Is Neuroscience Back In Vogue?

Sanofi is building up a neuroscience portfolio from its legacy MS and rare disease foundations **(p4)**

Stockwatch

A lackluster fourth-quarter earnings season at least didn't get any worse **(p18)**

Unsustainable Cancer Drug Prices

Researchers suggest using academic centers to derisk cancer drug discovery could tackle the problem **(p20)**

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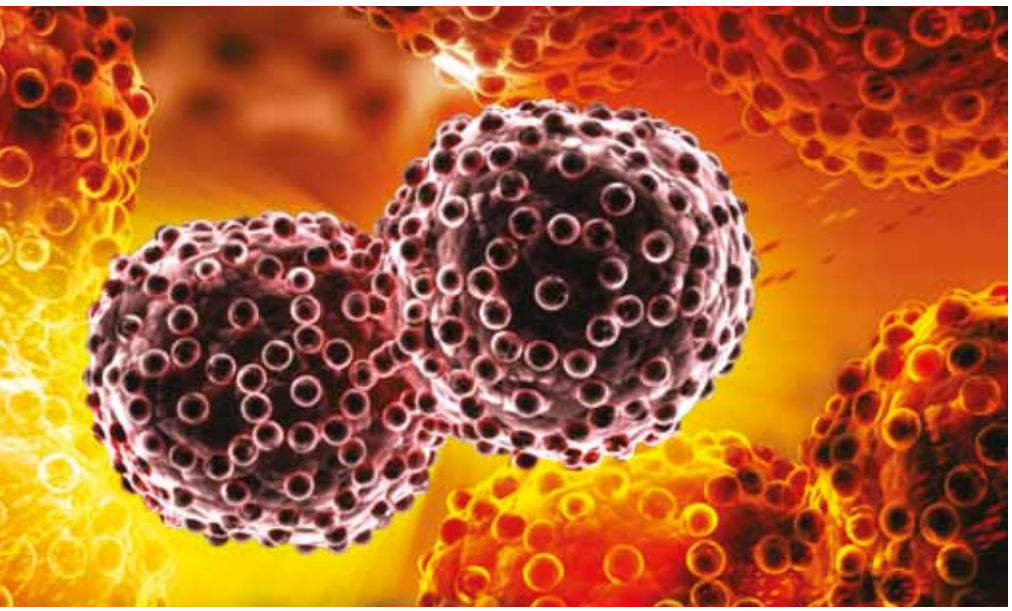

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NSCLC Momentum Goes To Merck And Roche

New cancer immunotherapies are doing well in lung cancer, with Merck's Keytruda picking up share in the first-line setting and Roche's Tecentriq in second-line. Bristol-Myers Squibb is banking on combo therapy to restore its momentum.

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It's been a turbulent few months for immuno-oncology and there's been a lot of speculation about what that will mean in terms of sales and market share. Coming out of the fourth quarter earnings calls, there have been early signs of change and a lot of posturing about the impact of combination approvals expected later this year.

Taking stock, Bristol-Myers Squibb Co.'s *Opdivo* (nivolumab) is holding on, but Merck & Co. Inc.'s monotherapy approval for its PD-1 inhibitor *Keytruda* (pembrolizumab) in first-line non-small cell lung cancer last October and Roche's approval for its PD-L1 inhibitor *Tecentriq* (atezolizumab) in the second-line setting have eaten into the momentum once enjoyed by Opdivo, the first PD-1 inhibitor to reach market in the US (see table on p7).

Bristol has lost some of its momentum in cancer immunotherapy, between Opdivo's failure in the CheckMate 026 study in first-line NSCLC and the company's recent decision not to seek accelerated approval in that setting for its proprietary combo regimen of Opdivo with its CTLA-4 inhibitor Yervoy (ipilimumab). Opdivo brought in $3.77bn for all of 2016 and $1.3bn in the fourth quarter, but US sales of $715m were flat from the third to the fourth quarters.

Keytruda earned $1.4bn in global sales in 2016, with fourth quarter sales of $483m, including $311m in the US. During Merck's Feb. 2 call, executive VP-Global human health Adam Schechter pointed out that of its US sales for the quarter, 40% occurred in the initial melanoma indication, 30% in lung, 15% in head-and-neck cancer and 15% in other cancers. Before the first-line monotherapy approval, Merck estimated that 25% of Keytruda's US sales derived from lung cancer.

Initial reports suggest adoption of immuno-oncology drugs in first- and second-line NSCLC is proceeding in line with FDA labeling, and that Merck is seeing strong uptake among first-line patients that meet the label: those with 50% or greater expression of PD-L1.

Looking at monthly sales trends from Symphony Health, Leerink analyst Seamus Fernandez noted that both Keytruda and Tecentriq saw good month-to-month growth in December (14% and 13%, respectively), whereas Opdivo fell 2% from November to December 2016. "Despite what might be overly optimistic estimates of Keytruda's early uptake in [first-line NSCLC], the acceleration into December bodes well for Merck's Keytruda and our expectation is that [it] will dominate this setting at least during the next two to three years," he concluded.

CONTINUED ON PAGE 7

IN THIS ISSUE

from the US editor

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Much like 2016 was labeled (perhaps unfairly) as a year with an unusual amount of celebrity deaths, it was a year marked by major leadership transitions across the biopharmaceutical industry. And, in the early weeks of 2017 we've already seen the surprise exit of Erez Vigodman as the CEO of Teva – leaving a leadership vacuum as the company adjusts to its expanded generics base and considers the future (see online for coverage of Teva's CEO search). Next month we'll see one of the most anticipated changes at the helm as Emma Walmsley takes over for Andrew Witty at GSK – the first female CEO of a big pharma. (If you haven't checked it out already, be sure to read our roundtable of all-women execs from the J.P. Morgan conference.)

With so much transition and upheaval, *Scrip* is launching a new "Focus On Leadership" series through which we'll explore the challenges and strategies for managing change. We've started off with "Five Golden Rules For Post-M&A Leadership Success." Keep your eyes open as we take on other leadership topics, and we'll see how 2017 starts to stack up.

exclusive online content

Prevention, Cure And Interception Vital For Janssen Cardiometabolic R&D

With readouts in trials of key drugs Invokana and Xarelto coming, Dr. James F. List of Janssen is also looking for assets designed to prevent, cure or even intercept the progression of key diseases such as obesity and NASH.

http://bit.ly/2l7fc0P

J&J Poised To Establish No-Strings Attached JLABS Outside America

As J&J announced the establishment of its eighth JLABS facility, Melinda Richter, head of J&J Innovation, JLABS, says that the company is actively looking to establish JLABS in Europe and Asia.

http://bit.ly/2lGsyOq

Teva Undertaking Strategic Review As It Searches For New CEO

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Execs were pushed for details during earnings call but offer minimal clarity. Teva is sticking by the guidance issued before its loss in Copaxone patent case, and is upping investment in promoting the brand while the decision is appealed.

