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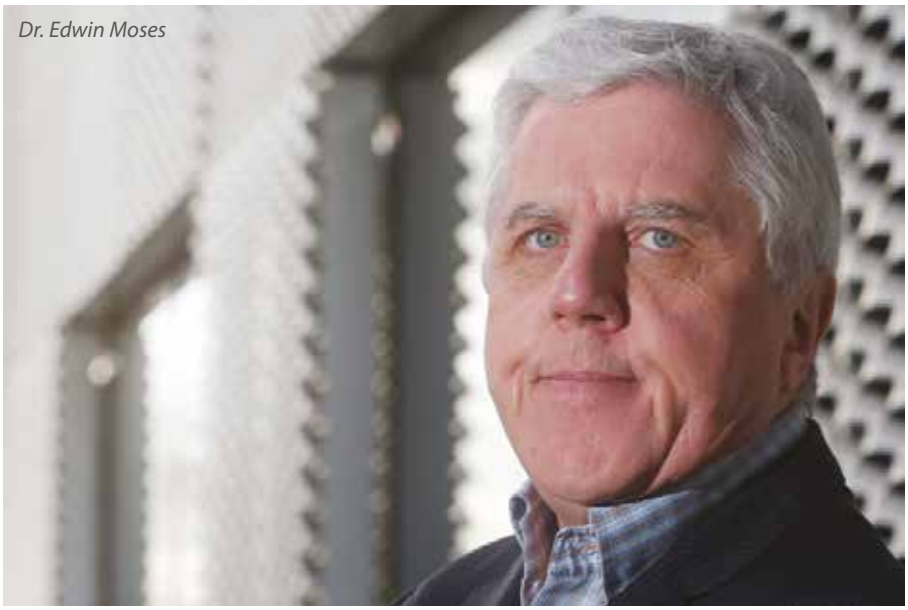
Dr. Edwin Moses

Credit: Ablynx

Novo's €2.6bn Ablynx Bid Opens The Door For Better Offers

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Novo Nordisk AS wants to acquire Belgian Nanobody developer **Ablynx NV** for €2.6bn to access its late-stage blood disorder drug caplacizumab, but Ablynx has rejected two offers from the diabetes giant because the figures "fundamentally undervalue Ablynx and its strong prospects for continued growth."

While a takeover would make sense for Novo Nordisk, which desperately needs to boost its pipeline outside of diabetes and already has a significant presence in the blood disorder market through its hemophilia portfolio, Ablynx may find a better suitor and a better deal elsewhere.

Jefferies analysts said in a Jan. 8 note that they expected counter-bids for Ablynx now that Novo Nordisk's two offers had been made public. Novo Nordisk approached Ablynx twice last month, offering €2.6bn in cash on its second attempt to acquire the biotech on Dec. 22, 2017. However, Ablynx is playing hard to get and has so far refused to negotiate.

Novo Nordisk's bid includes €28.00 per Ablynx share in cash up front, and up to €2.50 per share in contingent value rights, linked to the progress of two earlier-stage products, vobarilizumab and ALX-0171. Before the first offer, Ablynx's share price stood at €19.12 on Dec. 6; it closed at €25.91 on Jan. 5, 2018, equating to a market capitalization of €1.9bn. Ablynx has publicly responded to Novo Nordisk's offer, saying it fundamentally undervalued caplacizumab, the Ablynx pipeline, platform, technology, people, and know how.

Ablynx's CEO Dr. Edwin Moses added: "In addition to developing our proprietary pipeline, including preparing for the commercial launch of caplacizumab, we are engaged in a number of exciting strategic collaborations with major pharma companies, further validating the potential of our Nanobody platform. We firmly believe the continued execution of this strategic plan will deliver substantially more value to Ablynx shareholders than Novo Nordisk's proposal."

Analysts at Jefferies agreed that Novo Nordisk's offer was not up to par. "We view the base case €28/share to be a low-ball bid," they said. Jefferies has forecast peak worldwide sales of $500m for caplacizumab, which has already been filed with regulatory authorities in Europe and is due to be submitted to the US FDA this year.

CAPLACIZUMAB'S COMPATIBILITY

Caplacizumab, a first-in-class anti-von Willebrand factor Nanobody, is expected to launch in Europe in the second half of 2018 and in the US in the first half of 2019. Ablynx is developing the product as a treatment for acquired thrombotic thrombocytopenic purpura (aTTP), a rare blood-clotting disorder. The company presented detailed positive Phase III data from the HERCULES trial at the American Society for Hematology's annual meeting in December 2017, following a top-line data release in October last year.

Caplacizumab would be the first Nanobody therapeutic to launch in the US and Europe, as well as being the first approved drug for aTTP. Pharmavitae analyst

CONTINUED ON PAGE 7

BROUGHT TO YOU BY THE EDITORS OF **PHARMASIA NEWS, START-UP** AND **SCRIP INTELLIGENCE**

from the editor

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The year has got off to a bang with the annual J.P. Morgan Healthcare conference and EBD Group's Biotech Showcase running concurrently in San Francisco. Our reporters on the ground had it covered: read highlights in this issue and watch for future reports on the many interviews and presentations they attended.

Now, there are a couple of things to mention to you. I know that many of our readers are involved in clinical R&D and would like to make sure you are aware of Informa Pharma's Clinical And Research Excellence (CARE) Awards, which take place in Boston in April. There are 11 categories and the entry deadline has just been extended to Jan. 19. Find out more and enter here: https://pharmaintelligence.informa.com/events/awards/care-awards-2018

Pharma FEEDBACK

Secondly, we are seeking feedback from readers, to gain a better understanding of your needs and challenges and to help plan improvements to our content and its delivery.

We're here to serve you, so please let us know what you need from us by taking our brief "Pharma Feedback" survey.

You can click on this link if you're reading this as a PDF, or type in the following URL if you're reading it in print: bit.ly/2yXash2

Everyone who completes the survey is eligible to enter a prize draw for one of four Amazon gift vouchers valued at $100 (US).

We hope you will be candid about your opinions as we fine-tune *Scrip*.

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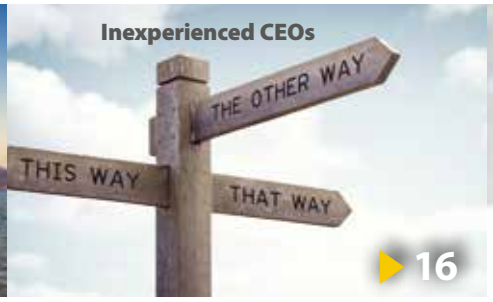

exclusive online content

28 New Drug Approvals In EU: Cancer Dominates, But RA, Skin & Blood Disorders Well Served Too
http://bit.ly/2CWdAkt
Twenty-eight new products containing a total of 29 new active substances were authorized for marketing in the EU in 2017, very much line with the 2016 tally. As in that year, oncology dominated the 2017 approvals, which also included new drugs for rheumatoid arthritis, skin & blood disorders, and hepatitis C.

Boehringer's Expanded Venture Fund: Innovation First, Returns Second
http://bit.ly/2Es8gBI
Boehringer Ingelheim more than doubled its venture fund from €100m to €250m, giving BI more access to early innovation via new capital, two new investment managers and a West Coast presence.

Microbiome Clinical Studies Loom Large In 2018
http://bit.ly/2CTfcKS
Events are moving fast in the microbiome field. The sector is expecting results from numerous initial clinical studies during 2018, from across a spectrum of approaches and mechanisms of action, which could lead to new rounds of financings and M&A activity.

Pfizer Pulls Plug But iTeos Has High Hopes For IDO1 Inhibitor
http://bit.ly/2mjRIFn
The Belgian biotech has regained the rights to an early-stage IDO1 inhibitor that has failed a Phase I trial but iTeos believes the drug's penetration to the brain makes EOS200271 a significant asset.

Deal Watch: Pfizer Begins 2018 With Two Deals, Including ALS Tie-Up With Sangamo
http://bit.ly/2mjEAzQ
In addition to its latest collaboration with Sangamo, Pfizer also teams with Arvinas on protein-degradation therapies. AstraZeneca sells off four mature products to ANI, while Summit enhances its antibiotic capabilities with Discuva buyout and out-licenses Latin American rights to ridinilazole.

Finance Watch: Mysterious Gossamer Raises $100m As VC Deals Surge Ahead of J.P. Morgan
http://bit.ly/2EqwWKy
Gossamer Bio, led by former Receptos CEO Faheem Hasnain and CMO Sheila Gujrathi, revealed $100m in seed and Series A funding during a week in which 17 companies revealed VC rounds totaling $891.2m, giving them good news to discuss during the J.P. Morgan Healthcare conference.

inside:

Celgene's $1.1bn Impact Buy Is First Of More Deals To Come In 2018 And Beyond

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Celgene Corp. has high hopes for its latest acquisition, **Impact Biomedicines**, whose fedratinib is envisioned as one of multiple blockbuster drugs in the company's mostly-partnered late-stage pipeline – and the purchase for $1.1bn up front is likely just one of multiple deals to come in 2018.

"We remain committed to business development," Celgene CEO Mark Alles said during the Q&A session after his presentation at the J.P. Morgan Healthcare Conference that kicked off on Jan. 8 and ends on Jan. 11 in San Francisco. "We're going to put a lot of capital against that," he added.

Celgene gave Medicxi Ventures – the sole venture capital investor behind Impact's $22.5m Series A round in October – a big return on its investment, since the deal's total consideration could rise to $7bn based on various regulatory and sales milestones. The biotech giant gains a myelofibrosis drug that will be submitted for US FDA approval this year, but investors still pushed Celgene's stock price down slightly on Jan. 8 based on the asset's risks, despite the company's confidence in fedratinib and its commitment to do more deals for portfolio-diversifying assets in 2018.

Shares of Celgene declined a modest 0.8% to $104.18 each after the company announced its deal with Impact late on Jan. 7 and presented positive sales guidance for 2018 during the J.P. Morgan conference.

Alles said during Celgene's first-of-the-day J.P. Morgan presentation that the company was committed to using its cash from sales of the multiple myeloma powerhouse *Revlimid* (lenalidomide) and other blockbusters – and from recent tax reform in the US – to do more deals this year. He noted that "if our mission is to discover new molecules and new medicines, you've got to be doing it with a network of partners."

Celgene is one of the more prolific dealmakers in the biopharmaceutical industry and investors largely have supported the partnering strategy, because of the company's need to diversify its income beyond Revlimid and hematology. However, Celgene has had some setbacks for some of its partnered programs that have shaken investors, including a high-profile failure of mongersen in Crohn's disease in October.

"Sometimes we have unfortunate events and we are disappointed and move on," Alles said. "That's why we structure deals the way we do."

Celgene will pay $1.1bn up front for Impact Biomedicines, up to $1.25bn based on regulatory milestones for fedratinib in myelofibrosis, and up to $4.65bn based on commercial milestones for the selective JAK2 inhibitor. Impact Biomedicines' executive team acquired rights to the drug from **Sanofi**, which had discontinued development of the drug based on Wernicke's encephalopathy (WE), an acute neurological condition associated with a vitamin B (thiamine) deficiency.

Both Celgene and Impact note that of eight cases of WE in clinical trials, almost none of them appears to be related to fedratinib. They anticipate a new drug application (NDA) filing with the FDA in mid-2018 in newly diagnosed myelofibrosis (MF) and for the treatment of patients who cannot tolerate or who are refractory to **Incyte Corp.**'s JAK1/2 inhibitor *Jakafi* (ruxolitinib).

NOT A 'ME-TOO' DRUG

Impact Biomedicines CEO and Co-Founder John Hood told *Scrip* in an interview at the J.P. Morgan conference that the efficacy of fedratinib in the Phase II and III MF studies completed by Sanofi was "astounding" and with the potential for better efficacy than Jakafi – dispelling concerns that Celgene is acquiring a "me-too" JAK inhibitor.

In particular, Hood noted that 50% to 60% of patients treated with fedratinib who could not tolerate or failed treatment with Jakafi responded to fedratinib with a reduction of spleen volume of at least 35% versus 26% to 42% with a 35% or greater reduction in spleen volume for patients treated with Jakafi in Incyte's studies. He said there would be an effort to seek approval for both first and second line treatment.

Impact President and Chief Business Officer Charlie McDermott noted that "no matter who's on the market, there's nothing approved for the second line."

Celgene's President of Hematology and Oncology Nadim Ahmed noted in the Q&A session after Alles's J.P. Morgan presentation that "there's a huge untapped opportunity in myelofibrosis," including in patients who can't be treated with or who stop responding to Jakafi.

The company sees fedratinib as a $1bn-per-year drug, making it one of 10 potential blockbuster products in Celgene's pipeline at a relatively low upfront cost.

