suzhou firm withdraw its approval application a month ago, but it seems the company is back on track.

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Q1 Was Slow For Deals, But That Could Change With One Big Transaction – PwC

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By volume, life sciences deal-making declined during the first quarter of 2018, although four fairly large deals meant that the aggregate value of such deals rose compared to the fourth quarter, PwC's deal practice notes in a new report. But the group thinks completion of one big transaction could open the floodgates, so to speak.

There has been a lot of speculation about an increase in deals with the US corporate tax reform that passed late last year, and **Takeda Pharmaceutical Co. Ltd.**'s pursuit of **Shire PLC** – currently valued at about $64.3bn, which would make it one of the largest biopharma deals ever – shows that mega-mergers are back on the table. *(Also see "Takeda Closes In On Shire With Revised £49/Share Offer" - Scrip, 24 Apr, 2018.)*

PwC's *Global Pharma & Life Sciences Deals Insights Q1 2018* report indicates that if one large-scale transaction goes through, it could unleash pent up demand on the part of other possible acquirers. *(Also see "Shire's Suitors: Takeda, Pfizer Seen As Likely To Bid; Amgen Could Enter Fray" - Scrip, 6 Apr, 2018.)*

In a foreword, PwC's US Pharma and Life Sciences Deals Leader Glenn Hunzinger said the fundamentals for deal-making – based on both asset demand and the availability of funds – have "never been better." Funding for deals is plentiful both because of relatively inexpensive financing, as well as the overseas cash freed up for US companies by last year's tax reform legislation.

"Pent up demand and surplus cash are expected to drive greater activity going forward," he wrote. "As a result, we believe the pharmaceutical and biotech sub-sectors will be active due to potential transformational deals combined with smaller, bolt-on acquisitions by larger companies," he added. "For the generics and specialty pharmaceutical sub-sectors where scale is critical, mid-tier companies are expected to consolidate, driving additional activity."

Hunzinger also predicted an increasing rate of corporate divestitures, driven partly by private equity buyers, although this may occur mainly in medical device sector. "Divestitures will likely continue to be a major focus of big pharma as they seek to extract value and reshape their portfolios," the report states. Overall, PwC anticipates increased deal activity during the second quarter of 2018.

CONSENSUS FORMING

PharmaVitae perceived a similar environment in its quarterly *M&A Analysis* report, published April 24. Consolidation in the payer arena should drive a cycle of large-scale M&A in biopharma, the report says, pointing specifically to **Pfizer Inc.** as a catalyst. *(Also see "Pfizer, Poised For A Tax Reform Windfall, Talks About Ways To Reinvest" - Scrip, 30 Jan, 2018.)* Noting the New York pharma's thwarted M&A bids in the past five years, the report predicts CEO Ian Read will continue "to stress the inevitability of upcoming consolidation and will seek to leverage the company's core competency in large-scale acquisitions."

"PharmaVitae expects such a deal to spark a trail of subsequent combinations, with the industry still largely fragmented," it continues. "This will be buoyed by the potential of the technology industry's prospective incursion, as biopharmaceutical companies aim to stake a claim in a future that will be largely swayed by data analytics and artificial intelligence capabilities."

RETURN OF THE MEGA-MERGER

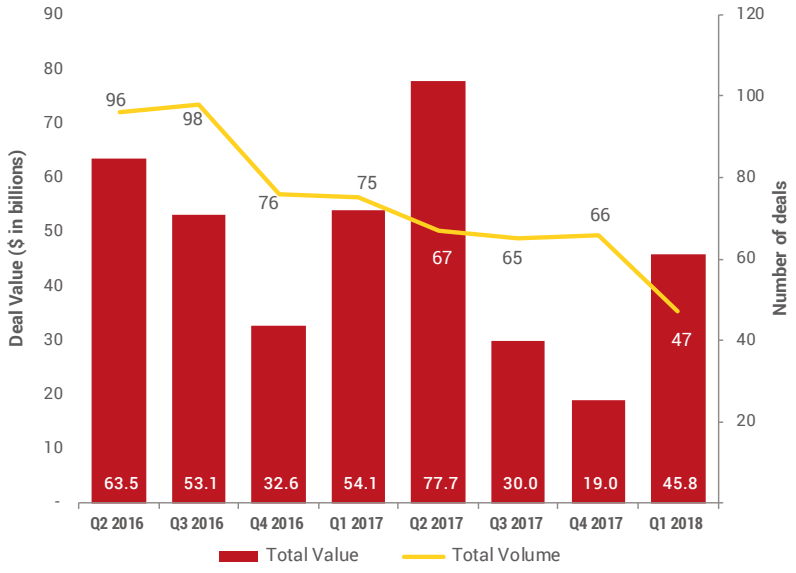
In March, Leerink Partners advised the market to expect the return of the mega-merger, listing Pfizer, **Merck & Co. Inc.** and **Roche** as the most likely acquirers of large assets in the biopharma sector.