Just a week out from losing its CEO, Teva Pharmaceutical Industries Ltd. needed to report annual results from a tough year and face tough questions about the company's direction. And while management noted that a full review was taking place, most of those questions will remain unanswered until a new CEO is in place.

"I've been the CEO one week. I think it's not even seven days now, so I cannot get into specifics," interim president and CEO Yitzhak Peterburg told the Feb. 13 fourth quarter and full year 2016 earnings call. That disclaimer applied widely across the current and future business of the company.

"As you very well know, 2016 was an extremely challenging year for Teva," Peterburg said. It included the integration of the generics business acquired from Actavis (now Allergan PLC) for $40.5bn, making Teva the global leader in generics. But the business overall struggled, and combined with a major loss in patent litigation over Copaxone, led first to the December departure of Sigudur (Siggi) Olaffson as the head of the generics business and then the ouster of CEO Erez Vigodman.

The combined hit of the court ruling and leadership vacuum kept analysts focused on the firm's search for a new CEO. Sol Barer, who replaced Peterburg as board chair, confirmed that it will be a global search and that the incoming CEO would have a seat on the board. "The Board has already begun a comprehensive search to identify a permanent CEO with significant pharmaceutical experience. We will take the time we need, with the assistance of a leading search firm, to identify the best leader to take Teva into the future," he said.

Teva's priorities remain "extracting all synergies related to the Actavis generic acquisition, successfully launching the key generic and specialty products we have planned for 2017, and generating significant cash flow to rapidly pay down our existing debt to maintain a strong balance sheet." Peterburg stated. The company is standing by the guidance for 2017 released in January.

Aside from that, a "total review of the business" is already under way, Peterburg said. "We will be looking at every part of our business, including our current global manufacturing footprint, key therapeutic areas, pipeline assets in both specialty and generics, and existing business lines and markets."

IN SEARCH OF NEW CEO

Beyond that, there was not a lot of clarity provided by management, despite repeated questioning from analysts. Various tidbits did emerge, but by and large Barer and Peterburg indicated that answers will ultimately come from the strategic review and the new CEO.

"We just need to focus, get our strategy right, and move forward," Barer said.

"This is a critical time for Teva, and we are here to fix what is not working, and as I have said, we will leave no stone unturned," Peterburg added.

He declined to speculate on a potential split of the business, saying "I want to make sure that we are now focusing on execution, we are focusing on really doing the best we can now. And while doing the solo reviews that I promised we will make sure that we are going to fix what's needed, and I think by that, it's enough."

All possibilities are on the table, Peterburg said, but he acknowledged that Teva has considered and rejected a split in the past.

COMING OUT OF A 'CHALLENGING' YEAR

Teva recorded a loss of $973m in the fourth quarter on a GAAP basis, "due to a significant number of one-time charges," chief financial officer Eyal Desheh noted, chiefly the purchase of Mexican pharmaceutical manufacturer Rimsa Labatorios in 2015 for $2.3bn.

"Following the acquisition of Rimsa, we discovered a significant fraud related mostly to product registration, testing and manufacturing processes, and we are working diligently with the local health authorities to remediate it," Desheh said. He added that the firm recently received approval to activate the plant and will begin ramping up production soon. "We strongly believe in this opportunity in the Mexican market; however, the time to market we lost and the costs of remediation led us to impair the acquired goodwill by $900m," the exec said.

Teva brought in revenues of $6.5bn for the quarter, and on a non-GAAP basis profit was up about 30% over fourth-quarter 2015 – but Desheh noted that was "all driven by inorganic growth, related mostly to the Actavis acquisition, and also to the joint venture with Takeda Pharmaceutical Co. Ltd. in Japan."

The fourth quarter was the last time Teva will split out the performance of the former Actavis generics business – which for that quarter contributed $600m in the US, $360m in Europe and $150m in the rest of the world, after divestitures associated with the acquisition.

Going forward, Teva will report the Generics and OTC business and Specialty business separately.

Generics overall yielded $3.7bn for the fourth quarter, up 44% over last year (driven by the Actavis integration), which comprised 57% of the firm's total quarterly revenues of $6.5bn. Copaxone sales were $1.015bn for the fourth quarter, up $55m compared to Q4 2015 – a diminishing share of Teva's total sales at 16%, compared to 20% in 2015.

For the year, Teva's revenues were $21.9bn, up 11% over 2015 due to the addition of the Actavis generics. Generic sales accounted for 55% of total sales, specialty drugs accounted for 20%, and Copaxone made up 19% of sales.

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Is Neuroscience Back In Vogue? Sanofi Preps For R&D Dominance

Sanofi is building up a neuroscience portfolio from its legacy multiple sclerosis and rare disease foundations by pursuing early-stage research in neurodegeneration, neuro-inflammation and rare brain diseases. Neuroscience professor and former Pfizer drug development leader, Rita Balice-Gordon, will use her academic assessment lens to find the best science and utilize patient groups to bridge the gap between research and neuro disease therapeutics making it all the way to market.

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Advances in science are making neuroscience a more appealing research space, despite recent failures for highly anticipated neurology drugs, such as Eli Lilly & Co.'s solanezumab in Alzheimer's disease. Big biotechs like Biogen and Celgene Corp. are already investing in the area, but now French big pharma Sanofi is making its play and has grand plans to take the lead.

Rita Balice-Gordon, who joined Sanofi in 2016 to mastermind the company's neuroscience revival, spent more than 20 years in neuroscience academic research before making the move into industry. She joined Sanofi from Pfizer Inc., where she had previously led the US firm's psychiatry and pain drug development units. In her academic career, Balice-Gordon was focused on synaptic plasticity and synapse formation, both in normal development and what goes awry with those processes in the context of disease.

She told *Scrip* that it was Sanofi's desire to expand its neuroscience pipeline and its history with MS that drew her to the position of head of neuroscience at the business. While she highlighted Sanofi's profile in MS, with *Lemtrada* (alemtuzumab) and *Aubagio* (teriflunomide) as marketed products, Balice-Gordon also noted that the company was not currently known as a leader or investor in neuroscience as a therapeutic area. But advances in the field over the last decade are one of the reasons she believes Sanofi will have greater success in this space now.

Balice-Gordon highlighted better biomarkers for neurodegenerative and neuroinflammatory processes in the brain, as well as cutting edge imaging methods (which have been shown to be useful in early-stage clinical trials to demonstrate target engagement or the efficacy of compounds) as two developments that will speed up research in neuro.

Rita Balice-Gordon

"There has never been a shortage of really cool ideas in neuroscience research," she said, but it has taken time for some neuro-technologies to catch up. Historically high failure rates for transferring early research into the clinic has also held back pharma companies getting too deep into this field. "There is a lot that is understood about cells in the brain, how they interact with targets and pathways, and how they are related to disease. But this is a therapeutic area where successful translation to the clinic is about half of the rate of areas like diabetes, cardiovascular, metabolism or oncology," she said.