Baird analyst Brian Skorney was skeptical about Celgene's blockbuster estimate for fedratinib in a Jan. 8 research note.

"Jakafi, the current [standard of care] in myelodysplastic syndromes (MDS), is currently on a run rate for just over $1bn in 2017, and peak estimates put it on track for about $2bn," Skorney wrote. "Though this could imply that fedratinib is a potential blockbuster opportunity for Celgene at a time when the company needs near-term, de-risked assets to supplement the top line, we think the market potential is much smaller given the existence of Jakafi and the safety profile for fedratinib."

LOW-RISK DEAL, MORE TO COME

But while the acquisition of Impact could total as much as $7bn based on fedratinib's future sales, Alles noted in the Q&A session that after the $1.1bn upfront payment the rest of Celgene's potential $7bn investment in the Impact deal is success-based, reducing the company's risk in the transaction. "If the product is successful, we will be grateful to pay those milestones," he added.

Jonathan Biller, senior vice president of tax and treasury at Celgene, noted during the Q&A session that the company won't have a big change in its tax rate under the recently passed tax reform legislation in the US, but Celgene will get to access about 60% of its cash that's sitting overseas. Alles noted at least some of that will be available for deals, so the company will have more firepower to take calculated pipeline risks.

As for growth from approved products, the company expects its fourth-quarter 2017 revenue to total $3.48bn, representing 17% year-over-year growth, with a 16% increase in full-year revenue to $13bn. For 2018, revenue is expected to rise 12% to a range of $14.4bn to $14.8bn. Guidance for 2020 was reaffirmed at $19bn to $20bn.

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Shire May Split Up – But Punting On Bigger Decisions For Now

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Following through on a strategy it first began talking about last August, **Shire PLC** announced Jan. 8 that it is creating "two distinct divisions" within the company – one focused on rare diseases, the other on neuroscience – and will begin reporting the operational metrics of each unit starting with its first quarter earnings report.

Intentionally left up in the air is whether Shire is thinking about a spinout or an initial public offering for the smaller neuroscience unit, comprised mainly of its ADHD franchise, including the mature products *Vyvanse* (lisdexamfetamine) and *Adderall XR* (amphetamine and dextroamphetamine) as well as recently launched *Mydayis* (mixed salts of a single-entity amphetamine product). During its second quarter earnings call last August, Shire CEO Flemming Ornskov said the company would conduct a strategic review of its neuroscience unit, to consider a possible spinout that would increase focus on rare diseases.

Shire plans to reveal during the second half of 2018 the specific direction in which it will take the neuroscience business – but for now, it's reorganization positions it for "enhanced optionality."

The Dublin-headquartered specialty pharma's stock finished trading down 5% to $149.10 on Jan. 8. Morgan Stanley analyst Vincent Meunier suggested that investors hoping for a quicker decision whether to spin out the neuroscience unit might be disappointed by the day's news.

Whether or not it comes from a position of strength, Shire cited the company's consistent growth since 2013 as its transitioned from a specialty pharma focused on ADHD to a biotech with a leading position in the rare disease arena. At J.P. Morgan it noted that its rare disease business – comprising immunology, hematology, genetic diseases/internal medicine and ophthalmics – brought in $10.9bn from fourth quarter 2016 through third quarter 2017, while neuroscience, consisting of neuropsychiatry and existing brands, brought in $3.9bn during that stretch. "Today is a clear glass half-full day for me," Ornskov told the media briefing. "I think this is a key moment in Shire's history that today we have reached the first decision about two great businesses – that is to separate them into two divisions. That speaks about the strength and the leadership position we've attained in rare diseases, but it also speaks to the fact that with neuroscience, we still have significant opportunity to grow and to expand that business and create significant value going forward."

ADDRESSING A HOST OF DIFFERENCES

Shire projects that the rare diseases unit will yield more than $13bn in sales in 2020, while the neuroscience will bring in more than $4bn. Ornskov did not directly address why Shire has reduced its overall revenue guidance for 2020 and also downplayed the reality that growth prospects seem brighter for the products and pipeline assets grouped under the rare diseases heading.

The CEO insisted, however, that the planned split derives from a position of company strength. "If we were not in such a strong health, we would not have the opportunity to entertain the opportunity of having two separate divisions, so I see it as an absolute opportunity to continue to grow the business and to show strength," he said.

Morgan Stanley's Meunier said it seems clear that Shire will look to business development activities to shore up both units, ranging from licensing deals to partnerships and to bolt-on acquisitions. Shire said it wants to position each of the two business units for growth, profitability, innovation and serving patient needs.

"All in all, we would expect further bolt-on acquisitions (financed by cash flow from neuroscience) in the next 12-18 months," Meunier wrote. "We would view this positively from a strategic standpoint; however, we acknowledge that finding quality assets at a reasonable price might prove challenging."

Ornskov said there were multiple reasons for splitting into two divisions, citing clear differences between the rare disease and neuroscience units beyond the gaps in their overall revenue and expected revenue growth. The rare disease products are approximately 90% biologics, with a healthy clinical development pipeline, a "high touch" personalized customer service model, and small field forces spread across a wide geography of 75 countries.

By contrast, the neuroscience unit consists strictly of small molecules, with a smaller pipeline. Commercially, it utilizes broad-based promotional tactics, including direct-to-consumer advertising, with larger field forces that focus on primary care and specialty physicians in the US and key international markets.

The goal for neuroscience is to focus on neuropsychiatric indications beyond ADHD, Ornskov said. He spoke of "stretch goals" of building out the ADHD geographic footprint to Japan and elsewhere, and also building upon the existing neuroscience pipeline, which he called "a great jumping-off point for growth and innovation." As highlights of the neuroscience pipeline, Shire listed SHP680, a prodrug of d-amphetamine in development for cognitive impairment disorders, and SHP615 (midazolam hydrochloride oromucosal), which is in development for convulsive status epilepticus in children.

Asked if the two-division split might end up resembling the spinout of **AbbVie Inc.** from **Abbott Laboratories Inc.** in 2013, Ornskov spoke of separating the firm's newer strength in rare diseases from its foundational emphasis in ADHD. At the moment, the reorganization into two units resembles **Pfizer Inc.**'s restructuring into business units focused on Innovative Health (growth products) and Essential Health (established products) as it evaluated whether to split off part of the company – a move it decided against in 2016.

After completing the strategic review begun last year, "it was obvious to us that the first step to do [with the neuroscience unit] was to give more focus to the business, to accelerate the significant increase we have in sales internationally, to build out the pipeline in ADHD, but also to obviously expand the very strong neuropsychiatry platform beyond ADHD," Ornskov said.

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Takeda Gets Serious About Cell Therapy With TiGenix Buy

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Takeda Pharmaceutical Co. Ltd. has bid €520m ($630m) to acquire Belgian biotech **TiGenix NV**, a company that is about to gain European approval of a cell-based treatment for complex perianal fistula in patients with Crohn's disease.

The acquisition fits with Takeda's previously stated plans to expand its portfolio of products in late-stage development in priority fields. TiGenix's *Alofisel* (darvadstrocel; Cx601) will add to Takeda's gastroenterology pipeline and eventually strengthen its presence in the US specialty care market; US approval of the drug is slated for late 2020.

The deal also marks "the first step of a real foray into regenerative medicine" for Takeda, Morgan Stanley analysts said in a Jan. 5 note.

The European Medicines Agency's scientific committee, the CHMP, gave a green light to Alofisel at the end of last year as a treatment for complex perianal fistula in patients with Crohn's disease (a form of inflammatory bowel disease; IBD). Full EU approval is expected in the coming months.

TiGenix and Takeda were already tied up in a July 2016 partnership for Alofisel, with Takeda holding exclusive ex-US license, development and commercialization rights to the therapy. TiGenix had planned to launch the drug itself in the US, but Takeda has stepped in to acquire all rights to the drug.

A spokesperson for Takeda told *Scrip* the acquisition was a natural extension of an existing partnership agreement between Takeda and TiGenix, which aimed to bring new treatment options to patients with gastrointestinal disorders. "GI is a core therapeutic area at Takeda, and we are pleased to have the potential opportunity to build upon our existing collaboration between Takeda and TiGenix… This also showcases our commitment to strengthen Takeda's presence in the US specialty care market and highlights our leadership in areas of GI associated with high unmet need," the spokesperson said.

Under their original deal, TiGenix retained the rights to develop Alofisel in new indications outside of Crohn's disease. The potential for Takeda to expand on Alofisel's success is a key attraction for the company as it acquires the smaller firm. "TiGenix's proprietary allogeneic stem cell platform, in addition to earlier stage pipeline assets and expertise, enhance Takeda's stem cell capabilities, which may present future R&D opportunities across our focus therapeutic areas," Takeda said.

The spokesperson added that Takeda was evaluating potential indications for Cx601 across fistulizing disease.

Analysts have forecast that annual sales of Alofisel, an orphan product, could reach $500m by 2027. With TiGenix taking the lead, a US FDA approval for the drug was expected in late 2020, with a US launch slated for 2021. However, Takeda could look to speed up this timeline in the large US market. Takeda's spokesperson was unable to comment on this matter until the acquisition of TiGenix was finalized. However, they said: "We will work closely with TiGenix to ensure a seamless transition in the management and responsibility of US development activities for Cx601 in the near future."

The impending approval of Alofisel in the EU is forecast to add $225m in peak revenues to Takeda's IBD portfolio by 2026. While the drug should enter the EU market later this year, its commercial potential will be limited to use as an add-on therapy at later lines, in a niche subpopulation of Crohn's disease patients with complex perianal fistulas, owing to its inconvenient intra-lesional injection administration route. "Nevertheless, potential approvals in the US as well as in Japan, if successful, will lift peak sales and extend its IBD market presence," Datamonitor Healthcare analyst Edward Thomason told *Scrip*.

CLICKING INTO PLACE

"Gastroenterology is a key therapy area for Takeda and the company's plan to buy out its partner seems a logical extension of their existing partnership, supplementing its pre-existing IBD position with *Entyvio*," Thomason said. Takeda's Entyvio (vedolizumab) was approved in the US for the treatment of Crohn's disease and ulcerative colitis in 2014.

Takeda intends to acquire 100% of the securities with voting rights or giving access to voting rights of TiGenix that are not already owned by Takeda (or affiliates) at a price of €1.78 per share. The Japanese big pharma will launch the proposed takeover bid shortly after approval of the bid prospectus and response from the Belgian Financial Services and Markets Authority (FSMA). The takeover offer is contingent on Alofisel obtaining EMA approval.

The deal "looks set to give Takeda full ownership of Europe's first allogenic stem cell therapy, and grants it access to the lucrative US IBD market where a Phase III trial was recently initiated," Thomason noted.

Regenerative medicine is also a key research focus for Takeda, and the TiGenix deal will boost the big pharma's infrastructure and collaborations as it aims to realize and deliver innovative stem cell treatments.

"Albeit, the Tigenix deal is small but it demonstrates Takeda's continued strategy to pursue M&A opportunities of a digestible bolt-on size," Thomason said. Armed with a strong cash flow and boosted by the recent divestments of non-core assets, "Takeda is poised to be yet more active in M&A in 2018," he said.

ONE TRICK PONY?

A price tag of €520m might seem small for a biotech firm that is about to get a regulatory seal of approval for its first product. In recent years, we have seen pharma companies pay top dollar for biotechs with product candidates much earlier in development.

The price is likely a reflection of TiGenix's limited pipeline. The company has little else to offer to an acquiring party once you removed its soon-to-be approved orphan therapy for Crohn's disease.

The company, which was founded in 2000, did have one product on the European market in the past – *ChondroCelect*, a cell implantation treatment for cartilage and joint repair – however this was withdrawn in July 2016. Due to the regulatory environment around autologous chondrocyte-based cell therapy products in Europe leading to a difficult competitive landscape for ChondroCelect, together with the lack of reimbursement in key European countries, TiGenix decided to stop selling ChondroCelect and focus instead on its allogeneic stem cell platforms.

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CONTINUED FROM COVER

Zara Fulton noted in October 2017 that "the impressive efficacy and safety of caplacizumab demonstrated in the Phase III HERCULES trial signals the potential impact of Ablynx's unique proprietary Nanobody technology."

It is this platform technology that could make Ablynx an acquisition target for other pharma players.

Novo Nordisk can offer Ablynx shareholders experience and a strong network within the market for blood disorders, and during a Jan. 8 conference call, the would-be acquirer's management highlighted its extensive experience in hematology as a reason why it was better placed to launch caplacizumab.

"The medical knowledge, commercial knowledge and regulatory knowledge of Novo Nordisk is highly likely to enable a faster roll-out, pursuing the full value potential of caplacizumab, compared to what it is realistically possible for a company of 400 to 500 people in Belgium to achieve," Novo Nordisk's CEO Lars Fruergaard Jørgensen said.