During the first quarter, life sciences deal-making totaled $45.8bn in aggregate estimated value, PwC's report states, up 141% over fourth quarter 2017 but down 15% from the first quarter of last year. However, the total of 47 deals declined from both prior time points, down 29% sequentially and 37% year-over-year.

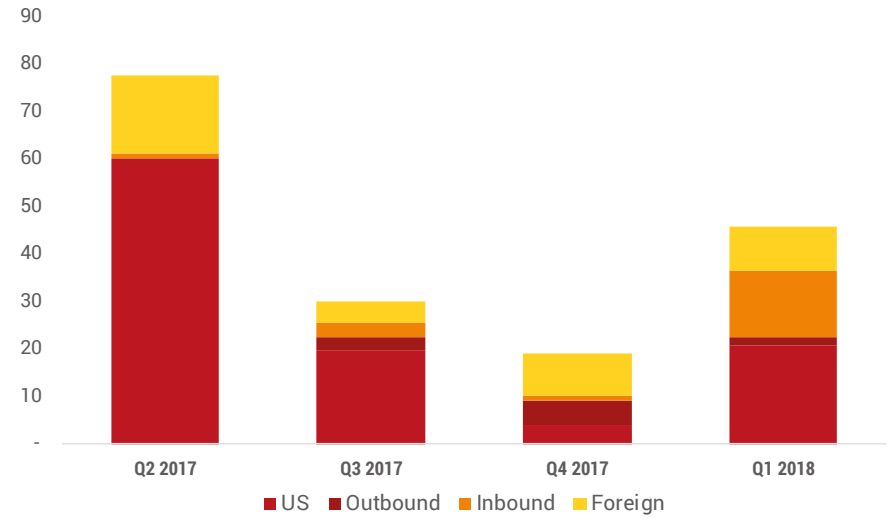
PwC notes that the decline in deal volume is a trend that began in the first quarter of 2017, except for a temporary spike during the second quarter. However, the 47 deals recorded during the first quarter of 2018 made for the lowest quarterly volume in two full years.

The increase in overall deal value during the past quarter – compared to the prior two quarters – can be attributed mainly to four deals (all in January) with estimated values of $5bn or more. These were a pair of acquisitions each by **Sanofi** and **Celgene Corp.** The French pharma's $11.7bn acquisition of

Life Sciences Deals, Aggregate Value, 2016-2018



External Investment In US Assets Increases



Bioverativ Inc. on Jan. 22 was the largest life sciences deal during the quarter, while it bought **Ablynx NV** for nearly $5.5bn on Jan. 29. Meanwhile, Celgene's $9.3bn buyout of **Juno Therapeutics Inc.** on Jan. 22 and its $7.0bn takeout of **Impact Biomedicines** on Jan. 7 were the second and third largest deals of the quarter.

"Q1 2018 had four deals larger than $5.0bn, which suggests that megadeals are expected to continue in future quarters, similar to the trends exhibited over the two years prior to the second half of 2017," the report notes.

TAX REFORM MAY DRIVE FOREIGN INTEREST

PwC also pointed out that deal-making between US-based companies comprised the largest share by aggregate value during the first quarter, compared to deals between non-US firms and so-called "inbound" deals in which a foreign company invests in a US asset and "outbound" deals in which a US company invests in an ex-US interest. During the fourth quarter, a majority portion of deal value featured non-US companies as both parties to the transaction, the report says.

INBOUND DEALS

Inbound deals comprised the second largest segment of life sciences deals by aggregate value during the first quarter, PwC adds, although the Sanofi purchase of Bioverativ drove a significant portion of that. *(See table.)* Still, the group expects the impact of tax reform to drive a continued strong pace of inbound deals.

"While inbound deals continue to represent a relatively small share of total value, we expect tax reform to drive a renewed focus for foreign companies looking to expand operations in the US in coming years," PwC predicted. Tax reform also will drive an increase in acquisitions by US firms, the report said.