However, Balice-Gordon is convinced that if Sanofi uses its internal research and external expertise – from academics, biotechs, CROs and, importantly, patient advocacy organizations that are heavily invested in this translational stage – then the company will have a way to bridge this historic gap and bring the success of neuroscience therapeutics across Phase I studies and into later-stage trials. She noted that through its legacy expertise in rare disease, the company has a robust network with patient advocacy and research organizations in rare diseases. "The passion for neuro certainly exists at Sanofi, the foundations for a world-class translational neuroscience group are in place and there is a big willingness and interest to be strategic in building on that core further to have good mechanisms and potential therapeutics in the clinic," she said.

A CRITICAL EYE

Early-stage research in neuroscience is plentiful according to Balice-Gordon, but she is being highly selective for Sanofi's clinical portfolio. "I find myself using a particular academic skill set repeatedly in my pharma life… and that is the skill set that one develops sitting on a grant review or National Institutes of Health (NIH) study section panel. I would hear dozens and dozens of fabulous ideas, cutting edge research, compelling preliminary data, really good credentialing of targets and pathways, and then have to select among them, essentially, the most likely to succeed."

Balice-Gordon will use this same lens to view and prioritize projects at Sanofi. She also asks herself a set list of questions about early stage projects to help find the diamonds in the rough:

- What has the highest likelihood of being robustly tested in healthy volunteers and in patients?
- What are the tools that Sanofi currently has to translate those projects to the clinic and where are there gaps?
- What is the likelihood the team can fill those gaps before the compound gets to patients?

"I use those criteria to help me identify what is the best of what we've got, where we need to go and invest, and how we can have a better chance of getting transformational medicines to patients," she said.

Balice-Gordon noted though that one of the challenges for her taking on this role at Sanofi, was the competitive climate in the Boston/Cambridge/Framingham corridor

in the US for recruiting the best and the brightest. "There is a tremendous wealth of opportunity, from start-ups to small biotechs to small and large pharmas and being competitive in this arena is something I think we need to be very mindful of as a company," she said.

FOCUS AREAS

Sanofi's neuroscience portfolio currently consists of three areas. The first is its legacy MS portfolio and early-stage programs in remyelination, neuro-protection and neuro-inflammation. Under this umbrella the company wants to expand into other neurodegenerative diseases.

The second part is a focus on genetic disorders in which the brain is the primary organ affected. This covers diseases such as Huntingdon's, amyotrophic lateral sclerosis (ALS), neuro-developmental disorders like Angelman's and Rett's disease, and a handful of other neuro-rare diseases. Within this space, Balice-Gordon is keen to "reach into our bag of tricks with respect to modalities for therapeutics beyond small molecules which, I think, are the traditional play in neuroscience." Here Sanofi's neuroscience head will explore the use of antibodies, peptides, antisense and RNA interference (RNAi) therapies. She is also keen to advance in gene therapy, which she labeled as "particular interesting in the context of neuro-rare disease."

Thirdly, Sanofi has legacy expertise in neuro-generative disorders like Alzheimer's disease and Parkinson's disease. "I am working with my colleagues to refocus these efforts on populations that we can identify and homogenize by the mutations that patients carry that predispose them to develop these diseases," Balice-Gordon said.

Balice-Gordon highlighted that Sanofi's neuroscience R&D team is focused on finding patient populations to test concept studies across nearly all areas of neuroscience research. She said the company would be "anchoring our work on human genetics that point us to tractable mechanisms." The company will seek patient populations that it can address in early clinical development for early signs of efficacy, before expanding into broader group of patients that either carry mutations that have yet to be identified or for whom the knowledge of mutations doesn't currently exist.

"This is very different from what many other companies are doing in neuroscience because there are other players who have chosen to focus on the larger symptomatic populations, for example in Alzheimer's or Parkinson's, rather than focusing on the translational piece from the lab to the clinic," Balice-Gordon said. She noted that this strategy has been used successfully in oncology, where, for example, patients are routinely stratified by the genotype of the neoplasm that they have developed. "We are using this as a thread to run through neuroscience research at Sanofi, but it is not all of what we do," she highlighted.

The notable exception is MS where there aren't established genetic drivers of disease, even though that landscape is evolving rapidly. "We know enough instead about the immune system/nervous system interaction to make some very educated guesses about mechanisms that are likely to be impactful to patients."

She added that Sanofi already had a rich data source of the impact of current medicines on the MS market, as well as a good biomarker strategy. "So the genetics, while it would be very enabling, is not as high impact as it is in some other disorders, for example ALS or Huntingdon's disease."

Seeing through 2017, Balice-Gordon has three goals for her new unit:

- to work with clinical and commercial colleagues to ensure the success and progression of the neuroscience programs already in the clinic
- to advance as rapidly as possible the most promising of the portfolio she has inherited
- to identify several novel, cutting-edge ideas to bring into the portfolio

IN THE PIPELINE

Sanofi has a Lemtrada follow-on drug, which uses a similar mechanism to the originator product but a more streamlined mode of delivery, in Phase I development for MS. It plans to move into Phase II/III trials for this product shortly.

In the realm of Parkinson's disease, the company has a Phase IIa glucocerebrosidase inhibitor program that started enrolling patients at the end of 2016. This compound, GZ402671, works by blocking the formation of glucosylceramide (GL-1), a key intermediate in the synthesis of GL-3. The trial will be the largest attempt so far to target treatment to this genetically defined Parkinson's population. Sanofi is also testing the drug in Fabry's and Gaucher's disease.

The company also has a Parkinson's program in partnership with Voyager Therapeutics Inc. for a gene therapy treatment, targeting patients with late-stage disease. The lead compound is currently in Phase Ib trials and data is expected from this study by mid-2017.

Balice-Gordon also highlighted that the company has several early-stage programs ranging loosely from concept whiteboard all the way to leads that are poised to go into toxicology and safety studies – these are predominantly targeting MS, neuro-rare and neuro-degenerative disorders. However, Sanofi's neuroscience chief has already identified gaps in the company's early-stage R&D that she intends to fill through a two-pronged strategy. Firstly, she wants to build up the company's internal expertise in protein structure. "Many of the neurodegenerative disorders that we study are disorders of protein misfolding and we are building our expertise in protein structure, biophysics and the cellular machinery that deals with these misfolded proteins," she said.

The second prong of the strategy is to look at the external landscape. Balice-Gordon said she had an energizing week at the annual JP Morgan Healthcare conference in January this year, where she considered several early-stage partnership or acquisition opportunities. "We are planning to bring in external opportunities that fit with our strategy and that we think can help us accelerate what we're doing," she noted, adding that she is in discussions already regarding a couple of opportunities for Sanofi. "I hope these conversations continue at a regular pace so that each year we are using both these internal and external drivers to build our portfolio."