"We believe we can add substantial value for Ablynx shareholders," he added.

However, caplacizumab faces no immediate competition within TTP, so a faster launch by a few months would have a limited impact. Furthermore, Fulton said in late 2017 that "caplacizumab will experience high market penetration due to the lack of indicated drugs for aTTP and its impressive efficacy and safety as demonstrated in both the Phase II TITAN study and Phase III HERCULES trial."

Caplacizumab's closest competitor in TTP is **Shire PLC**, which is also developing an anti-von Willebrand factor treatment, known as SHP655. The drug was granted FDA Fast Track designation in March 2017 and Shire is poised to launch a Phase III study for SHP655 in the first quarter of 2018.

A PIPELINE WITH POTENTIAL

Novo Nordisk's takeover bid for Ablynx comes as no surprise as it looks to diversify its portfolio in the face of increasing competition and pricing pressures in the diabetes market, Datamonitor Healthcare company analyst Oliver Spray told *Scrip*. "The deal signifies Novo Nordisk's intent on pursuing bolt-on deals in rare diseases that remain largely insulated from pricing pressures," he said. Spray added that caplacizumab complements Novo Nordisk's already sizeable hematology portfolio, which generated sales of $1.6bn in 2016.

But as a company focused intently on hematology and metabolic diseases, Novo Nordisk might not be the best buyer to optimize the potential Ablynx's broad portfolio and platform technology.

Aside from the soon-to-be approved aTTP therapy, Ablynx has in its pipeline a Phase II candidate, vobarilizumab, for rheumatoid arthritis and systemic lupus erythematosus, and ALX-171, also in Phase II, for respiratory syncytial virus. The company also has other candidates, both partnered and alone, in preclinical and clinical development, all based on its Nanobody platform.

Novo Nordisk is one of Ablynx's development partners, having signed a deal in November 2015 to use its Nanobody antibody drug fragment platform to develop multi-specific drug candidates, but is not the only larger firm Ablynx has arrangements with. Its list of collaborators includes **Boehringer Ingelheim GMBH**, **AbbVie Inc.** and **Merck KGAA**. Parties outside of the biotech's network of partners could also show an interest in Ablynx now that Novo Nordisk has laid its cards on the table.

"The possibility of a counterbid still remains – other likely contenders include **Gilead Sciences Inc.** and **Amgen Inc.**, which have access to large reserves of overseas cash and are thus able to contend with the substantial price premium being negotiated by Ablynx," Spray said.

Analysts from Baird Equity Research also think other bidders could come forward with offers for Ablynx, specifically **Alexion Pharmaceuticals Inc.** "We do believe caplacizumab is a unique and attractive asset to a number of therapeutic companies. We have previously noted the almost completely complementary potential of marketing caplacizumab alongside of *Soliris* for patients with thrombotic microangiopathies, making it an ideal target for Alexion, in our view," senior research analyst Brian Skorney said in a Jan. 8 note.

Novo Nordisk's CEO said that the company was not aware of any counterbids for Ablynx. "It is not our understanding that any other bidder is pursuing the target, but now that it is out in the open that we are interested we will have to see how it develops," he noted. The Danish firm's €2.6bn bid for Ablynx was based on publicly available information only. Jørgensen added that the company's primary motive for announcing the rebuffed takeover offers was to assure that Ablynx shareholders were aware of the bids.

Jørgensen added color on the next steps Novo Nordisk might take to win over Ablynx based on a higher bid: "I think it would be natural to up the bid based on discussions with the board of Ablynx and based on additional insights due diligence might reveal. It is premature at this point in time to speculate on any subsequent raise, but one would say it is customary in these processes that a mutually acceptable price level is developed through such negotiations."

Novo Nordisk's buyout offer is short of analysts' expectations of a fair price for Ablynx. As a crude comparison, the day before Novo Nordisk reported it had made two bids for Ablynx, **Celgene Corp.** announced that it had agreed to buy **Impact Biomedicines** for $1.1bn upfront and a further $1.25bn dependent on successful regulatory approvals of the biotech company's blood cancer drug (see page 4).

Impact is a company built around a single asset, fedratinib, which is in Phase III trials for myelofibrosis, whereas Ablynx has a strong pipeline across various therapy areas, an orphan drug product with very high approval expectations and a proven drug discovery platform on offer.

Jefferies analysts said a reasonable bid for Ablynx would be €36 per share assuming caplacizumab is approved, up from Novo Nordisk's current offer of up to €30.5 per share in total. "Given this profile and Ablynx being on the cusp of potentially launching a highly profitable rare disease drug in capla[cizumab], we could envisage other pharma/biotech to express an interest," the analysts said.

It is expected that Novo Nordisk will swiftly come back to Ablynx with a higher offer and then push for a quick close on this deal because the public offer puts Novo Nordisk in jeopardy of alerting other bidders.

However, its "lack of acquisition history" makes it hard to determine how far Novo Nordisk is willing to go for assets it wants, Bernstein analysts said in a Jan. 8 note.

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Tax Reform 'Provides Environment For M&A Surge'

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US tax reform legislation signed into law this past December is expected to help spur an increase in biopharma M&A activity in 2018, including the possibility for mega-mergers, possibly even a deal in which one of the big pharma companies absorbs another – a result not seen since the industry-changing events of 2009.

This is among the projections provided in EY's *2018 M&A Firepower Report*, issued Jan. 8 to preview the year ahead in business development activity for the life sciences sector, including biopharma, biotech and medtech. With the US tax legislation enacted last month making it possible for the 10 largest US-based life sciences companies to repatriate about $160bn in offshore cash at lower tax rates, an environment conducive to significant and substantial M&A activity is developing, Jeff Greene, EY's global life sciences transaction advisory services leader, said in an interview.

Overall, EY predicts that life sciences M&A activity in 2018 will outstrip the $200bn seen in 2017. Companies are expected to focus on capital-allocation strategies – including deal-making – that can generate non-organic revenue growth, the report says, and 60% of life sciences leaders recently surveyed by the financial advisory firm say they actively plan to pursue M&A in 2017.

"We think there are two aspects – one, [$160bn] is a fair amount of money, so it will tend to facilitate more M&A, particularly by the US-based companies that are bringing this cash [home]," Greene told *Scrip*. "The other part is that the passing of the tax legislation resolves a material piece of uncertainty that had been hanging over the economy and the industry for most of 2017."

"We heard a lot of companies – from the C-suites to the corporate development people to the M&A people and beyond – talk about the prospects for tax reform and repatriation in particular," he added, "and the fact that it wasn't happening, that they didn't have visibility into when it was going to happen, was definitely holding up deals, particularly at the larger end of the spectrum."

It's conceivable the industry could see a mega-merger in 2018, Greene said, as biopharmas will be driven to protect their profitability, maintain competitive advantage in key therapeutic areas and build scale that can help offset new supply chain challenges. While declining to specifically name any likely acquirers or buyout targets, he said combinations among the 25 largest biopharmas globally are more likely in the coming environment.

One driver of such activity might be the fact that biopharmaceuticals are a relatively fragmented industry – each of the five largest companies (**Pfizer Inc.**, **Novartis AG**, **Roche**, **Sanofi**, **Johnson & Johnson**) controls no more than 5% of total market share, the EY report notes. Further illustrating this fragmentation is the fact that the 25 largest companies held a combined 61% market share in 2017.

"When we look at all the reasons for industries to consolidate – reducing costs, increasing scale, spreading fixed costs over a larger volume, getting scale in other ways such as market access or owning a disease quote-unquote so that you have a critical mass of knowledge from the R&D aspects through commercialization so that you're well positioned with KOLs – all of those factors go into the potential for transactions in general," Greene pointed out.

EXPECT DEALS FOCUSED ON ONCOLOGY, DIABETES

In terms of therapeutic areas, he anticipates activity particularly in oncology and diabetes. In cancer, a burgeoning number of drug candidates, approved products and approved combination therapies is resulting in a very crowded space that should be amenable to consolidation as questions of which drugs or combos work in what particular setting get sorted out, Greene said.

In diabetes, he expects the pressure of heightened competition to drive deal-making. "Diabetes continues to be a challenging area so you are likely to see more transactions there," Greene said, "whether they're horizontal or are attempts by different players to own more of the disease, to be able to put together what we call a care platform, that you're not just focused on the drug or the device, but on both, as well as potentially services and then using different kinds of data in a more holistic way in order to improve wellness, to modify patient behavior, to improve health over time or prevent disease. We see all kinds of opportunities there."

Greene thinks a less uncertain policy environment in the US pertaining to drug pricing also might loosen the spigot for large deals. "I think a year ago we weren't quite sure what the new administration was going to do in terms of potentially intervening in drug prices – and I think everyone is more relaxed about that now," he explained. "You have a new head of the FDA who's focusing on things like accelerated generic approvals and biosimilar approvals, as opposed to talking about some extreme sorts of price controls."

One factor that might restrain large deal-making, however, is that with plentiful capital availability from both public and private sources and increasing company valuations, biotechs should be able to hold onto their programs longer, seeing them through to value-creating inflection points. But Green's expectation is that this factor will just lead to higher valuations in biotech takeouts, not downward pressure on transactions being closed.

Across the board, deal-makers will be more cognizant of finding a true strategic fit – rather than, say, just a potentially short-term infusion of increased revenue, Green said. With deals in recent years often not yielding the expected level of benefit to shareholders – particularly for companies in the specialty pharma and generics sectors – merger partners should be questioning how each company reinforces the other's strengths to provide real synergies, either on the cost or revenue side, he suggested.

"Things are pretty fairly priced across the board, so in order to extract real value for shareholders, that strategic fit is going to have to be there, the financial diligence, other kinds of valuation analysis is going to have to be pretty rigorous, the execution of the integration plan is going to have to be very focused, thorough and long-term, from planning through closing through years after in terms of executing to get value out of these [transactions]," Green said.

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Europe's Biopharma Sector Could Be In For Bumper Year

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Analysts are saying that 2018 should be a big year for European pharmaceuticals firms, both large and not so large, and many of them are expected to be part of sector consolidation and innovative drug launches.

When it comes to the biotech sector, Peter Welford and Lucy Codrington at Jefferies see Belgium's **Ablynx NV**, the subject of €2.6bn unsolicited cash takeover bid from **Novo Nordisk AS** (Jan. 8), as their top stock pick for 2018. Their enthusiasm is based on the positive Phase III HERCULES data presented at the American Society for Hematology in December on caplacizumab for acquired thrombotic thrombocytopenic purpura (aTTP), a rare blood disorder.

The analysts believe caplacizumab is a potential game-changer for Ablynx that remains largely underappreciated by investors despite the highly profitable commercial opportunity in this orphan disease." Further back in the pipeline it has a Phase II candidate, vobarilizumab, for rheumatoid arthritis and systemic lupus erythematosus, and ALX—171, also in Phase II, for respiratory syncytical virus, while a broad immuno-oncology collaboration with **Merck & Co. Inc.** could generate substantial future income given that potential milestones total over €5.7bn.

Ablynx has turned down the €2.6bn offer and earlier approaches so it looks like Novo will have to raise its bid, while other companies could also make a move. Ablynx has a number of big-name partners, including **Merck KGAA**, **Boehringer Ingelheim GMBH** and **Novartis AG**.

Jefferies also sees another Belgian biotech – **Galapagos NV** – as an interesting stock based on the prospects for filgotinib, which is partnered with **Gilead Sciences Inc.** for rheumatoid arthritis, saying the potential blockbuster could also be effective for inflammatory bowel disease (IBD). The analysts issued a note saying that Galapagos' cystic fibrosis collaboration with **AbbVie Inc.** should also provide "an abundance of catalysts for the stock".

The broker also predicted that **Genmab AS** would enjoy "continued impressive sales trajectory" of *Darzalex* (daratumumab), its **Johnson & Johnson**-partnered multiple myeloma drug and it also likes the look of **Ipsen**. Welford and Codrington remain confident that the French's group's *Somatuline* (lanreotide) should capture a significant share of the US neuroendocrine tumor market driving blockbuster peak sales and they also see significant potential for **Exelixis Inc.**-partnered *Cabometyx* (cabozantinib), which the group markets in Europe for renal cell carcinoma.