PharmaVitae also concluded that US M&A prospects received "a major boost" thanks to the tax reform enacted last December, which lowered the federal corporate income tax rate from 35% to 21%, which it said will make deals more accretive. Likewise, the reduction of tax on overseas profits to 15.5% should be beneficial to deal-making. "Repatriation and the lowering of corporate tax have stimulated the biopharmaceutical industry's appetite for US-based M&A," the report states.

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(Images: PwC Deals: *Global Pharma & Life Sciences Deals Insights Q1 2018*)

Mereo Halts Plans For US Listing

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UK-based **Mereo BioPharma Group PLC** has postponed its plans for an $80m Nasdaq listing because of challenging market conditions – a decision that has knocked its UK stock price.

Mereo's stock, traded already on the London Stock Exchange, had spiked on the news the company would float on Nasdaq. However, its price has tumbled again after the company announced it was halting this move.

Mereo announced on April 9 that the company would list American Depositary Shares on the Nasdaq Global Market to raise around $80m. But in an April 26 statement, Mereo said "current market conditions are not conducive for an offering on terms that would be in the best interests of its shareholders."

Despite the uncertainty, a spokesperson for the company said, "Mereo's share price increased by 12% during the listing process and remains above the price at the start of the process."

The spokesperson also told *Scrip*, "The Nasdaq Biotech Index's (NBI) decline during 2018 has created challenging market conditions in the US and there is no doubt that the markets have been very volatile, leading both to nervousness and a very price-conscious environment for IPOs and follow-ons." These conditions led Mereo's board to take the decision to withdraw the global offering and postpone the proposed listing.

Additionally, the spokesperson noted that "many of the recent development stage biotech IPOs have not performed post admission" in the US. The biopharma, which is developing therapeutics for rare and specialty diseases, had a net cash, short-term deposits and short-term investment balance of £52.5m as of Dec. 31, 2017. It noted that this funding would provide a strong cash runway to deliver on its next key clinical program milestones and corporate objectives.

Mereo's CEO said in a statement: "We remain well funded and are confident in the future development and potential value of our pipeline."

The company told *Scrip* it was considering what its next steps would be and that it "will update the market once we have formulated our plans."

CONTINUED ON PAGE 20

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Mereo expects to report data this year for two of its key pipeline products. The company expects to see topline results from the Phase II ASTEROID trial of BPS-804 in osteogenesis imperfecta between May and September 2017.

Mereo said it was currently preparing to move forward with a pivotal study of BPS-804, a novel antibody for osteogenesis imperfecta, with fracture rate as the primary endpoint.

Furthermore, the company expects data from the Phase IIb safety extension study of BGS-649 in hypogonadotropic hypogonadism (HH) in the fourth quarter of 2018.

In March this year, the company reported positive topline data from its Phase IIb dose-ranging clinical trial for BGS-649 in obese men suffering from HH. Biomedtracker analysts said at the time that preliminary results showed the Phase IIb trial had encouragingly met all primary, secondary, and exploratory endpoints with a dose response relationship demonstrated. "We await release of the full quantitative results in Q4 2018 to further elucidate the aromatase inhibitor's clinical profile," they noted.

BGS-649 is differentiated by its mechanism of action as an aromatase inhibitor, which is unique compared to the majority of testosterone replacement therapies on the market and in the pipeline. Biomedtracker analysts noted that "since available therapies may adversely impact male fertility through LH and FSH [luteinizing and follicle stimulating hormone] suppression, there is need for treatments without these issues."

A NEUTROPHIL ELASTASE INHIBITOR

This year will also see Mereo initiate a Phase II proof-of-concept clinical trial with AZD-9668, a reversible inhibitor of human neutrophil elastase, in patients with severe alpha-1 antitrypsin deficiency. Mereo licensed AZD-9668 from **AstraZeneca PLC** in Oct. 2017 for an initial upfront payment of $5m.

Mereo's final pipeline program is for BCT-197, a MAP kinase inhibitor in development as an oral first-line therapy for patients with acute exacerbation of chronic obstructive pulmonary disease. Mereo's spokesperson said the company continues to seek a partner for this compound. In late-2017, Mereo reported mixed topline Phase II data for BCT-197 from the AETHER trial.