As Sanofi continues down this path, compiling a fresh neuroscience portfolio, Balice-Gordon said the challenge will be "to build not only a research engine but also an early development engine that is ready to receive the best projects that advance through the research portfolio. We have this in us – we are working to build it – and we have the willingness from our commercial colleagues to be very broad in their thinking about the landscape and positioning these opportunities for success."

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Acordia Prepares For An Inhaled Levodopa Filing

Acorda's $525m purchase of Civitas in 2014 is now set to bear fruit, with new Phase III data for an inhaled formulation of levodopa, the main attraction of the deal, looking strong enough both to warrant approval filings and please payers.

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Acorda Therapeutics Inc. is planning regulatory filings in the US by the end of the second quarter, and in the EU by the end of the year, for its inhaled levodopa product CVT-301 for use as a rescue therapy in Parkinson's disease. Shares in Acorda rose as much as 16% in trading on NASDAQ on Feb. 9.

New Phase III results from the 12-week SPAN-PD study show CVT-301 led to statistically significant improvements in Unified Parkinson's Disease Rating Scale-Part 3 score compared with placebo – the trial's primary endpoint. On the back of the data, experts say the product could become a new rescue therapy of choice to treat "off" periods in fluctuating Parkinson's patients.

If right, this would vindicate Acorda's $525m purchase of Civitas Therapeutics Inc. back in 2014, which brought the product into its portfolio. That deal was based on strong data from a Phase IIb study of CVT-301 earlier that year. Civitas was spun out of Alkermes' pulmonary delivery business back in 2011.

> 'CVT-301 has good chances of being well-received by payers, physicians, and patients'

Levodopa remains the gold standard across all stages of Parkinson's disease, but disease progression is associated with the onset of peaks and troughs in the drug's levels. These lead to "off" periods (where the drug has "worn off" before their next dose) during which there is inadequate motor control, as well as peak-dose dyskinesia, where patients display drug-induced involuntary movements.

CVT-301 is designed as an adjunct to oral versions of the product for patients experiencing these motor fluctuations. Patients take the product themselves to return to an "on" state but without inducing dyskinesia. By giving the drug via the lungs, the digestive system is bypassed allowing for fast onset of action in the brain.

"Acorda clearly understands the unmet needs in Parkinson's disease, and where some of its major commercial opportunities lie," commented Ines Guerra from Datamonitor Healthcare. Despite the longstanding role of levodopa in Parkinson's disease treatment, motor complications remain the most important limitation in its long-term use, she said, and it is estimated that 50–80% of patients develop response fluctuations after five to 10 years of levodopa treatment. "Off" periods can severely impact patients' quality of life, and few therapies have been shown to address them effectively, and quickly. "Acorda is therefore targeting an area of high unmet need with CVT-301, and could very well benefit from the sparse competition," she added.

Current strategies to circumvent the problem include an increase in dosing frequency of levodopa, or the use of AbbVie Inc.'s carbidopa/levodopa pump, Duopa, which allows for a continuous administration and stabilizes levodopa levels. But there are limitations to both: an increased pill burden with the first, whereas Duopa requires an initial surgical intervention and can be associated with infections. Another option involves the as-needed use of an injectable apomorphine formulation, such as the subcutaneous metered-dosed dopamine agonist product, Apokyn, which has a quick onset and short duration of action.

Indeed, this product could prove CVT-301's most direct competitor, at least in the short term, Guerra says. "But Acorda's drug should have the upper hand. CVT-301's fast onset of action is boosted by its inhalable route of administration, which is both less invasive and more convenient for patients."

But there is one other threat on the horizon. Sumitomo Dainippon Pharma Co. Ltd./Sunovion Pharmaceuticals Inc. expect to file for US approval of the sublingual apomorphine product, APL-130277, in the first half of this year. This product is also fast-acting, and its oral formulation should be patient-friendly. "Acorda will need to move fast, but overall CVT-301's expected earlier filing should enable the experienced Acorda to effectively position the drug as the rescue therapy of choice for fluctuating Parkinson's patients experiencing "off" episodes," said Guerra. "Assuming Acorda employs a competitive pricing strategy, CVT-301 has good chances of being well-received by payers, physicians, and patients."

Analysts at Leerink agree that CVT-301 is a compelling prospect for Acorda, probably more so than its other acquired Parkinson's asset tozadenant. This Phase III product was bought with Biotie Therapies of Finland for £363m last year and, as an oral adenosine A2a receptor antagonist, has a new ("and somewhat risky") mechanism of action; it is also aimed at the adjunctive market.

SPAN DATA

SPAN-PD – CVT-301's single Phase III pivotal trial – is a placebo-controlled study investigating the effect of two different doses of CVT-301 (84mg and 60 mg) in the motor function of fluctuating Parkinson's disease patients. All patients were receiving a stable oral regimen of carbidopa/levodopa, and CVT-301 was self-administered up to five times daily for 12 weeks, as a rescue treatment for patients experiencing "off" periods.

In SPAN-PD, CVT-301 84 mg led to a reduction of 9.83 points in UPDRS III score compared to a reduction of 5.91 points with placebo (p=0.009). No major safety concerns were identified during the study, and pulmonary tests revealed no notable safety signals. While cough was reported with both CVT-301 doses, it was usually mild. Only three out of 227 patients treated with CVT-301 discontinued the study due to this adverse event.

Acorda is currently conducting two studies to assess the long-term safety profile of CVT-301. Up to 12-month data from these studies are expected by the end of the first quarter of 2017 and the planned filings are contingent on these.

The full data will be presented at medical meetings in due course.

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CONTINUED FROM COVER

Roche Chief Operating Officer Daniel O'Day told its Feb. 1 earnings call Tecentriq is off to a good start in the second-line lung cancer indication launched in October. "It's too early yet to give you market shares in that area because the data is just too fresh," he added. "But we're definitely off to a good start with a comprehensive study program that's allowing us to be competitive in that second-line setting." According to the Swiss pharma, Tecentriq held a 60% market share and reported 2016 sales of CF157m (about $158m).

OPDIVO'S SLOWDOWN

During Bristol's Jan. 26 earnings call, Chief Commercial Officer Murdo Gordon maintained that Bristol had been able to defend its position in second-line NSCLC "as expected." "We are exiting 2016 at around a 40% share of overall second-line lung," he said. "And we are seeing the IO class in general increase in its penetration of second-line lung. Mainly, most of our erosion in second-line has been attributable to the launch of Tecentriq in the fourth quarter."

Bristol is bracing for further impact from the potential early entry of a Keytruda/chemo combo. "In the US, we expect Opdivo will be roughly flat with the potential to show growth, and we will focus on defending our second-line position and driving adoption in other indications." The company highlighted that it has regained share in renal cell carcinoma and recently launched in head-and-neck cancer; it will also focus on increasing use in melanoma and just cleared FDA for bladder cancer.