Also mentioned in favorable dispatches is **Shire PLC**, thanks to the successful integration of **Baxalta Inc.**, plus future upside from the late-stage pipeline. The Jefferies analysts claim that that concerns surrounding competitive pressure to its industry-leading hemophilia franchise from **Roche**'s newly-launched *Hemlibra* (emicizumab) "are overblown, in our view," while significant Phase II-III pipeline news "could heighten confidence in Shire's long-term organic growth prospects, with new products *Xiidra* (lifitegrast) for dry eye disease and lanadelumab for hereditary angioedema also likely to be a focus." *(Also see "Shire Tempts Busch From Bayer As It Eyes Top Spot In Rare Diseases" - Scrip, 1 Dec, 2017.)*

Jefferies' least preferred stock is **UCB Group** and the analysts said they remained concerned over the longevity of Belgian goup's top-line growth and the pipeline's commercial potential. They believe biosimilars of the anti-TNF blockbusters *Remicade* (infliximab) and *Enbrel* (etanercept) pose a major threat to UCB's *Cimzia* (certolizumab pegol) and while bimekizumab has produced promising Phase IIb data in psoriasis, ankylosing spondylitis and psoriatic arthritis, UCB is lagging behind already-approved anti-interleukin-17 competitors.

Over at Bernstein, analysts Wimal Kapadia and Rushee Jolly have also been looking at the European market and they too are concerned about UCB's prospects – the Brussels-based group will have pipeline read-outs though 2018, "but we not convinced these will lead to moves higher," they said in a note.

Like their counterparts at Jefferies, the Bernstein analysts are somewhat bullish on the European biopharma sector in 2018 and are also expecting a good year for Genmab and Shire. Their top pick is Merck KGaA "which has a pipeline catalyst-rich two years ahead, with expectations limited and valuation attractive." *(Also see "Mid-level Player In A Big-league Market; Merck KGAA Plots A US Strategy Beyond Bavencio" - In Vivo, 26 Dec, 2017.)*

Bernstein's Tim Anderson also issued an investor note on the big players in Europe, highlighting in particular **AstraZeneca PLC** and Novartis. The former stock got an upgrade from the analyst to outperform in September and Anderson described it as "a long-term, high-growth name with a full pipeline and several drivers of revenue/margin/earnings per share expansion. Some investors like it, some hate it, many remain undecided." *(Also see "AstraZeneca's Pipeline Reaps Rewards Of Return To Science" - Scrip, 21 Dec, 2017.)*

As for Novartis, he noted that the Swiss major has been a top pick since January 17 and is "the easiest story to tell." Anderson argued that the company offers "superior long-term growth and a full pipeline," adding that the heart drug *Entresto* (sacubitril/valsartan) is "ramping" and the eyecare unit Alcon is "going". He also noted that a "new likeable CEO," Vas Narasimhan, is also taking over. *(Also see "Revamped Novartis In Good Shape At 3Q Ahead Of CEO Succession" - Scrip, 24 Oct, 2017.)*

The analyst was concerned about the prospects for **GlaxoSmithKline PLC**, saying the stock has been in slow free-fall over dividend concerns and coming competition for its HIV franchise. As for Roche, Anderson wrote of "mixed feelings" as it is "probably the best R&D company, but biosimilar risk is the elephant in the room [that] squashes growth, unless pipeline delivers even more than it already has."

Back to Jefferies' Welford and Codrington who concluded that they are optimistic that robust fundamentals should drive share price outperformance for the overall biotech sector in Europe in 2018. This will be helped by recently-passed US tax reform enabling repatriation of offshore cash, "which while more favorable for US than European stocks, does now allow big pharma/biotech managements to make decisions with all the facts."

The sector is also going to benefit from clinical data and potential launches of exciting new technologies and therapies such as gene therapies, immuno-oncology combinations and CAR-T drugs, they add, helped by a favorable regulatory landscape on both sides of the Atlantic.

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Tax Reform At Last, Allergan's Job Cuts, Teva Turnaround, Biogen's Cash, And Getting FDA-Friendly

JESSICA MERRILL, EMILY HAYES & MANDY JACKSON

Now that US corporate tax reform is a reality, drug makers are ready to see the results in their 2018 balance sheets. Tax reform was a good news story for US-based drug makers in what was a relatively lackluster opening day at the J.P. Morgan Healthcare Conference on Jan. 8 in San Francisco. Nonetheless, companies seemed reticent to shine a spotlight on the legislation, maybe because it is viewed by some as a giveaway to corporations. Generally, investors were the ones that raised the topic in breakout sessions.

Shutterstock: Rudy Balasko

Most US biopharmas appear poised for a windfall. In some cases, that will come in the form of a lower tax rate given that the legislation reduces the corporate income tax rate to 21% from 35% as of Jan. 1. In other instances, it will come from stockpiles of cash that has been held overseas and can now be repatriated at a rate of 15.5%.

Drug makers said they expect to direct the savings toward share buybacks, dividends, business development and R&D.

Johnson & Johnson Chief Financial Officer Dominic Caruso said tax reform will be a positive for J&J and generally for the industry, but he insisted it will not change the company's capital allocation strategy. "Our primary focus on allocating capital after investing in our business is to our dividend," he said, followed by M&A and share repurchase.

Merck & Co. Inc. CEO Kenneth Frazier similarly commented that the legislation will not change the company's capital allocation, but said the expectation is that the running tax rate will be lower. "We are going to continue to use our cash and to use our resources to do things we have been doing," Frazier said. "With the kinds of deals we've been ideally targeting, we've had enough access to cash and we have enough power on our balance sheet to do those deals before tax reform."

Celgene Corp. said it will maintain its historic tax rate but will be able to access 60% of its cash that has been held overseas.

Regeneron Pharmaceuticals Inc., on the other hand, has the opposite situation. The company expects to see its tax rate drop considerably in 2018 but will not repatriate any cash from overseas.

"We have been in existence for 30 years, but we haven't been overseas for a while, so we have no repatriated cash coming back," CFO Robert Landry said. The company's blockbuster eye drug *Eylea* is sold outside the US by **Bayer AG**. The company will benefit, however, from a tax rate that is expected to drop to 15%-19% from 26%-29% in 2017.

"It's certainly going to be for Regeneron a very positive story," Landry said. CEO Len Schleifer said the resources will be invested mainly in R&D, as well as shoring up the company's manufacturing infrastructure.

ALLERGAN'S SAUNDERS DEFENDS PATENT MOVES

Allergan PLC warned during its third quarter earnings report in November that it would have to cut costs, including jobs, with generics for the company's blockbuster dry eye disease drug Restasis (cyclosporine) coming to market sooner than anticipated. *(Also see "Allergan Readies Cost Cuts As Restasis Generics Approach" - Scrip, 2 Nov, 2017.)* CEO Brent Saunders defended the company's controversial Restasis patent-protecting moves during an interview at the J.P. Morgan conference as a mean of trying to prevent those layoffs.

The company revealed in a US Securities and Exchange Commission (SEC) filing five days before its J.P. Morgan presentation on Jan. 8 that it would fulfill that promise by laying off 1,000 employees and cutting 400 open positions in Allergan's commercial and other operations. Allergan's restructuring costs will total $125m, but the employment reduction and other changes will save $300m to $400m.

"Anytime you do a layoff it's heart-wrenching. It's I think the hardest decision any leader has to do," Saunders said. "Which is why we were so tenacious in trying to preserve our intellectual property, was in large part to avoid something like this."

He said some employees have recognized that Allergan engaged in extreme measures to protect the Restasis patents and the revenue stream that supported their jobs.

The company went as far as to shift ownership of its Restasis patents to the Saint Regis Mohawk Tribe and then licensed the intellectual property back from the Native American tribe at the low cost of $15m per year, so that Allergan could use the tribe's sovereign immunity to get an inter partes review (IPR) proceeding in front of the US Patent and Trademark (PTO) Patent Trial and Appeal Board (PTAB) dismissed. *(Also see "Allergan Shifts Restasis Patents To Native American Tribe To Invoke Immunity From IPR" - Scrip, 9 Sep, 2017.)* Despite the controversial deal, the Restasis patents were invalidated by a district court ruling in separate patent litigation with generic drug makers. *(Also see "Allergan May Rue Mohawk Tribe Deal As Court Invalidates Restasis Patents" - Scrip, 16 Oct, 2017.)*

When asked how he feels about the Mohawk Tribe deal now, Saunders said: "I think we have to be very careful about protecting the intellectual property ecosystem in the US. I think it's in a very fragile position today."

He explained that Allergan believes in "the Hatch-Waxman regime" which has created "a very robust generic marketplace," but the IPR system is broad, unpredictable and doesn't have "the

benefits of jurisprudence or precedence." Saunders said that as innovators the industry should be concerned about what happens with the IPR process, and noted that some of the company's laid off employees "realize that we really did everything we could to protect this intellectual property." Those efforts continue with an appeal of the district court decision in the works and an ongoing IPR process. *(Also see "Mohawk Tribe Questions Patent Board's Impartiality In Restasis Case" - Pink Sheet, 4 Jan, 2018.)*

"We arguably put our reputation – my reputation – on the line. I would do it again if I could save the jobs of those people," Saunders said. *(Also see "Too Bold By Half: Allergan's Latest Moves And Pharma's Leadership Deficit" - Pink Sheet, 12 Sep, 2017.)*

TEVA ON RAISING SOME US GENERIC DRUG PRICES

It was standing room only at **Teva Pharmaceutical Industries Ltd.**'s presentation on the opening day of the J.P. Morgan meeting as investors crowded in to hear details on CEO Kare Schultz's turnaround plans. The new CEO unveiled the initial wave of his plan, including a massive 25% workforce reduction – or 14,000 jobs – in December. *(Also see "Schultz Swings The Cleaver At Teva, Cutting 25% Of The Workforce" - Scrip, 14 Dec, 2017.)*

Schultz offered more clarity on earlier comments that Teva would raise the price on some unprofitable US generic drugs or cut them altogether, which drew attention and raised questions about how Teva might navigate the tricky price negotiations. He said the effort would impact only about 10% of the SKUs in Teva's US generics portfolio.

"It doesn't mean that we stop supplying our customers," he said. "It just means that we have started negotiations where we have explained to our big customers these SKUs…are not sustainable from our point of view. We are fine with discontinuing them, but we are also fine with renegotiating the price to a sustainable level." Raising the price doesn't necessarily mean a big change, he added. For example, it could be something like raising the price from 50 cents to 60 cents, he said.

Schultz said the unprofitable products came about because Teva's prior management focused on maximizing revenue over operating profit.

"If you maximize revenue, you will take nearly any deal you can get just to get the volume," he said.

But he insisted the unprofitable drugs represent a relatively small part of Teva's overall profitability.

"It's our own responsibility to talk to our customers about it and create a stable situation," he said. "It would also be unsustainable long term for US customers if we didn't do this."

Teva's number one priority for now is reining in spending and positioning the company to begin repaying its debt obligations, around $32bn. Schultz said Teva will provide 2018 financial guidance along with its fourth quarter sales and earnings release, the first financial guidance to be provided by the new management.

BIOGEN: MONEY TO BURN ON BUSINESS DEVELOPMENT

Biogen may be busy on the business development front in 2018. CFO Jeffrey Capello said the company has the potential to leverage up to $37bn in cash if needed, resources the company could invest in business development.

"When you have $37bn potentially… that gives you a lot of flexibility other companies don't have," he said. Biogen has nearly $7bn in cash on the balance sheet, but the projection includes other opportunities to leverage the balance sheet and cash flow projections for the next five years.

CEO Michel Vounatsos said the focus remains on early stage deals, with an emphasis in neuroscience, where the company has built a focused pipeline. Nonetheless, investors are eager for more late-stage assets, despite the company's early success with the launch of *Spinraza* (nusinersen) for spinal muscular atrophy (SMA). Some investors are concerned about the sustainability of the company's sales in multiple sclerosis.

Biogen unveiled plans to move a new gene therapy into the clinic for SMA by mid-year and to begin Phase III testing of a new drug from stroke in-licensed from **Remedy Pharmaceuticals Inc.** last year. The drug will begin Phase III testing for large hemispheric infarction, a type of stroke where brain swelling leads to a disproportionately large share of stroke-related morbidity and mortality.

KEEP ON KNOCKIN' AT FDA'S DOOR

Pharmaceutical companies should take advantage of contacting a more flexible US FDA while they have it, experts urged during a Jan. 8 panel at the 2018 Biotech Showcase on the impact of new leadership and new initiatives at the agency.

On the first day of the Biotech Showcase, held concurrently with the J.P. Morgan meeting, presenters spoke highly of new FDA commissioner Scott Gottlieb in a number of different sessions. *(Also see "Q&A With US FDA Commissioner Scott Gottlieb" - Pink Sheet, 9 Nov, 2017.)*

During a Biotech Showcase panel, Nancy Bradish Myers, president and founder of **Catalyst Healthcare Consulting, Inc.**, said that one of the biggest changes happening at the FDA now is that from the top there is an "encouragement to the reviewers and others to be a little bit more forward thinking about new technologies and using that flexibility in new and novel ways."

The current leadership is encouraging everyone to be more creative in their approaches, as if a message has come from on high: "let's try it."