Biomedtracker analysts said at the time that while the primary endpoint was met in the AETHER trial (reduction in FEV1 from baseline to day seven) for both the high and low dose of BCT-197, statistical significance was not achieved for a standard COPD endpoint comparing FEV1 reduction in the placebo and BCT-197 arms.

"This suggests that the reduction in FEV1 was only marginally larger in the BCT-197 arms than in the placebo arm and could have been due to chance," the analysts said.

Updated results from the AETHER study will be presented next month during the late-breaking session at the American Thoracic Society (ATS) 2018 International Conference on May 21.

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Crescendo In Largest European Biotech Series B Of Year

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UK-based **Crescendo Biologics Ltd.** has raised $70m (€57m) through a series B financing to progress its lead program CB307 into clinical studies – marking the largest European series B financing of 2018 so far.

Crescendo is developing multi-functional biologics in oncology, known as *Humabodies*, that are focused on targeted T-cell engagers. The company has a pipeline of multiple preclinical programs, including one asset partnered with **Takeda Pharmaceutical Co. Ltd.**

Peter Pack, CEO of Crescendo, told *Scrip* the company was able to secure substantial series B funding because it had a novel way of targeting and activating specific T-cells. "This is a huge topic in the immuno-oncology space and we have developed a novel mechanism to do this, which we think is safer and more specific than current approaches," he said.

The financing round represents the largest disclosed series B biotech financing in Europe in 2018. Crescendo previously raised $28m in a series A round in December 2013.

Pack also highlighted that the company had managed to attract investment from different sources, including existing and new European investors and a Chinese/US establishment.

The series B round was led by Andera Partners (formerly Edmond de Rothschild Investment Partners), which holds Europe's largest life science fund, Biodiscovery V. Other participants included Quan Capital, with its life sciences fund Quan Venture Fund I, and existing investors Sofinnova Partners, IP Group, EMBL and Takeda Ventures.

"We have attracted diverse funds… It is important for us that we have attracted the largest life science financier in Europe, Andera Partners, and that we have kept our former investors. We have a really fascinating mix of investors, it will be interesting to see how the dynamics work," Pack said.

The company's lead asset CB307, a novel bispecific T-cell engager for the selective activation of tumor-specific T-cells exclusively within the tumor microenvironment, is closest to the clinic. This drug is being tested in castration-resistant prostate cancer and is expected to enter human clinical trials within 18 to 20 months.

The series B financing will see Crescendo through proof-of-concept trials with its lead asset and allow the company to grow its pipeline, exploring the use of Humabody drugs in other cancer indications.

As Crescendo approaches the clinic with its first drug, Pack said it had added development expertise to its team. He also said the company, over the last few years, had been slowly shifting away from discovery to focus on drug development.

Last year Crescendo named Philip Bland-Ward chief scientific officer and Edward Stewart chief business officer. Bland-Ward came to Crescendo from **Kymab Ltd.**, where he was responsible for leading its most advanced development program; and Stewart joined the company from **Merrimack Pharmaceuticals Inc.**, where he previously managed the company's business development strategy.

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GSK's Head Of Artificial Intelligence Unveils R&D Goals

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GlaxoSmithKline PLC's John Baldoni stepped down from a senior role within the big pharma's R&D executive committee in 2017 to take charge of the company's use of artificial intelligence for drug discovery and development. In an exclusive interview with *Scrip*, he sheds light on the UK drug major's internal AI unit and the diseases it hopes to target through machine-driven R&D.

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Baldoni highlighted that roughly 30% of the cost of drug development was generated in the phase between target identification and proof-of-pharmacology. "On average, it usually takes about six and a half years and one third of the cost of drug development to get from the idea to the molecule, and our goal is to significantly reduce that," he said.

Baldoni approached GSK's top management internally to influence the use of AI within the company's R&D operations, after following the machine reading and learning technology trend in other sectors, such as the financial sector. He is also a leader for the ATOM initiative (Accelerating Therapeutics for Opportunities in Medicine), a public-private consortium that integrates high-performance computing, shared biological data from public and industry sources, and emerging biotechnologies to accelerate the discovery of effective cancer therapies.

The response to Baldoni's proposal was varied, he said. "There was skepticism around me but Patrick Vallance and the decision-makers at the senior level felt this was an opportunity – and a relatively inexpensive experiment to do in our environment – to see whether AI will play and create value for the sector," Baldoni said. Vallance, who at the time was Baldoni's boss as GSK's president of R&D, has since stepped down from the company.