COMBOS COMING

There will be further impact on the second-line setting based on greater first-line use of immunotherapies – either patients receiving Keytruda monotherapy or one of many coming combinations.

All of the immuno-oncology contenders are rushing forward with comprehensive combination programs. Merck is out front with the chemo combo pending at FDA with a May 10 user fee deadline. And Bristol's announcement that it won't be pursuing accelerated approval for Opdivo plus its CTLA-4 inhibitor Yervoy has left a window for AstraZeneca PLC, which expects data for its anti-PD-L1 durvalumab plus its CTLA-4 inhibitor tremelimumab from the MYSTIC trial later this year.

> 'My expectation is that with time we will see that treatment regimens are more and more personalized'

Following in Merck's footsteps, Roche has prioritized chemo combinations. O'Day said his company has "a very comprehensive program across a very comprehensive set of chemotherapy backbones" for lung cancer combination therapy. But Bristol Chief Scientific Officer Francis Cuss maintained that it has "the broadest first-line lung program in the industry," with IO/IO and IO/chemo combinations. "So, while the competitive landscape continues to evolve, we believe our combinations will have a role to play in first-line lung."

Merck execs asserted during their call that the first-line market ultimately will be fragmented. "My expectation is that with time we will see that treatment regimens are more and more personalized," Roger Perlmutter, president of Merck Research Laboratories said. "I do not expect that one size will fit all here and that every cancer patient will receive the same combination, whether it's chemotherapy or immunologic manipulation. My feeling is, though, that Keytruda will prove to be foundational in these settings because of its very broad impact in a wide variety of different tumor types at different stages of disease, as we've shown."

INCREASING KEYTRUDA USAGE

Merck also expects to gain ground in the second-line NSCLC space, thanks to an October label update that expands its patient base from those with 50% expression of PD-L1 to those with as little as 1% expression. The firm has seen sequential increases in Keytruda sales each month since that approval and the approval in first-line NSCLC. According to Symphony Health data, US sales of Keytruda rose 14% from $78m in October to $89m in November and then another 14% to $101m in December.

BMO Capital Markets conducted a survey of 31 US oncologists who were early adopters of IO, released Jan. 25, showing that immuno-oncology drugs are penetrating the NSCLC space for eligible patients, about 85% of the market, with utilization consistent with FDA labeling. This includes rapid uptake of Keytruda in the first-line setting (with roughly 20% market share) and of Tecentriq in second-line (about 10%), BMO analyst Alex Arfaei said.

Arfaei noted that this showed rapid uptake of Keytruda in the first-line setting, and that Keytruda was achieving penetration in the first-line setting "at a much

CONTINUED ON PAGE 8

Quarter-over-quarter Growth, %			Year-over-year Growth, %	
	Keytruda	Opdivo	Keytruda	Opdivo
2014 Q4	1,150%	298%		
2015 Q1	66%	212%		
2015 Q2	33%	176%		
2015 Q3	45%	138%	3875%	8077%
2015 Q4	35%	56%	328%	3108%
2016 Q1	16%	69%	200%	1633%
2016 Q2	26%	28%	185%	704%
2016 Q3	13%	11%	124%	276%

View graph showing sales comparison for Opdivo and Keytruda here: **http://bit.ly/2l3pvAs**

CONTINUED FROM PAGE 7

faster rate" than in the second-line market. "Keytruda's average reported market share in 1L NSCLC is about 20%, consistent with the size of the 50%+ PD-L1 segment," just three months after approval, indicating rapid uptake among lung cancer specialists.

Shutterstock: Sergey Nivens

Expect initial Keytruda/chemo combo use to be in relatively healthy patients, before expanding

That trend "bodes well for broader adoption of Merck's Keytruda in first-line following its probable label expansion [for combination use] in May 2017," he said. Lung cancer is the dominant contributor in BMO's forecast for Keytruda out through 2026 (roughly 60%-70%); Arfaei projects sales totaling $3.9bn for Keytruda in 2017, about 2% below consensus estimates.

The physician survey also indicated strong immuno-oncology adoption (75%-80%) in second-line NSCLC, driven by both Keytruda and Tecentriq, the analyst noted, and physicians are reporting increased PD-L1 screening, in line with what Merck reported on its Feb. 2 earnings call.

During that call, Merck said it expects relatively quick uptake for Keytruda/chemo in the first-line setting following FDA approval. Initial adoption will likely occur in healthier patients, Schechter predicted. Right now, first-line usage is limited to patients with at least 50% expression of PD-L1, but adding the combination regimen should broaden usage to non-squamous patients, including those negative for PD-L1 expression, he said.

"From what we can tell, physicians will be much more apt to use the combination in patients that they deem to be relatively healthy," Schechter said. "They are going to evaluate it patient-by-patient and see where they believe that the combination of the two would outweigh potential side effects and so forth. So, I think, initially, it will be used in patients that are relatively healthy and those where they would be thinking about using Alimta anyway."

"After that, we believe that it will go into patients that are relatively healthy where they are not necessarily thinking about Alimta, but they might start to use Alimta in combination for Keytruda to treat those patients and get better results," he added. "And then, lastly, over time we think that even in patients that are less healthy, [oncologists] will probably, after having a lot of exposure to the combination, begin to use it in those patients as well."

Merck is also continuing with the confirmatory trial for first-line monotherapy use, KEYNOTE-042, testing Keytruda in patients with PD-L1 levels as low as 1% – despite Opdivo's failure in CheckMate 026 at a 5% threshold. In response to questioning, the company noted it was keen to see if Keytruda's benefit applied beyond patients with 50% or higher PD-L1 expression.

BEYOND LUNG

Beyond lung cancer, Merck is seeking to move Keytruda into a number of additional cancer settings, with Perlmutter noting the company is supporting more than 430 studies investigating the drug. Upcoming data highlights for Keytruda include second-line MSI-high colorectal cancer, expected in May; melanoma adjuvant use, expected in August; and a second study of Keytruda plus chemo in first-line NSCLC, expected in September.

[Editor's note: For more analysis of the evolving PD-1/L1 inhibitor market, see Biomedtracker's report on "The Emergence of PD-1 Immunotherapies: An Analysis Between Keytruda and Opdivo in NSCLC."]

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Akari Tick-Based Drug Better Than Alexion's Soliris?

Akari Therapeutics is looking to ticks to provide a new therapy that it hopes will offer a safer and cheaper alternative to Alexion Pharmaceuticals' Soliris for some rare orphan diseases.

Akari Therapeutics PLC – which has a pipeline of tick-derived molecules selected to suppress mediators of chronic inflammation in wide range of orphan disorders – expects a Phase II topline data readout soon for its lead candidate that it hopes will open the way for Phase III trials later this year in the rare blood disease paroxysmal nocturnal hemoglobinuria (PNH).