"I think it's a time for people to be more creative than they have been in the past," said Bradish Myers, an attorney and former special assistant and senior strategic advisor in FDA's Office of the Commissioner. She warned that if companies don't try to be more creative, then FDA can't be creative in response.

"There's a lot of 'hey come in and talk to us.' It may not be every reviewer or every division that really wants to exercise that flexibility to the max, but there are groups that are because they are focused on the patient and what the patient really needs," Bradish Myers said.

David Horowitz, partner at the Hogan Lovells law firm and formerly deputy general counsel at the US Department of Health and Human Services (HHS) and head of the office of compliance at FDA's drug center, added that there is a lot of variability – some FDA officials are more eager to change and be more creative than others.

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Walmsley On Diversity, Amgen's Overseas Cash, Growing Opdivo, Mylan On US Generic Pricing

JESSICA MERRILL, EMILY HAYES & MANDY JACKSON

GlaxoSmithKline PLC CEO Emma Walmsley had her J.P. Morgan Healthcare Conference debut on Jan. 9 in San Francisco in front of a standing room crowd in the Grand Ballroom of the Westin St. Francis. The audience was eager to hear more about her plans to prioritize pharmaceuticals and innovation. But it also was a feel-good moment at a time when the industry is growing increasingly aware of its diversity problem – particularly in the top leadership ranks.

Gender diversity was a prominent topic at the industry's biggest business meeting of the year, given the societal movement under way.

Walmsley became the first woman CEO of a big pharma when she took the reins at GSK last year, succeeding Andrew Witty.

The chief executive kept the J.P. Morgan presentation focused on her first two priorities: delivering growth for shareholders as well as discovering and developing innovative medicines. But during the breakout session that followed, she also acknowledged that being the first woman to break into the top ranks of big pharma comes with a responsibility to lead the industry on the issue of diversity.

"These jobs come – and I'm knew at it – with enormous privilege and a tremendous responsibility," she said after being prompted by an investor to address the elephant in the room. "I recognize the responsibility that I have as a leader … I want to represent diversity in that sense."

But the industry's diversity problem isn't just about gender, Walmsley said. "I am just as fast and focused on diversity of representation in terms of the LGBT agenda, in terms of race, in terms of personality."

"You cannot be a modern employer in an industry that should be future-facing and modernizing arguably much more aggressively than it is … without being very demanding on this topic, both as an individual, as a CEO, but also as a leadership team and a company," she said.

It's common sense, Walmsley said, because the industry should represent the population it's serving.

AMGEN TO DO DEALS WITH OVERSEAS CASH

Amgen Inc. Executive Vice President and Chief Financial Officer David Meline said during the Q&A session following the company's J.P. Morgan Healthcare Conference presentation that at the very least under US tax reform the company will not see its tax rate go up and the rate is expected to be around 18% to 19% in 2018.

However, like many other biopharmaceutical companies presenting at the meeting, Amgen's biggest benefit from tax reform appears to be the ability to use its cash held overseas – a stockpile of about $39bn. The legislation, CEO Robert Bradway noted during the Q&A, puts Amgen on a level playing field with its competitors headquartered outside of the US.

So what will Amgen do with all of that money? "Our priority first and foremost is to expand our portfolio," Meline said, noting that the company is "very active" in business development.

Amgen is under pressure to bring new products to market as some of its blockbusters face biosimilar competition.

But the company probably isn't likely to execute a large M&A deal, because Bradway and Meline reiterated their prior thinking about deal-making. Amgen is focused on transactions that add molecules within its six main therapeutic areas, accelerate the company's global build out, and improve its data skills.

"We have increasing flexibility for business development," Meline said. "We have very stable and very strong cash flow – a good balance of equity and debt capacity."

After allocating appropriate funds to execute deals, he added, "we will consider the most efficient way to deliver cash to investors" through increased dividends or buybacks.

MYLAN'S BRESCH BRINGS UP SHORTAGES

Mylan NV CEO Heather Bresch said there are concerns about generic drug shortages as price pressure on certain high-volume, low-cost generic drugs continues to mount in the US.

"It's probably the starting point for a lot of conversations with our customers," she said in an interview. "They are concerned about the products that are high volume."

Generic drug makers make just cents on some of the most high-volume generic drugs that represent the bulk of the drugs used in the US. Generic manufacturers make most of their profits on the first-to-file ANDAs where they have exclusivity for a limited period of time.

The US generic drug market has come under increasing pressure in the last two years, partly due to consolidation in the distribution chain and also because FDA is successfully working through a backlog of ANDAs to get more generics onto the market, in part to lower US drug spending.

The result presents a bit of a conundrum in the generic drug industry. The situation is one of the issues that is posing challenges to troubled **Teva Pharmaceutical Industries Ltd.**, which is in the midst of laying off 25% of its workforce. It's not the only one, however, and some companies – including Mylan – have been better able to navigate the situation through geographic expansion and complex generics.

As part of its turnaround plan, Teva has vowed that it will raise prices on some non-profitable US generic drugs – about 10% of SKUs – or discontinue them.

"We saw the story play out with injectables years ago. Prices were ultra-competitive. It forced people out of the market, and then we had shortages," Bresch said.

But Bresch said Mylan will make its way through the challenges by remaining steady, relying on its diversification strategies, and being patient.

"I do think things have a tendency to swing extreme and then recalibrate," she said. "I think we will find ourselves there, and Mylan will benefit from having that steady hand."

OPDIVO'S BILLIONS: THERE'S MORE WHERE THAT CAME FROM

Bristol-Myers Squibb Co. CEO Giovanni Caforio highlighted the strong sales track record of the company's PD-1 inhibitor *Opdivo* and multiple billion dollar opportunities in various indications during its presentation at the J.P. Morgan meeting on Jan. 9.

First approved by FDA in December 2014, Opdivo (nivolumab) now has $4.9bn in annualized sales, 14 approved indications in the US, 250 global approvals and over 30 registrational trials are ongoing in multiple tumor types.

Sales in non-small cell lung cancer (NSCLC) in the US in recent quarters have been stable despite greater competition from competitors in the PD-1/L1 family. Some results from the first-line CheckMate 227 study in first-line NSCLC are expected in the first half of 2018.

Caforio also pointed out that there are multiple billion dollar opportunities in other indications, including renal cell carcinoma (RCC). Opdivo is approved for second-line metastatic RCC and a filing for use with the CTLA-4 inhibitor *Yervoy* (ipilimumab) in first-line metastatic RCC is under FDA review, with an April 18 user fee date.

The first-line RCC market is twice as big as second-line RCC, Caforio noted, and the combination has potential to become the standard of care in the intermediate-to-poor risk segment of the first-line disease. CheckMate-214 is the only Phase III study to show a survival benefit for a new agent in this setting, he said.

"I really feel that renal can be an over $1 billion opportunity for Opdivo," Caforio said.

Opdivo is also rapidly becoming the standard of care in second-line hepatocellular carcinoma (HCC) since approval for this indication in the third quarter of 2017, the exec said. Opdivo already has made its mark in terms of market share, which has come at the expense of **Bayer AG**'s *Stivarga* (regorafenib).

"This is a small opportunity in second line, but it is an important indicator of the potential role of Opdivo and importantly, of the need for new agents in this disease. In fact, today our share is well above 60% and continuing to grow in second line," Caforio said.

The Phase III CheckMate-459 study of first-line HCC study that will read out in the second half (*see graphic*).

Gastric cancer represents another billion-dollar opportunity for Opdivo, he said.

VIEHBACHER-BACKED BOSTON'S PIPELINE

Boston Pharmaceuticals Inc. was not a typical start-up when it launched at the end of 2015. It raised $600m from Gurnet Capital – the $2bn investment fund run by former **Sanofi** CEO Chris Viehbacher – so that it could rapidly acquire and develop compounds de-prioritized by big pharma and other companies or stuck in the valley of death without adequate funding to progress into clinical proof of concept.

The model called for Boston to sell or out-license molecules once they achieved proof of concept – a stage that some of the firm's acquired assets are just now entering.)

Boston has acquired seven assets – four of which are clinical-stage – and Co-Founder and CEO Robert Armstrong told *Scrip* in an interview during the J.P. Morgan conference that the company expects to add three to five assets in 2018. The current pipeline includes three autoimmune disease programs, including a lupus drug candidate; two oncology programs, including one in breast cancer; one cardiovascular asset, designed to treat atrial fibrillation; and an anti-infective program.

To date, Boston has reviewed more than 450 molecules. The 22-person company is agnostic when it comes to therapeutic area and drug modality.

"When we created this company, Chris and I recognized that there's always a disconnect between innovation and the capital that's available," Armstrong said. He explained that R&D teams are generating more and more new and innovative molecules, but funding is not keeping up with the need for cash to progress all of those programs.

Both big and small companies struggle to fund all of the programs in their pipelines and frequently put drug candidates on hold to focus on core therapeutic areas, despite a desire to get shelved compounds to patients, as noted by **Pierre Fabre Group** President and CEO Frederic Duchesne in Boston's Jan. 4 announcement that it in-licensed global rights to the selective potassium channel blocker F17727.

"While our R&D and commercial focus has shifted away from cardiology, we are committed to ensuring that promising compounds are advanced through strategic partnerships to the benefit of patients," Duchesne said.

Smaller biopharma companies reach out to Boston when they are having trouble accessing cash, but also when they have to narrow their focus and look for someone who can develop de-prioritized assets.

"Platform-based companies have always had this problem – they outpace their ability to raise funding and pursue development," Armstrong said. Of its seven acquired compounds, three came from pharma and four from biotech. Boston hopes to buy 20 to 25 molecules with its existing capital and plans to spend $25m to $30m each on development of the assets through proof-of-concept data.

And if Boston's efforts are successful, the economics are attractive for licensors who are patient enough to wait for most of the value from their deals with the company. "The innovator ends up with roughly a third of the value at the back end," Chief Financial Officer Ian Sanderson said.

J&J DEALS IN PREDICTING ALZHEIMER'S RISK

Some of **Johnson & Johnson Innovation LLC**'s latest collaborations are aimed at helping predict risk for Alzheimer's disease early and noninvasively, at a time when the field is still reeling from the latest string of failures.

J&J and other sponsors are not giving up on targeting amyloid, rather they are moving prevention, before symptoms have even developed.

Among a dozen new collaborations announced on Jan. 4, just before the J.P. Morgan meeting kicked off, J&J Innovation unveiled a deal with Toronto-based **WinterLight Labs, Inc.**, which has developed artificial intelligence technology that it says can help non-invasively predict dementia and neurodegenerative diseases long before clinical symptoms are apparent.

Early changes in the brain may be detected with positron emission tomography (PET) imaging scans, but this is expensive and Seabrook noted that there are not enough PET centers in the US to allow screening of everybody who is at risk, so there is a need for alternatives, such as WinterLight's artificial intelligence algorithms, which enable testing of the ability to remember faces, names and events.

In another newly announced deal, J&J Innovation said it will be working with the Northern California Institute for Research and Education and the San Francisco Veterans Affairs Medical Center to explore the use of speech recognition technology and neuropsychological assessments for monitoring brain health in elderly people.

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IPOs In Review: Biopharma Offerings Bounced Back In 2017 As Returns Rose

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Biopharmaceutical companies launched 42 initial public offerings in the US in 2017 versus 30 in 2016 as stock values rose. But biotechnology in general endured a rough fourth quarter, raising the question of whether returns will be high enough to support as many or more IPOs in 2018.

The average return for the biopharma IPO class of 2017 as of Dec. 29 – last year's final day of trading – was 33.2%, which was a near tripling of the 11.2% return at the end of 2016 for therapeutics firms that went public in the US that year. But biotech's outperformance versus other industries ended during the last few months of 2017, suggesting that the IPO boom could bust this year.

The big average return was helped by a few companies whose stock traded particularly well, including the antibody developer **AnaptysBio Inc.**, which launched the first IPO of 2017 at $15 per share and closed up 571.5% at $100.72 at year's end, making it the biggest gainer by far last year. The San Diego-based company has multiple early- and mid-stage programs in the clinic for cancer as well as autoimmune and inflammatory diseases – including atopic dermatitis, psoriasis, asthma and food allergies – on its own and with partners.

Seventeen drug developers that closed first-time offerings in 2017 ended the year in negative territory and 23 provided IPO investors with positive returns as of Dec. 29 (*see table below*), including three companies with triple-digit returns. In addition to AnaptysBio, **argenx SE** was up 271.4% and **UroGen Pharma Ltd.** gained 186.2%.

However, two companies that priced offerings late in 2017 didn't list their shares on the US stock market before the end of the year.