To get this AI experiment started, GSK has identified a biological pathway it wants to explore – the big pharma is particularly interested in "targets of difficult diseases of the brain," Baldoni said. However, the company is yet to publicly announce the specific diseases it will target.

The company expects to work with four different collaborators and two academic advisers who are interested in learning how an AI approach would be used to develop drugs for this particular disease. GSK believes the pathway it is targeting through this drug discovery experiment plays a role in several diseases that have been difficult to discover drugs for. "We see this as a confluence of science and technology in the brain; artificial intelligence methodologies being applied to these very intractable diseases that have plagued society forever and we just think that this is a good combination," Baldoni said.

GSK's AI leader added that the disease GSK has targeted was not an easy one to use as a test case. However, he would "rather prove the approach on something that is meaningful rather than easy."

AI PARTNERSHIPS

The AI drug discovery unit at GSK has only six members, currently, but the group is working with external partners. For example, in July 2017, GSK signed a drug discovery collaboration with **Exscientia Ltd.**, a UK-based company that automates drug design with its AI-based platform. Under the agreement, Exscientia will receive research payments from GSK that could reach more than $42m. The pair will use GSK's pharma know-how and Exscientia's AI-enabled platform to discover small molecules to treat up to 10 targets chosen by GSK.

Baldoni added that the big pharma has "a number of other deals that are in the making right now." He said the company intends "highly leveraging outside experts in this space."

Striking an AI deal was tricky to start with though, Baldoni noted. "It was so new that the finance people, the legal people and the business development people, they were learning as things progressed," he said.

Also, to complete a deal in this domain, GSK had to give third parties access to its data prior to an agreement. "That's something that GSK hadn't done before," Baldoni said. GSK has previously granted external groups access to large quantities of data for molecules it had no commercial interest in. But AI partnerships require the company to reveal "millions of compounds where we have deep interest in the molecules," he said.

EXPERIMENT TIMELINE

GSK's AI team has completed a first iteration of designing molecules using its new machine-enabled approach; those molecules are now being tested in human relevant assays of the disease.

"One of the components of our approach is that we want to really go into human-like test systems," Baldoni said. "We don't want to do very simple biochemical assays to demonstrate that the molecules work. We want to see how these molecules work in a very complex micro-environment." The team has also recently launched a second

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

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Selected clinical trial developments for the week 20–26 April 2018

LEAD COMPANY/PARTNER	COMPOUND	INDICATION	COMMENTS
PHASE III INTERIM/TOP-LINE RESULTS			
Merck & Co. Inc.	relebactam plus imipenem/cilastatin	carbapenem-resistant infections	RESTORE-IM1; favorable efficacy and side effect responses.
Alexion Pharmaceuticals Inc.	ALXN1210, every eight weeks	paroxysmal nocturnal hemoglobinuria	Switching endpoints non-inferior to *Soliris*.
AveXis Inc.	AVXS-101, gene therapy	spinal muscular atrophy, type 1	STRIVE; signs of efficacy.
GW Pharmaceuticals PLC	*Epidiolex* (cannabidiol) oral solution	Lennox-Gastaut and Dravet syndromes	GWPCARE5; clinical improvements.
AbbVie Inc.	upadacitinib	rheumatoid arthritis	SELECT-SUNRISE; met primary endpoint, in Japanese patients.
AstraZeneca PLC	*Imfinzi* (durvalumab) with or without tremelimumab	non-small cell lung cancer (NSCLC), third-line	ARCTIC; combination missed endpoints, monotherapy encouraging.
UPDATED PHASE III RESULTS			
Biogen Inc.	*Spinraza* (nusinersen)	spinal muscular dystrophy	SHINE; benefits sustained.
Alder Biopharmaceuticals Inc.	eptinezumab	episodic migraine	PROMISE1; increased migraine-free intervals, quality of life.
Teva Pharmaceutical Industries Ltd.	fremanezumab	chronic migraine	HALO CM, EM; efficacy confirmed.
Biohaven Pharmaceuticals Holding Co. Ltd.	rimegepant	migraine	Durability of clinical effects.
Neurocrine Biosciences Inc.	*Ingrezza* (valbenazine)	tardive dyskinesia	Kinect 3, 4; improved symptoms.
Flexion Therapeutics Inc.	*Zilretta* (triamcinolone acetonide) Inj	osteoarthritis	Robust treatment responses.
Zogenix Inc.	ZX008 (low-dose fenfluramine)	Dravet syndrome	Reduced seizures, well tolerated.
Celgene Corp.	ozanimod	multiple sclerosis	RADIANCE, SUNBEAM; reduced relapse rates.
Ionis Pharmaceuticals Inc.	inotersen	hATTR amyloidosis polyneuropathy	Benefits observed, sustained response.
Paratek Pharmaceuticals Inc.	omadacycline	community-acquired bacterial pneumonia	OPTIC, OASIS 2; high response rate, non-inferior to moxifloxacin.
Achaogen Inc.	plazomicin	urinary tract infections	EPIC, CARE; high response rates, well tolerated.
Melinta Therapeutics Inc.	*Vabomere* (meropenem and vaborbactam)	bacterial infections	TANGO II, efficacy in patients with co-morbidities.
PHASE III INITIATED			
Vertex Pharmaceuticals Inc.	VX-445, tezacaftor and ivacaftor	cystic fibrosis	A triple regimen.
Aldeyra Therapeutics Inc.	reproxalap	conjunctivitis, allergic	Topical ocular administration.
AveXis Inc.	AVXS-101, gene therapy	pre-symptomatic spinal muscular atrophy types 1,2,3	SPRINT; a one-time dose.
PHASE III ANNOUNCED			
Synthetic Biologics Inc.	ribaxamase (SYN-004)	*Clostridium difficile* associated diarrhea	In the US.