Akari's lead molecule is Coversin, a recombinant small protein derived from a native protein discovered in the saliva of the Ornithodoros moubata tick. The protein modulates the host immune system to allow the parasite to feed without alerting the host to its presence or triggering an immune response.

If successful, the second-generation complement inhibitor will compete with Alexion Pharmaceuticals Inc.'s extremely expensive *Soliris* (eculizumab), currently the only approved complement C5 inhibitor. But Soliris – which is not a cure and must be taken on an ongoing basis – can cost more than $550,000 per year, adding up to enormous costs over a patient's lifetime. The average wholesale price for Soliris is $542,640 per year, according to the health insurance trade group America's Health Insurance Plans. It is infused by a healthcare professional once a week for the first month and then every two weeks for up to 26 weeks.

As it is not an antibody, Coversin can be given by small volume subcutaneous injection, making patient self-administration possible and avoiding the necessity for regular, time-consuming and costly intravenous infusions, Akari's CEO Gur Roshwalb told *Scrip*.

sten.stovall@informa.com, 10 Feb 2017

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Intercept Increases Chance Of NASH Success

Intercept Pharmaceuticals Inc. is making a pair of protocol changes to the pivotal trial of its *Ocaliva* (obeticholic acid or OCA) in non-alcoholic steatohepatitis (NASH), but it maintains those will increase the odds of producing successful data, without pushing back the timelines in any material way. Despite the protocol changes announced Feb. 10, Intercept said it should complete enrolling sufficient patients (about 750) by mid-2017 for an interim efficacy evaluation, likely in 2019, that could lead to accelerated approval in NASH. The estimate for the interim analysis in 2019 remains unchanged, while enrollment is now projected to conclude sometime mid-year rather than during the first half of the year. The New York-based biotech designed the PHASE III REGENERATE trial in 2015 to replicate OCA's success in the Phase II FLINT study, in which it showed statistical significance on two measures: improvement in fibrosis score and resolution of NASH. REGENERATE initially was set with co-primary endpoints of fibrosis improvement and no worsening of NASH and resolution of NASH without worsening of fibrosis. Now, based on discussions with FDA, Intercept is revising the protocol so that the trial can succeed if either of those endpoints is met.

joseph.haas@informa.com, 10 Feb 2017

COMPASS Success For J&J/Bayer's Xarelto

The early termination of the Phase III COMPASS outcomes study of Johnson & Johnson/Bayer AG's Factor Xa inhibitor Xarelto opens the door for a new arterial disease indication that could mean a new chronic use and a competitive advantage over other novel anticoagulants, if the company succeeds in getting a label change. Janssen Pharmaceuticals Inc. and partner Bayer, which markets the drug outside the US, announced Feb. 8 that *Xarelto* (rivaroxaban) met the study's primary endpoint for preventing major cardiovascular events in this patient population and that the trial was stopping early on the recommendation of the independent data monitoring committee, instead of continuing to its March 2018 end date. Participants will shift to receiving Xarelto via an open-label extension study. The global study of more than 27,000 patients, which was run in conjunction with the Population Health Research Institute, tested the drug at doses of 2.5 mg twice daily or 5 mg once daily, both on top of 100 mg aspirin once-daily, compared to aspirin alone.

emily.hayes@informa.com, 10 Feb 2017

Bristol Shrugs Off Lirilumab Failure

Innate Pharma SA and partner Bristol-Myers Squibb Co. moved quickly to reassure investors that their cancer drug lirilumab remains on track for combo trials in both solid and liquid tumors despite the drug's failure in the Phase II EffiKIR trial to hit its main endpoint of leukemia-free survival (LFS). EffiKIR, sponsored by Innate to assess the efficacy of lirilumab as a single-agent maintenance therapy for senior patients with AML in first complete remission, found no statistically significant difference in LFS or other efficacy endpoints between the trial's placebo arm and its two treatment arms. One treatment arm, 1 mg/kg once per month, was discontinued in March 2015 based on the recommendation from the Data Safety Monitoring Board. Lirilumab is a human monoclonal antibody that blocks the interaction between Killer-cell immunoglobulin-like receptors (KIR) on Natural Killer (NK) cells and their ligands. By blocking these receptors, it allows activation of NK cells, and, potentially, destruction of tumor cells, the two companies say. Bristol has a "robust development plan" for lirilumab that includes multiple combination therapy trials across a number of tumor types. "These studies are ongoing and as always our plans will continue to be informed by evolving data," the spokesperson added. Bristol itself is investigating lirilumab in six studies in a range of solid tumors and blood cancers. Lirilumab, Innate's most advanced clinical asset, was out-licensemd to BMS in 2011. That agreement included $35m up front and $430m in milestones, for a total value of $465m.

sten.stovall@informa.com, 6 Feb 2017

Axovant's RVT-1 To Redeem 5HT6 Class?

The failure of Lundbeck Inc./Otsuka Pharmaceutical Co. Ltd.'s idalopirdine in two more Phase III trials is yet another blow for Alzheimer's disease research and for serotonin 5-HT6 antagonists, though there is still some reason to hold off on death rites for the drug class until Axovant Sciences Ltd.'s intepirdine (RVT-101) Phase III readout later this year. Lundbeck/Otsuka announced the failure of the Phase III STARBEAM and STARBRIGHT studies of idalopirdine in moderate to severe Alzheimer's disease on Feb. 8 and said the data do not support a regulatory approval. Idalopirdine had already failed in the Phase III STARSHINE study in September 2016. Development has been suspended. All three studies measured efficacy of the drug on top of anticholinesterase treatment, using the Alzheimer's Disease Assessment-cognitive subscale (ADAS-cog) as the primary efficacy measure. The drug was safe and well-tolerated in the studies, but failed on the primary efficacy endpoint, Lundbeck and Otsuka reported. Detailed results will be presented at scientific meetings and published in peer-reviewed journals this year.

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Takeda's Planned Emerging Markets Deal: India Yay Or Nay?

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Takeda tantalizingly disclosed during its third quarter results that it has set aside funds for an acquisition worth around $450m in an undisclosed emerging market. What are the likely targets?

Takeda Pharmaceutical Co. Ltd. already appears to have a firm candidate in mind for a planned acquisition in an undisclosed emerging market, given remarks made by chief financial officer James Kehoe during the Japanese company's fiscal third quarter conference call.

The executive disclosed that a JPY40.8bn (roughly $362m) sum had already been put into escrow "for a potential future acquisition in emerging markets," a transaction he indicated would be worth around $450m in total.

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However, he stressed, the consummation of the deal would be dependent on "a series of conditions that need to occur to make us comfortable with completing the acquisition," declining to elaborate any further.