Genprex, Inc. said on Oct. 13 that it priced 2.5m to 4.5m shares at $5 each and expected the offering on Nov. 6, but indicated in a Dec. 12 US Securities and Exchange Commission (SEC) filing that it planned to sell 1.3m shares at $5 to gross $6.5m. However, the novel cancer therapy developer also took out a $200,000 loan in December and its shares still are not trading on the stock market.

Meanwhile, **Cue Biopharma Inc.** priced 8.8m shares at $7.50 each on Dec. 27 and grossed $66.2m from the offering, but the Cambridge, Mass.-based company's stock didn't start trading on the Nasdaq until Jan. 2. The immunotherapy specialist is developing biologics that are designed to engage and modulate the activity of disease-specific T cells in cancer and autoimmune disorders.

DOLLARS RAISED ROSE

In addition to the number of biopharma offerings, the IPO market in 2017 bested 2016 in another important measure – therapeutics companies raised $4.2bn or $102.8m on average last year versus a total of $2bn or $67.4bn on average in the prior year. Drug developers raised a total of $5.4bn via IPOs in 2015 or $86.8m on average.

But will the rising number of offerings and booming proceeds from IPOs continue in 2018? That's hard to say, given the fourth quarter 2017 decline in biotech stock values.

The Nasdaq Biotechnology Index (NBI) outperformed the broader Nasdaq and the Dow Jones Industrial Average through the third quarter, and advisors to the industry said they expected capital to flow into biopharma IPOs in 2018 as long as the sector continued to outperform other industries.

But things changed in the fourth quarter after big pharma and large biotech companies reported largely disappointing third quarter financial results, contributing to a 2.4% decline in the NBI between its Oct. 5 peak and the end of 2017. The index grew 21.1% for the year, but the Nasdaq gained 28.2% and the Dow Jones rose 25.1% between the end of 2016 and the end of 2017.

Even so, the biggest biopharma IPO of the year was completed by the neurodegeneration specialist **Denali Therapeutics Inc.** in December with $287.5m in gross proceeds. It was one of two first-time offerings by drug developers last month; the other was a $150m IPO completed by oral chemotherapy drug developer **Odonate Therapeutics LLC**.

Armo BioSciences Inc., **resTORbio Inc.**, **Solid Biosciences LLC** and **Menlo Therapeutics Inc.** filed paperwork with the SEC in December to note their intention to go public in the US.

Redwood City, Calif.-based Armo closed a $67m Series C-1 venture capital funding round at the end of August to fund clinical development of AM0010 – a pegylated form of interleukin-10 (IL-10) that's in development for lung and pancreatic cancers – and preclinical programs. The company said in its Dec. 29 SEC filing that it will raise up to $86.3m to fund late-stage trials for AM0010 and advance other programs.

The Boston-based resTORbio, which has the TORC1 inhibitor RTB101 in development for age-related indications, said on Dec. 5 – less than a week after it raised a $40m Series B venture round at the end of November – that it confidentially filed paperwork with the SEC to support an IPO. The company later revealed in a Dec. 29 filing that it intends to raise up to $85m, primarily for the development of RTB101.

Solid Biosciences of Cambridge, Mass., said in a Dec. 29 SEC filing that it will raise up to $100m to fund the company's mission of curing Duchenne muscular dystrophy (DMD). Lead product candidate SGT-001 is a gene transfer therapy that's being tested in a Phase I/II clinical trial. It is designed to restore functional dystrophin protein expression in patients' muscles in an effort to slow or possibly halt progression of DMD independent of genetic mutation or the stage of the disease. The company raised a $42.5m Series B round in November 2015 and a $50m Series C round last April.

Armo's Redwood City neighbor Menlo Therapeutics filed a registration statement with the SEC on Dec. 28 that said it will raise up to $97.8m to fund the development of serlopitant – a small molecule inhibitor of the neurokinin 1 receptor (NK1 R) that's in Phase II trials as a treatment for pruritus (itch) associated with dermatologic conditions and as a treatment for refractory chronic cough. The company raised a $50m Series C round in July.

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2017 US IPO Performance Through Year End

COMPANY	GROSS PROCEEDS	IPO PRICE	DEC. 29 CLOSING PRICE	RETURN
AnaptysBio Inc. (ANAB)	$86.3m	$15	$100.72	571.5%
Jounce Therapeutics Inc. (JNCE)	$117.1m	$16	$12.75	-20.3%
ObsEva SA (OBSV)	$96.8m	$15	$9.76	-34.9%
BeyondSpring Inc. (BYSI)	$54.3m	$20	$29.08	45.4%
Therapix Biosciences Ltd. (TRPX)	$13.8m	$6	$5.34	-11%
Tocagen Inc. (TOCA)	$97.8m	$10	$10.25	2.5%
Verona Pharma PLC (VRNA)	$89.3m	$13.50	$11.87	-12.1%
Zymeworks Inc. (ZYME)	$63.6m	$13	$7.59	-41.6%
Ovid Therapeutics Inc. (OVID)	$75m	$15	$9.87	-34.2%
UroGen Pharma Ltd. (URGN)	$66.9m	$13	$37.21	186.2%
Biohaven Pharmaceuticals Holding Co. Ltd. (BHVN)	$193.5m	$17	$26.98	58.7%
G1 Therapeutics Inc. (GTHX)	$116.7m	$15	$19.84	32.3%
argenx NV (ARGX)	$114.7m	$17	$63.14	271.4%
Athenex Inc. (ATNX)	$75.9m	$11	$15.90	44.5%
Immuron Ltd. (IMRN)	$6.1m	$10	$5.29	-47.1%
Dova Pharmaceuticals Inc. (DOVA)	$86.3m	$17	$28.80	69.4%
Mersana Therapeutics Inc. (MRSN)	$75m	$15	$16.43	9.5%
Aileron Therapeutics Inc. (ALRN)	$56.3m	$15	$10.54	-29.7%
Avenue Therapeutics Inc. (ATXI)	$38m	$6	$3.62	-39.7%
Akcea Therapeutics Inc. (AKCA)	$143.8m	$8	$17.36	117%
Kala Pharmaceuticals Inc. (KALA)	$103.5m	$15	$18.49	23.3%
Sienna Biopharmaceuticals Inc. (SNNA)	$74.7m	$15	$18.15	21%
Clementia Pharmaceuticals Inc. (CMTA)	$137.9m	$15	$18.98	26.5%
Zealand Pharma AS (ZEAL)	$90m	$17.87	$13.60	-23.9%
Krystal Biotech Inc. (KRYS)	$45.5m	$10	$10.52	5.2%
Zai Lab Ltd. (ZLAB)	$172.5m	$18	$21.23	17.9%
Deciphera Pharmaceuticals Inc. (DCPH)	$138.8m	$17	$22.67	33.4%
Nightstar Therapeutics Ltd. (NITE)	$86.3m	$14	$13.12	-6.3%
NuCana BioMed Ltd. (NCNA)	$114m	$15	$10.11	-32.6%
Rhythm Pharmaceuticals Inc. (RYTM)	$138m	$17	$29.06	70.9%
OptiNose Inc. (OPTN)	$138m	$16	$18.90	18.1%
Genprex Inc. (GNPX)	NA	$5*	NA	NA
Ablynx NV (ABLX)	$230m	$17.50	$24.99	42.8%
Spero Therapeutics Inc. (SPRO)	$83.6m	$14	$11.75	-16.1%
Allena Pharmaceuticals Inc. (ALNA)	$74.9m	$14	$10.06	-28.1%
InflaRx GMBH (IFRX)	$106m	$15	$20.95	39.7%
Erytech Pharma SA (ERYP)	$144m**	$23.26	$22.02	-5.3%
Arsanis Inc. (ASNS)	$66m**	$10	$12.76	27.6%
scPharmaceuticals Inc. (SCPH)	$102.1m	$14	$12.09	-13.6%
Odonate Therapeutics Inc. (ODT)	$150m	$24	$25	4.2%
Denali Therapeutics Inc. (DNLI)	$287.5m	$18	$15.64	-13.1%
Cue Biopharma Inc. (CUE)	$66.2m*	$7.50	NA	NA
Average Return:				**33.2%**

*Genprex launched an offering, but has not yet concluded the IPO or listed its shares on the US stock market. Cue launched its offering in 2017, but its stock didn't start trading until 2018. **Includes concurrent private placements: $20m for Arsanis and $19.1m for Erytech.

Inexperienced Biotech CEOs Impact Investor Confidence – Analyst Research

JESSICA MERRILL jessica.merrill@informa.com

The tenure of US large-cap biotech CEOs has declined dramatically over the last 15 years, contributing to reduced confidence in the sector, according to an analysis by Leerink Partners' analyst Geoffrey Porges. Meanwhile, the tenure of CEOs at US pharma companies increased during the same period.

In a Dec. 26 note to investors, Porges determined that the median tenure of large cap US biotech CEOs has decreased from 11 years in 2007 to one year in 2017 in an evaluation of seven large cap biotechnology companies every five years from 2002 to 2017 (**Alexion Pharmaceuticals Inc.**, **Amgen Inc.**, **Biogen Inc.**, **Celgene Corp.**, **Gilead Sciences Inc.**, **Regeneron Pharmaceuticals Inc.** and **Vertex Pharmaceuticals Inc.**).

"We believe investors, understandably, find it hard to have confidence in these new executives given their lack of track record, and the recent history of the group is unlikely to inspire confidence," Porges said. "The limited potential of these relatively inexperienced biotech CEOs to focus their companies and deliver necessary structural changes in their companies and the industry was one of the themes for our cautious large cap biotech sector outlook for 2018."

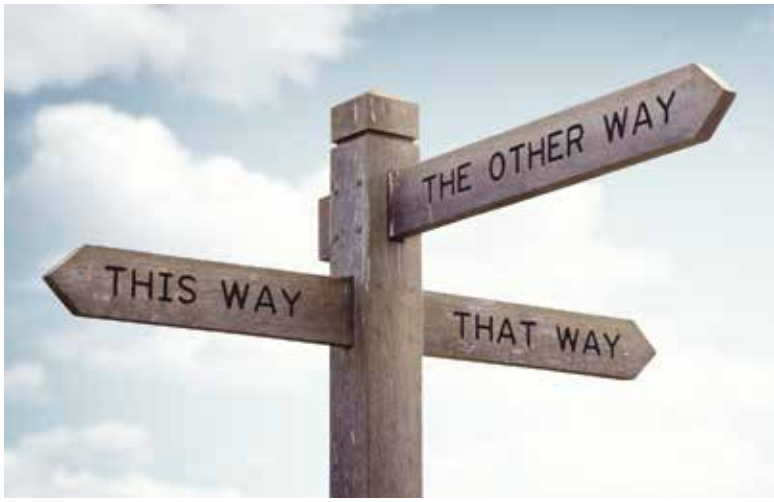
Management confidence is low and revenues for high-profile biotech products are slowing due to competitive pressures, resulting in a cautious outlook for the sector from Porges.

New biotech executives also hold less power, with the board of directors holding back power over junior CEOs. Only 30% of the CEOs hold a dual board chairman position, while CEOs of pharma companies have maintained a dual chairman role 80% to 100% of the time over the period of the analysis. Porges noted it is less common generally in biotech for a CEO to hold both positions, however, given that company founders are often physician/scientists who rely on a business leader as chairman. Nonetheless, the percentage is lower in the five years from 2012 to 2017 than the 40%-60% in 2002 through 2012.

"We believe the lack of strong authority in these leadership positions in biotech companies is certainly suggestive of a lack of immediate opportunity for transformative changes in companies or industry structure," Porges said. "This limitation in authority is also likely to be particularly true with respect to the ability of CEOs to win board approval for large M&A deals."

US biotech companies did move through a period of leadership shakeups in 2016 and 2017. Celgene CEO Mark Alles, previously president, succeeded Robert Hugin on March 1, 2016, with Hugin remaining as chairman. Alexion CEO Ludwig Hantson stepped into the post in March 2017 from **Baxalta Inc.** following a series of missteps by management. *(Also see "Alexion CEO Hantson Tasked With Kicking Growth Momentum Into Gear" - Scrip, 27 Mar, 2017.)* In March 2016, Gilead's John Milligan took the reins from longtime CEO John Martin, who remains chairman. The transition was viewed as a smooth succession plan given the long experience of both executives.

Biogen tapped Michel Vounatsos to succeed George Scangos as CEO in January 2017 after just a brief stint as chief commercial officer of the company. Stelios Papadopoulos remains chairman, having taken on the role in June 2014.



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> 'This disparity in tenure is one of the largest we have seen for the two industries and is consistent with our view that many of the largest companies in biotech are at a crossroads in their evolution'

Of the seven companies included in the Leerink analysis, Regeneron's founder Leonard Schleifer has the longest tenure, serving as CEO since the company's inception in 1988, while Roy Vagelos has held the chairman role since 1995. Regeneron has not outlined a succession plan, but the topic has come up in recent investor discussions as the company has matured. Vertex's Jeffrey Leiden has worked as chairman and CEO since 2012, and Amgen chairman and CEO Robert Bradway has also served as CEO since 2012 and chairman since 2013.