Source: Biomedtracker

CONTINUED FROM PAGE 21

project, which will see this first tranche of molecules tested against a second disease target.

Baldoni said there were three races a pharmaceutical company must win to excel in drug development:

- the race to the molecule;
- the race to the clinic;
- and the race to the market.

For a company to be successful it must win in each one of those races.

"The race to the molecule is probably the place where you can create the most value for a company," Baldoni said. "Pick the right targets, make molecules that will modulate that disease, and quickly determine whether or not your hypothesis is correct. This is where there is a lot of failure in the industry. A huge amount of failure," he said.

He noted that roughly 5,000 molecules were generated for every candidate that made it into human studies, and even then, the failure rate was roughly 85% to 90%.

"There's a lot of failure there. If you can reduce that failure by just a little bit you're creating a lot of value and you help that organization win the race to the clinic.," Baldoni said, adding that GSK's senior management recognized the benefits of speeding up molecule creation, and potentially getting to drug targets with greater relevance.

A DESERVED TEST

"I think society deserves this from big pharma," Baldoni said, when asked why he wanted to lead AI use at GSK. He is also motivated by the use of AI in other sectors, such as the financial sector, where machine learning is used to detect fraud or predict growth areas.

Baldoni noted that while a lot of companies were testing computer-driven technologies in aspects of drug development, they were not using AI in all areas. GSK will take a different route, pulling all its AI experiments together under one business unit.

"The idea that you're going to segment this into six or seven different workflows and not integrate them, I don't think is going to create the best flow of molecules to treat those diseases," Baldoni said.

Integration is possible at GSK because in 2015 the company started to consolidate all its data into one system. GSK spent time and money to have 2,500 databases consolidated into one platform that was searchable with good quality, curated data in it, Baldoni noted. "This created a great data source for artificial intelligence use, machine learning requires good quality data." *Published online 30 April 2018*

Dr. Gerrit Hauck has been appointed as chief technology officer and member of the management committee at **Basilea Pharmaceutica Ltd.**, effective May 1. He will succeed ***Dr. Günter Ditzinger*** who will take on new responsibilities at Basilea. Hauck joins Basilea from Sanofi, where he was cluster head synthetic molecules and a member of Sanofi's research stage gate committee. Basilea has also announced that ***Dr. Josef Künzle***, head of global quality management and a member of the extended management committee, will retire on Oct. 31. He will be succeeded by ***Dr. Anne Stehlin***, who joins Basilea from Novartis Pharma AG where she was global head of product quality lifecycle management. She will initially serve as Basilea's deputy head of global quality management until Oct. 31.

Joanna Shields has been appointed group CEO at the private artificial intelligence company **BenevolentAI**, with immediate effect. Shields most recently served as the UK Minister for Internet Security & Safety, a special advisor to the UK government on the digital economy, and chair & CEO of TechCityUK. Prior to her work in government, Shields spent 25 years in senior leadership positions at companies including Facebook, Bebo/AOL, Google, Decru/NetApp, RealNetworks, Veon and EFI.