The revelation is predictably generating speculation on which market and specific company Takeda may be targeting, but the vague statements create more questions than answers. Does the "series of conditions" refer to quality or compliance problems, or other issues relating to governance or management at the target firm that require resolving? Or is there simply a disagreement over price?

With deal valuation a complex calculation taking into account multiple factors, including the future value of any pipeline assets, it is also difficult to accurately infer a likely company size from the expected $450m price tag.

But a quick look at Takeda's current emerging markets performance and past words and actions might at least provide some clues as to the likely focus.

EM PERFORMANCE

Takeda's latest results already show strength across several key emerging markets, where total underlying revenue in the sector in the nine months to Dec. 31 was up 5% to JPY204bn, accounting for around 16% of the group total. On an underlying basis, the company's prescription drug sales grew 8% in China, 6% in Russia, and 10% in Brazil, to JPY42.8bn, JPY30.0bn and JPY28.0bn respectively, in the same period.

While these figures are still modest, they do indicate a well-established presence in these three core emerging markets, reflecting Takeda's strategic focus on the oncology, CNS, and gastrointestinal therapy areas. The 2011 acquisition of Nycomed SPA and its emerging markets business for pantoprazole added particular strength in the GI field.

However, one major emerging market does not figure in the highlighted performance - India, which remains such a small part of Takeda's business that it is not usually broken out.

FOR INDIA

This market has long been viewed as an area where the company's direct presence has been limited, despite the interest expressed in the past few years by CEO Christophe Weber and other executives and Takeda's stated intention of developing a "balanced footprint" across Asia. The rising incidence of diseases including cancer would also seem to fit well with the company's therapeutic focus.

Back in (pre-Nycomed) 2010, Takeda outlined a basic strategy for its expansion in India, which included commercial alliances and feasibility studies to look at future expansion.

The alliances component has already borne some fruit. For example, there was a 2012 collaborative deal with Advinus Therapeutics Pvt. Ltd. for inflammation and metabolic diseases, and Takeda is working with gvk bioSciences Private Ltd. to repurpose drugs. It also has more recent agreement with Zydus to co-develop a chikungunya vaccine.

Nevertheless, Takeda still has only a small local sales subsidiary set up in 2011 and a Nycomed legacy API production joint venture, Zydus Takeda Healthcare Pvt. Ltd., with Zydus Cadila, both based in Mumbai. Given the size and growth of the Indian pharma market, there would seem to be plenty of potential for a targeted M&A deal to boost this modest presence.

POSSIBLE TARGETS?

One industry veteran in India told *Scrip* that a $450m price tag suggests that the target company could have a current turnover of around INR10-15bn ($148-223m), going by general valuation expectations for such transactions.

"Clearly India can and should rank high on Takeda's priority," the veteran told *Scrip*.

It would seem that the most likely target would be a company that can provide

the local infrastructure for the development, commercialization and marketing of Takeda's newer key branded global growth products such as *Entyvio* (vedolizumab) for ulcerative colitis and Crohn's disease and *Ninlaro* (ixazomib) for multiple myeloma, or a pipeline and/or marketed portfolio aligned with the company's core therapeutic areas.

Takeda is also developing a suite of initiatives to improve access to its medicines in emerging markets, which it could potentially apply in India, mirroring patient assistance moves taken by another Japanese firm, Eisai Co. Ltd.

One indicator of potential change was the realignment of Takeda's India leadership last year, with its former country general manager stepping down and a commercial executive, Ashok Bhattacharya, moving into the top country slot. Might this signal a more aggressive commercial approach?

AGAINST INDIA

While seven years should have been sufficient to develop a business expansion blueprint under the 2010 India plan, the apparent lack of progress might indicate a fundamental change in business priorities under the new senior management, previous statements notwithstanding.

A lot has happened since then. There was a period of what were seen as overvaluations of Indian firms, and there was the Nycomed deal. In the past, Takeda has been said to have been in talks with a number of Indian firms, but nothing has come to fruition.

Executives at the Japanese firm have hinted at concerns over India's intellectual property policies and the threat of compulsory licenses, and may also be cautious over the disastrous experience of Japanese pharma peer Daiichi Sankyo Co. Ltd. with Ranbaxy Laboratories Ltd. (now part of Sun Pharmaceutical Industries Ltd.).

Other observers like Viren Mehta, managing member of Mehta Partners LLC, a strategic business advisory firm, note how Takeda is actively globalizing while at the same time streamlining its model centered around collaborations.

However, Mehta doesn't expect Daiichi Sankyo's unfavorable experience with Ranbaxy to weigh down Takeda's growth initiatives in markets like India. "Experiences of other companies in India do not color this strategic thinking as these are mostly company-specific," he told *Scrip*.

"India continues to grow in importance globally, just as Indian companies seek resources, both financial and skillsets, to advance their globalization, while the Japanese market remains challenging. Takeda will continue to expand beyond Japan, and especially in the emerging markets," Mehta predicted.

> Given the size and growth of the Indian market, there is plenty of potential

Mehta Partners has been involved in Indo-Japan deals and claims to have conceptualized the purchase by Sun of a mature product portfolio from Novartis in Japan. Another India firm, Lupin Ltd., followed suit with the acquisition of a basket of long-listed products from Shionogi & Co. Ltd.

Another Indian expert echoed similar views, suggesting a potential uptick in momentum for Indo-Japan pharma alliances despite the previous "grim" experiences and against the backdrop of the evolving geopolitical scene and other global pressures.

Even so, possible targets that have cropped up in the Indian rumor mill appear to offer little more than manufacturing, APIs and formulations expertise (an area where Takeda has already been rationalizing), or large portfolio of generics and little real innovation.

Given its multiple partnerships with Takeda, Zydus might be one obvious candidate, but would seem to be too big for a deal in the $450m range.

In addition, Zydus itself has been an active dealmaker, most recently acquiring the small US firm Sentynl Therapeutics and several pain assets, and also a portfolio of diverse products from Merck & Co. Inc., which really fall outside Takeda's core interests.

There has been some speculation in the past that India's Micro Labs may be on Takeda's radar, though this could not immediately be verified whether the firm might still be in play. In a recent interview with *Scrip*, Weber stated that "we are not in a geographical expansion mode," and that any emerging markets M&As would be targeted to build up an already strong presence.

Targeted deals to help develop local portfolios through diverse products were also on the table, he added, as long as these are margin-accretive. (In 2015, for example, Takeda acquired Toplam Kalite, a subsidiary of Turkey's Neutec Ilac Sanayi Ve Ticaret AS, and its portfolio of 13 branded generics in the gastroenterology, respiratory, metabolic and musculoskeletal areas.)

CHINA, OTHERS?

While any deal in India would fill an obvious gap, what else might be in the mix? Takeda already has a well-developed set of operations in China, including for R&D, production and sales, along with a holding entity that could potentially smooth the process for any local acquisition, so could choose to add commercial capability there.