"The increase in turnover and the decline in tenure in the last two years are really unique to this period in the industry's development," Porges said.

While the experience of US large cap biotechs declined, the tenure of pharma CEOs increased to five years during the same period from 2012 to 2017, Leerink concluded. The research included six large cap US pharma companies (**AbbVie Inc.**, **Bristol-Myers Squibb Co.**, **Johnson & Johnson**, **Eli Lilly & Co.**, **Merck & Co. Inc.** and **Pfizer Inc.**

"This disparity in tenure is one of the largest we have seen for the two industries and is consistent with our view that many of the largest companies in biotech are at a crossroads in their evolution," Porges said.

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Spark Innovates On Pricing And Reimbursement

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Spark Therapeutics Inc. will be the first drug maker to bring a gene therapy to the US market – *Luxturna* (voretigene neparvovec-rzyl) for a rare inherited blindness – and now the company is pioneering new reimbursement approaches to pay for what will be an expensive one-time treatment.

The company revealed the price of Luxturna Jan. 3: $425,000 per eye for a total cost of $850,000 for most patients, following a lot of speculation that it could be the first drug in the US to cross the $1m threshold. Spark surprised by pricing the drug below what CEO Jeffrey Marrazzo had previously said would represent fair value, given the drug's anticipated long-term benefit for patients and their caregivers.

At the same time, Spark announced several programs aimed at enhancing access to the treatment, including a novel outcomes-based rebate program tied to a long-term durability measure, a distribution strategy that will let payers front the cost of the medicine, rather than providers, and the submission of a proposal to the Centers for Medicare & Medicaid Services that would pave the way for higher rebates to be paid out over time.

"The whole point was for us to design a whole bunch of options for people to ensure that patients have access," CEO Marrazzo said in an interview.

Some payers reacted positively to Spark's pricing and reimbursement approach. The New England insurer Harvard Pilgrim was the first to sign on to the outcomes-based reimbursement plan.

"I think most of us expected it to come out at about $1m, so $850,000 for two eyes, given that expectation, doesn't seem unreasonable," said Harvard Pilgrim's Chief Medical Officer Michael Sherman.

Marrazzo said the company decided on the final price after many discussions with payers, patients and providers.

"It was really how do we balance all of that feedback and get to a price point where we felt we would be capturing a reasonable amount of the value, but not taking all of the value," he said. "My view is that this is about building a company and not about a product."

Not everyone was pleased. The public advocacy group Public Citizen called the "near-million-dollar price" for Luxturna "an outrage that will hurt struggling families and raise premiums for all of us."

Luxturna cleared FDA as the first traditional gene therapy approved in the US in December as a one-time treatment for patients with biallelic RPE65 mutation-associated retinal dystrophy, a rare inherited form of blindness that only effects a few thousand patients in the US. One of the concerns of industry, payers and patients is how the US health care system will be able to front the cost of expensive one-time gene therapies when so many more are expected to reach the market in the coming decade.

That's where Spark has tried to work creatively with payers on a payment strategy for Luxturna. Marrazzo said the company is willing to do even more when it comes to creative rebate plans and payment strategies but is also limited by existing rules and regulations.

OUTCOMES-BASED REIMBURSEMENT

Under an outcomes-based reimbursement plan, Spark would pay rebates to payers to offset the cost of Luxturna at two time points if the efficacy of the drug fails to deliver: one at 30 to 90 days and another at 30 months. The short-term and long-term measures will be based on full-field light sensitivity threshold (FST) testing scores, which will be established for each eligible patient at baseline prior to administration.

In clinical trials, patients experienced an improvement in vision within 30-90 days following treatment, which is how the company determined the window of time to be appropriate for measuring efficacy. "The 30-month check would be about whether that improved vision was continuing to be stable out to 30 months," Marrazzo said.

The company would not disclose the amount of the rebate it is offering but said the company has agreed to offer the maximum amount it can while taking into account government price reporting requirements. By law, Medicaid is guaranteed a 23.1%. discount off the average manufacturer price for branded drugs or the best price offered anywhere, whichever is lower. A rebate that reduced the list price for Luxturna to below the 23.1% discounted threshold would thus set a new best price for Luxturna that would have to be provided to all Medicaid programs.

That's one reason Spark is separately in discussions with CMS about potentially waiving the best price requirement. The company has submitted a proposal to CMS to conduct a demonstration project for Luxturna that would enable the company to offer greater rebates tied to clinical outcomes – and out to a longer time period. Spark believes CMS could offer a one-time waiver, although the issue is one the agency is grappling with.

Harvard Pilgrim is so far the only payer that has signed on to the outcomes-based reimbursement plan, but Marrazzo said the company is far along in negotiations with several others.

Harvard Pilgrim's Sherman said the outcomes-based reimbursement plan relieves some of the risk for the insurer if the treatment doesn't work as hoped. At the end of the day, if Luxturna and other gene therapies do represent lifetime treatments, the cost may very well be reasonable, he said. "The bigger problem for us and the greater concern is if they are not effective. Then, they really aren't worth it," he said. "These agreements provide a mechanism for paying less when they are ineffective."

Harvard Pilgrim and many other payers have designed outcomes-based reimbursement plans for other drugs, but the challenge can be agreeing on a well-defined endpoint that can be met in a reasonable timeframe to measure efficacy. In the US, individuals frequently change insurers, which is why payers are concerned about paying a high upfront cost for a drug when the long-term benefits may be absorbed by a rival. When it comes to gene therapies, which could last a lifetime but are still untested long-term, the timeframe for measuring success is even harder to define.

Sherman said the 30-month timeframe seemed like a reasonable compromise in the case of Luxturna.

"One of the approaches was not to let better be the enemy of good," Sherman said.

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"There are many reasons to say, 'This is complicated. Let's not think about it for a few years.'"

But "we said, 'let's work through the issues'. We said, 'longer might be better, but 30 months, let's start there'," he added.

The company is also confident that it will be able to cash in on the longer-term rebate if the efficacy of Luxturna doesn't hold up, even if the patient has moved to a new insurance plan, partly because of the uncertainty around new gene therapies. Spark has committed to maintaining a patient database to measure long-term safety and efficacy, which means visual response should be manageable to track long-term, especially since the prevalence of the condition is so limited. Harvard Pilgrim expects the number of patients under its coverage universe that will be treated with Luxturna is under 10.

A NOVEL DISTRIBUTION STRATEGY

Spark has also sought to circumvent some of the challenges facing providers when it comes to buying high-priced specialty medicines by encouraging the payers to front the cost of the treatment and handle the distribution instead of the provider. Specialty medicines like Luxturna that are administered by physicians in hospitals are purchased by the hospital, which then charges payers a markup on the product. This traditional "buy and bill" model doesn't necessarily make sense for payers or hospitals when the cost of the drug is so high.

Spark will enter into an agreement with commercial payers under which the payer or its specialty pharmacy, purchases Luxturna, and the payer will separately contract with the treatment center to provide the treatment. Pharmacy benefit manager **Express Scripts Holding Co.** has agreed to use the new contracting model within its specialty pharmacy arms CuraScript and Accredo.

Spark views the arrangement as beneficial to both payers and providers. Payers don't have to absorb a hefty markup on the drug, and providers don't have to front the cost of an $850,000 drug. At the same time, the contracting payer has to agree to cover Luxturna consistent with the label, process a patient's benefit request expeditiously, and agree to cap out-of-pocket expenses at the in-network limit.

Sherman agreed the arrangement is advantageous from Harvard Pilgrim's point of view. He contrasted the situation to that of the two recently approved high-priced CAR-T cancer therapies from **Novartis AG** and **Gilead Sciences Inc.**, which hospitals are buying directly and marking up. "A hospital might add 5%, 10%, 15% to the price," he said.

Instead, he said Harvard Pilgrim will agree to pay the hospital fairly for handling and managing the administration of the gene therapy, which in the case of a surgically administered drug like Luxturna, would have a standard payment schedule. The arrangement also helps to facilitate the outcomes-based reimbursement strategy.

"How does that work if the provider has paid for the drug rather than the payer?" he asked. The tests will be underway soon, and the learnings will be applied to future gene therapies.

As Marrazzo put it, "These steps are critical to set a precedent that we are going to work towards being as innovative in our access models as we are in our labs and our clinical investigations."

Published online 3 January 2018

England Sees Past Price Tag To Back GSK Bubble Baby Gene Therapy: **http://bit.ly/2Dg0QAm**

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Boehringer Ingelheim Confident Of A Happier Ending In NASH Than HCV

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Boehringer Ingelheim GMBH has been down this path before, but this time will be different, it says. In 2014, BI shuttered a hepatitis C program consisting of two clinical candidates due to a perceived lack of advantages compared to companies more advanced in HCV, but in non-alcoholic steatohepatitis (NASH) a different set of factors will give the German pharma time to catch up and even take advantage of expertise obtained from its efforts in HCV.

The family-owned company has one candidate in clinical development for NASH – the Phase II oral amine oxidase copper-containing 3 (AOC3), inhibitor BI 1467335 – which it believes can address the multi-factorial disease with metabolic and anti-inflammatory benefits. But in November, BI signed a pair of partnerships with RNA-interference-focused biotechs – **Dicerna Pharmaceuticals Inc.** and **MiNA Therapeutics Ltd.** – that will aid in its goal to investigate NASH via a host of different targets and therapeutic approaches, Michael Mark, the pharma's global head of cardiometabolic diseases research, said in an interview.

NASH is a therapeutic space with no approved drug therapy as of yet, but bursting with competing programs, including four that have reached Phase III, addressing a variety of targets. While **Intercept Pharmaceuticals Inc.**, **Genfit SA**, **Gilead Sciences Inc.** and **Allergan PLC** lead the race to bring the first individual NASH drug to market, a consensus has emerged among key opinion leaders that combination therapy ultimately will best serve NASH patients, as happened previously in HCV and HIV.

In June 2014, BI decided to exit HCV drug development – it had protease inhibitor faldaprevir and non-nucleoside polymerase inhibitor deleobuvir in late-stage development – because the data those candidates had yielded to that point appeared to offer no viable differentiation compared with HCV drugs brought to market or in development at competitors such as Gilead, **Merck & Co. Inc.** and **AbbVie Inc.** Mark told *Scrip* there are several important distinctions that can prevent another "too little, too late" finish for BI in NASH.

"Number one, the number of patients is much higher," he said. "Second, there is no approved drug, and even those assets that we see now in advanced clinical stages according to our discussions do not fulfill the needs of patients with NASH or cirrhosis. So this is clearly an open space and there is a high therapeutic need for the future."

BI's existing experience in liver disease, its understanding of fibrosis from its work in respiratory disease and its broad base of knowledge in cardiometabolic disease also will lend advantages, Mark asserted. For now, while BI has only one NASH candidate in the clinic, it is reviewing its overall portfolio for internal candidates that might offer potential if re-purposed to address NASH, he added. The review will look at drug candidates in obesity, diabetes and kidney disease as well as other therapeutic areas.

"BI is very active in cardiometabolic diseases research and our understanding of this area is not only in diabetes and obesity but also complications and comorbidities of diabetes as well as comorbidities," Mark said. "Since we know that roughly 70% of obese type 2 diabetics suffer from [non-alcoholic fatty liver disease] and 30%-40% of type 2 diabetics have NASH, I think that's a logical thing [that this expertise could benefit its work in NASH]."

TRIAL ENROLLMENT CHALLENGE MAY DELAY PHASE IIA DATA

The pharma entered the NASH race specifically in 2015, when it optioned and later licensed worldwide rights to the then-Phase I BI 1467335 from **Pharmaxis Ltd.** BI initiated a Phase IIa study of the drug last August, but Mark declined to offer a timeline for data from that study, citing the oft-heard issue of patient recruitment.

Because the gold standard for diagnosing NASH and assessing disease progression remains liver biopsy, many trials require two such procedures – one for eligibility and one at the end of treatment – and NASH patients often are resistant to signing up for such an invasive regimen, especially for early- and mid-stage candidates. But the issue has challenged even companies leading the race, as Genfit pushed back the timelines for its Phase III study of elafibranor last April.

"The recruitment has started, the initiation of various sites has been successful," Mark noted. "It's such early days so I can't speculate on when the data might be available. We also realize that there are a number of clinical trials going on from various companies in NASH that compete for patient enrollment." Biomedtracker gives BI 1467335 a 24% likelihood of approval – average for a Phase II NASH candidate – and does not provide an estimated arrival date for data from the planned 150-patient study.