OMEICOS Therapeutics, a Berlin-based biopharmaceutical company developing first-in-class small molecule therapeutics for the prevention and treatment of cardiovascular and ophthalmic diseases, has appointed ***Dr. Alexander Gebauer*** to its management board. Gebauer will lead the company's clinical development efforts. He has also been appointed chief executive officer and chairman of the recently founded US-based subsidiary, OMEICOS Ophthalmics. Gebauer has more than 25 years of R&D experience within the biotechnology and pharmaceutical industry.

Pharnext SA has appointed ***Amit Kohli*** chief operating officer responsible for leading Pharnext's corporate strategy and operations. Kohli was previously general manager of clinical diagnostics at Eurofins in Brussels, and before that, he was a regional business director at Becton Dickinson, for Russia, Turkey, the Middle East and Africa. Kohli also held a number of leadership roles at Sanofi.

Recursion Pharmaceuticals, a biotechnology company that combines artificial intelligence, experimental biology, and automation to discover drugs at scale, has hired ***Dr. Kevin Lynch***, as chief business officer. Lynch joins Recursion after 22 years at AbbVie, where he most recently served as vice president of search and evaluation and before that as director of licensing and business development.

Sonde Health Inc., an affiliate of PureTech Health developing a voice-based technology platform for monitoring and diagnosing mental and physical medical conditions, has appointed ***Thai Lee***, president and chief executive officer of SHI International Corporation, to its board. Lee is the co-founder of SHI International Corporation, where she currently serves as president and chief executive officer.

Jon Neal has taken up the position of managing director, UK and Ireland for **Takeda UK Ltd**. He was previously the oncology business unit director, sitting on the UK senior leadership team. He succeeds ***Adam Zaeske***, who has moved to a new position as Takeda's regional lead for gastroenterology across Europe and Canada. Neal will be succeeded as UK oncology business unit director by Emma Roffe who previously led the oncology medical affairs team.

Bone Therapeutics has appointed ***Dr. Claudia D'Augusta*** to its board as a non-executive director. D'Augusta has more than 20 years' experience in corporate finance, capital markets and M&A. She is currently chief financial officer at TiGenix N.V. and is part of the management team at TiGenix, which Takeda has announced its intention to acquire. Prior to TiGenix, D'Augusta held various other senior financial positions across a number of international public and private companies. She replaces ***Wim Goemaere***, formerly chief financial officer, who will step down as a non-executive director.

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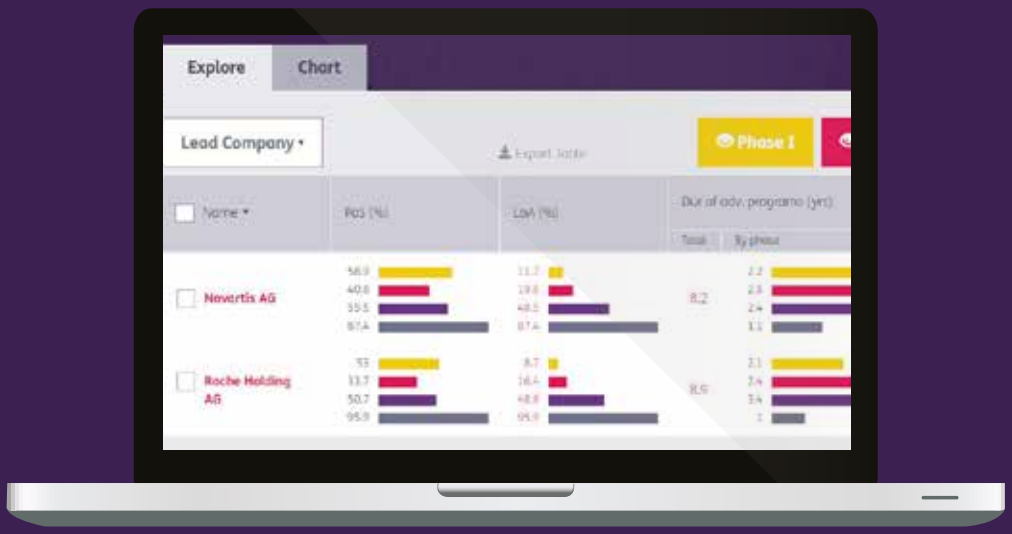

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