BI's over-arching strategy in NASH involves learning more about the pathophysiology of NASH and its precursor, NAFLD. That goal was part of the rationale behind the RNAi collaborations signed in November with Dicerna and MiNA. Neither BI nor Dicerna has disclosed the target of their research partnership, but Dicerna CEO Doug Fambrough told *Scrip* at the time of the deal that each had been investigating the same difficult-to-drug target on its own.

Mark said the efforts with Dicerna [See Deal] and MiNA [See Deal] will address inflammation and fibrosis, and may yield candidates complementary to BI 1467335. "This is a multifactorial disease with a metabolic angle, an inflammation angle and a fibrosis angle," he stated, "and that means since we don't understand fully the pathophysiology of NAFLD/NASH, we have to really probe different pathways, different angles of the pathophysiology of NASH to help the patients."

Both the Dicerna and MiNA collaborations are in preclinical stage right now, the exec added. But BI is betting that adding the biotechs' knowledge of small-interfering RNAs and small-activating RNAs with its expertise in multiple therapeutic areas and clinical development will prove "a perfect fit for a partnership," he said.

Both partnerships are investigating novel targets not being looked at by any other company in the NASH space, Mark added, so "we think we could really open the door for a new wave of therapeutics in liver diseases, NAFLD or even cirrhosis."

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Roche's Head Of Partnering On Deal Strategies And Aligning Attitudes

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Sophie Kornowski-Bonnet

Increasing pressure on big pharmas to fill their drug development pipelines means internal partnering teams face greater scrutiny and the bar for successful deal-making has been raised, says Dr. Sophie Kornowski-Bonnet, head of **Roche** Partnering.

"There was a time when you would hear that partnering is a wining and dining job – in fact it is everything else," said Kornowski-Bonnet during an exclusive interview with *Scrip* in late 2017. Pharma partnering is an intricate field, she elaborated, focused on aligning ambition, expertise and expectations; the celebration comes at midnight when a team has worked from sunrise to eventually get a contract agreed.

Leading partnering in a big pharma is a "complicated job where you get no limelight and no exposure," Kornowski-Bonnet said. Moreover, compounds often do not make it to patients at all. "But you have to get back up and keep on doing it, keep on seeking innovation."

THE ROCHE WAY

An R&D-focused company, 45% of Roche's pipeline is made up of partnered assets. "We actively search for great science that complements our internal research, and once we bring in assets from partners we treat these as 'in-house' science – we have the same way of looking at both internal and external projects," Kornowski-Bonnet said. Together, Roche's and **Genentech Inc.'s** partnering organizations manage more than 200 active partnerships.

Roche Partnering scouts worldwide for partners and screens around 2,000 projects a year – trialing between 50 and 60 deals. The partnering team is mostly focused on early-stage, novel assets. It is organized by therapy area, mirroring the way the big pharma is setup for R&D and commercialization and its philosophy is to "always and only look for innovative science," Kornowski-Bonnet said.

"The idea is to dramatically impact the way diseases are treated to make a real difference for patients. What we have within Roche is very strong expertise in development, regulatory and commercialization, as well as pricing and access to medicines," Kornowski-Bonnet said. The partnering team not only wants to bring new drugs into the pipeline but "we want to be sure they get to patients; the ultimate goal is to make a difference for patients."

Kornowski-Bonnet, who joined Roche in 2007 from **Merck Sharp & Dohme**, said the drug major was different to other pharmas when it came to partnering because it was extremely close to the science but also open-minded. "This means we are strategically focused but also opportunistic. Oftentimes, other companies are looking for specific assets or technologies. We are screening more broadly, looking for strong science," she said.

WORKING A DEAL

Roche follows a classical partnering strategy. It seeks partnering opportunities at conferences and events, companies reach out to big pharma directly about deal opportunities or Roche contacts interesting developers. Meetings take place and after a stage of due diligence the company might enter into a deal. "Throughout the process, we go through internal review committees because we are not bringing in the innovation for our partnering group, we are bringing it in for Roche," Kornowski-Bonnet noted.

> 'There was a time when you would hear that partnering is a wining and dining job – in fact it is everything else'

While putting decisions through various committees can be cumbersome, Kornowski-Bonnet said it guaranteed that teams were truly aligned and committed when a deal was struck. She highlighted Roche's partnership with **SQZ Biotechnologies Co.** as an example.

"We started looking at the company, we were intrigued and we ended up doing a deal with them. Often, one deal triggers another with that same company – so you are co-creating, which is extremely exciting for our team," Kornowski-Bonnet said. "If you were to sit in on an alliance meeting between Roche and a partner, you wouldn't be able to tell who is from Roche and who is from the partner company because it becomes one team working together," she added.

A spin-out company from Robert Langer's lab at the Massachusetts Institute of Technology, SQZ is developing an autologous "cell squeezing" therapy for cancer. The original December 2015 drug development deal could be worth more $500m to SQZ, based on upfront and potential clinical, regulatory and sales milestone-based payments.

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

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

Selected clinical trial developments for the week 29 December 2017 – 4 January 2018

LEAD COMPANY/PARTNER	COMPOUND	INDICATION	COMMENTS
Phase III Interim/Top-line Results			
Ardelyx Inc.	tenapanor	irritable bowel syndrome with constipation	T3MPO-3 safety extension; effective and well tolerated.
Insmed Inc.	*Arikayce* (amikacin) liposome inhalation	respiratory tract infections caused by *Mycobacterium avium* complex	INS-312 long-term extension study; response seen.
Updated Phase III Results			
Foamix Pharmaceuticals Ltd.	minocycline (FMX-101) topical foam	moderate to severe acne	Open label extension, positive safety data.
Innovation Pharmaceuticals Inc.	brilacidin	mucositis in head & neck cancer	Delayed onset of severe oral symptoms.
Insmed Inc.	*Arikayce* (amikacin) liposome inhalation	non-tuberculous mycobacterial lung disease caused by *Mycobacterium avium* complex	CONVERT (INS-212); durable efficacy.
Phase III Initiated			
Deciphera Pharmaceuticals Inc.	DCC-2618	gastrointestinal stromal tumor (GIST)	INVICTUS; a pan-KIT and PDGFR-alpha inhibitor.
BeiGene (Beijing) Co. Ltd./ Celgene Corp.	tislelizumab	liver cancer	An anti-PD-1 antibody.
Atara Biotherapeutics Inc.	tabelecleucel (ATA129), a T-cell immunotherapy	EBV-associated post-transplant lymphoproliferative disorder	ALLELE, MATCH; in patients with rituximab refractory disease.
Liquidia Technologies Inc.	LIQ861 (treprostinil) dry powder	pulmonary arterial hypertension	A new form for inhalation.
Omeros Corp.	OMS721	thrombotic microangiopathy	In patients with hematopoietic stem cell associated disease.
Avenue Therapeutics Inc. (Fortress Biotech Inc.)	tramadol, iv	post-surgery pain	A safety study.
Phase III Announced			
Dova Pharmaceuticals Inc.	avatrombopag	chemotherapy-induced thrombocytopenia	In patients with grade 3 or 4 disease.
Omeros Corp.	OMS721	IgA nephropathy	To start in early Feb., 2018
Zensun (Shanghai) Science & Technology Co. Ltd.	*Neucardin* (neuregulin 1-beta)	congestive heart failure	A recombinant human protein.
Novartis AG/Delenex Therapeutics AG	brolucizumab (RTH258)	wet age-related macular degeneration	A two-arm extension study.

Source: Biomedtracker

CONTINUED FROM PAGE 21

PARTNERING CHALLENGES

Roche has more than 70 new molecular entities in its pipeline, but the company sits within a very competitive industry where many large pharmas are facing pressure to replenish their pipelines. Kornowski-Bonnet said this pressure and urgency to fill pipelines was the biggest change for the innovative pharma sector over the last five years. However, the breadth and depth of Roche's pipeline means the company must be choosy about its partners. "This is more of an internal challenge – deciding on which projects to best spend resources on," she said.

Kornowski-Bonnet said that due to the increasing competition across the drug development industry and the need to fill R&D pipelines, the bar had been raised in recent years for partnerships. Big pharmas are doing more internal pressure testing on potential partner compounds now than they did in the past.

One of the biggest challenges for the partnering group is balancing the timing of a deal for both the partner and Roche. "You have to keep an eye on this without putting anyone under pressure," Kornowski-Bonnet said, adding that she managed this by maintaining thorough dialog with all parties. "Through a good exchange, generally you get to the right place," she said. "Also, I believe that if a deal is not meant to be, it's not meant to be – if you can't get it organized then the alignment between the partners wasn't there."

Another challenge is getting Roche and its partners onto the same page; agreeing deals with companies that share its R&D mindset. Many times, it was not a terms sheet that was most important to Roche in its deal-making, Kornowski-Bonnet noted, but a partners' reaction to the deal specifications. Deal-term discussions can reveal whether a company is in the relationship for the long-term and show whether a potential partner "cares about the science and is excited about finding new frontiers with us or if it is a quick return they are after," she said. The answers to those types of questions are important to Roche when selecting partners.

A NEW YEAR

For 2018, Roche's partnering head has two key goals. One is to significantly impact the Roche pipeline. "This can be through deal-making or through rejecting deals," Kornowski-Bonnet said. "You explore the options and can find that there is nothing better than what you have in-house, and that brings in learnings too."

Kornowski-Bonnet's second goal is for the partnering team "to have fun and do good work." Unlike leaders in R&D or commercial divisions, she noted that she didn't have a pipeline to work with, instead she had a team. "I want my team to have a great year. A good team has energy – they find things, they go for it, they try and fail sometimes, but they pick up, go back and find something else."

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APPOINTMENTS

Big changes were announced at **Oculis**: the Icelandic clinical-stage biotech named ***Riad Sherif*** chief executive officer, succeeding ***Páll Ragnar Jóhannesson*** who becomes chief financial officer and managing director in Iceland. Sherif had been area president of Europe, Middle East and Africa at Novartis AG's Alcon Inc. Meanwhile, ***Sabri Markabi***, formerly Alcon's SVP, chief medical officer and head of R&D, will become Oculis' chief scientific officer. Oculis' co-founders ***Einar Stefánsson*** and ***Thorsteinn Loftsson*** have become chief innovation officer and chief research and technology officer, respectively while ***Florent Gros***, a managing director at Novartis Venture Fund, joined Oculis' board as chairman. Oculis is also moving its corporate headquarters to Lausanne, Switzerland from Reykjavik while its R&D operations will remain in Iceland.

Clinical-stage biotech **PellePharm Inc.** has appointed ***Sanuj K. Ravindran*** president and chief executive officer. In parallel, Ravindran has joined BridgeBio Pharma, PellePharm's lead investor, as CEO-in-Residence, to advance its broader orphan dermatology portfolio. Previously a practicing physician, Ravindran's most recently was chief business officer at aTyr Pharma Inc., a clinical-stage rare disease-focused biotech where he led corporate and financial strategy, business development. Before that Ravindran was senior vice president of corporate development for The Medicines Company. He began his industry career as a venture capitalist for 10 years with Burrill & Company, Radius Ventures and Asian Healthcare Fund.

Syntimmune Inc., which is developing immune disease therapies targeting the neonatal Fc receptor (FcRn), appointed ***Jean-Paul Kress*** as its president and CEO, replacing ***David de Graaf***. Prior to joining Syntimmune, Kress headed global therapeutic operations at Biogen Inc., overseeing its rare and specialty disease teams. Before that Kress was North America head at Sanofi Genzyme where he helped launch several therapeutic products, including dupilumab.

Privately held **Sterna Biologicals GmbH & Co. KG** has appointed ***Christian Pangratz*** CEO, bringing to it his 25 years of life sciences experience, notably in the areas of strategic planning, corporate and business development, alliance and project management, new product planning, marketing and sales. A spin-off from Germany's Marburg University.

Paris-quoted **Nicox SA** appointed ***Tomas Navratil*** vice president and head of development, a newly created position at the group where he will be responsible for leading non-clinical and clinical development activities while reporting to Nicox CSO ***Michael Bergamini***.

Cambridge, Mass.-based **Proclara Biosciences** appointed ***David Michelson*** chief medical officer. He will be joining the biotech, which develops novel therapies for diseases caused by protein misfolding, from Merck Research Laboratories where he served for over a decade as vice president and therapeutic area head with responsibility for clinical research in neuroscience, pain, anesthesiology and ophthalmology.

California-based **Denovo Biopharma LLC** appointed ***Ronald Shazer*** as chief medical officer. He most recently served as chief medical officer for Inspyr Therapeutics Inc. and previously as Chief Medical Officer at Tracon Pharmaceuticals Inc. Shazer has held increasingly significant roles leading clinical research teams at Pfizer Inc., Bristol-Myers Squibb Co., Arena Pharmaceuticals Inc. and Exelixis Inc..

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