The company is already a controlling shareholder in biologics-focused Guangdong Techpool Bio-Pharma Co. Ltd. through a Nycomed legacy relationship, but the stated deal size of around $450m appears too large for any potential buyout.

Brazil and Russia remain the other candidates to build on an existing presence and we also shouldn't rule out activity in the vaccines sector, another key pillar of Takeda's broader global business.

One Indian expert suggested the Japanese giant may be interested in building on its past transaction with Neutec in Turkey, with an eye on Neutec's prowess in the respiratory space. Neither firm could immediately be reached for an official comment.

The guessing game can be a frustrating one and until any deal is done, there will be more food for thought than easy answers.

The only things we can say with some certainty are that any emerging markets M&A by Takeda will be carefully targeted, aligned with core therapeutic interests, and most probably providing development and commercial strength for its key branded global growth products.

From the editors of PharmAsia News, with contributions from Anju Ghangurde in Mumbai.

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Express Scripts Projects Higher Spending

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The three most expensive drug categories, on a per-member/per-year basis for the PBM's clients, increased by 19% or more in 2016, and similar growth is expected in the next three years. Per-patient spending on HCV drugs, however, declined by 34% last year.

The three most expensive drug therapy classes in the US market in 2016 – inflammatory conditions, diabetes and oncology – increased in expense for health plans on a per-member/per-year (PMPY) basis by at least 19%, a trend that is expected to continue during the next three years, Express Scripts Holding Co. noted in its 2016 Drug Trend Report, released Feb. 6.

The other therapeutic area in Express Scripts's top 15 with double-digit growth was HIV, the sixth-most expensive, up 21.7% compared with the previous year.

Of the classes with lower PMPY costs, the headliners were hepatitis C, down 34% due to declines in both utilization and unit cost (the cost of a one-day supply of medication), and heartburn/ulcer disease, down 24%, attributed almost entirely to reduced unit costs. The generic version of Nexium (esomeprazole), which reached the market in February 2015, fueled a 38.5% drop-off in unit costs for that drug. Utilization of this class also fell 1.3% in 2016, the report said.

Overall, Express Scripts reported that the growth rate for prescription drug spending among health plans using its pharmacy benefit management services increased 3.8% during 2016, a 27% decrease from 2015, when Rx spending by payer clients rose 5.2%. The company also noted that one-third of employers using its formulary and/or other services experienced a decrease in pharmaceutical spending from 2015 to 2016.

The most expensive drug classes for 2016 largely were the same as in 2015, although contraceptives and depression medications moved into the top 15 and mental/neurological disorders and compounded drugs dropped out, which Express Scripts attributed to new strategies to reduce unnecessary use of compounded drugs. The first full year on the market for generics of *Abilify* (aripiprazole) contributed significantly to a 32% reduction in unit cost within the mental/neurological disorders category. While generic drugs continue to chip away at drug spending in major categories, Express Scripts is not projecting significant cost savings from biosimilars.

In the inflammatory drug class, Pfizer Inc./Celltrion Inc.'s biosimilar *Inflectra* (infliximab-dyyb) launched in November, but has not had much time to make an impact on spending in this class. Express Scripts also noted that with Johnson & Johnson's *Remicade* (infliximab) accounting for only 1.7% market share in the class last year, "low market share results in smaller available savings margin."

Although there are 15 available therapies to treat disorders like rheumatoid arthritis and psoriasis, AbbVie Inc.'s *Humira* (adalimumab) and Amgen Inc.'s Enbrel (etanercept) accounted for a combined 70% market share in this space. Both saw double-digit unit-cost increases during 2016. In fact, Humira Pen was the most utilized drug in terms of market share in the class, while the original formulation finished third, behind Enbrel. Celgene Corp.'s *Otezla* (apremilast) and J&J's *Stelara* (ustekinumab) rounded out the top five.

Biosimilars of Humira and Enbrel have been approved by FDA, but patent disputes have delayed their launches. Express Scripts projects that per-patient spending in the inflammatory class will continue increasing by about 30% each year from 2017-2019, reflecting expansion of both unit cost and utilization. It expects the increase to be 29.7% this year, rising to 32.1% in 2018 and then falling slightly to 31.7% in 2019.

DIABETES SPEND INCREASE

Despite intense competition in diabetes, Express Scripts reported a 19.4% drug spend increase, comprising a 5.3% uptick in utilization and 14.1% higher unit cost. This trend is anticipated to remain static over the next three years, with a 20.5% increase this year, 19.3% in 2018 and 18.2% in 2019. The increases will be driven by "steady inflation for branded drugs, especially insulins," as well as rising use of the DPP4 and SGLT2 inhibitor classes as additive therapies.

Generic metformin was the most widely used diabetes drug in 2016, taking a 35.7% market share. The combined insulin class accounted for 40.2% market share, led by Sanofi's Lantus (insulin glargine) and Eli Lilly & Co.'s HumaLog KwikPen (insulin lispro). Insulins led to a 9.9% increase in PMPY spend on the year, more than half the increase recorded for the diabetes category.

MAINTENANCE THERAPY

Oncology drug spending rose 21.5% on a PMPY basis in 2016, with utilization increasing 11.9% and unit cost up 9.6%. Like diabetes, Express Scripts projects a steady rate of increase in the near term: 22.1% this year, 22.0% in 2018 and 20.5% in 2019. Driving these continued increases will be use of oncology drugs as maintenance therapy, the report said.

The generic chemotherapy drug capecitabine finished second in market share among cancer drugs in 2016, while branded and generic *Gleevec* (imatinib), the Novartis AG leukemia drug, was third. Celgene's multiple myeloma therapy *Revlimid* (lenalidomide) posted the highest market share and the three drugs combined took nearly one-third of oncology market share. Express Scripts noted that generics yielded some savings in 2016, but not enough to offset the increase in spending due both to utilization and unit-cost inclines.

"The increasing prevalence of self-administered medications will result in higher utilization and cost through the pharmacy benefit," the report states. "The first generic to Gleevec launched in February 2016 and resulted in limited savings; however, the availability of generics will not offset the high prices of branded oncology drugs."

HCV DECLINE

By contrast, the dramatic decrease in spending to treat the hepatitis C virus (HCV) resulted from significant declines in both utilization and unit cost. Utilization careened sharply by 27.3%, while widespread discounting and increased competition sliced unit cost by 6.7% in a class that drew significant criticism for high prices in prior years. Express Scripts expects these trends to continue, with a 21.8% reduction in spending in 2017, then 30% in 2018 and 34.7% in 2019.

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Ionis Takes Another Shot

Ionis Pharmaceuticals Inc. has been in it for the long haul, developing antisense drugs for more than 25 years. But now partnered and independently-owned drugs are in late-stage development and the company appears poised to make the transition from platform technology provider and drug developer to commercial biotech. First, the company's partner Biogen Inc. is launching the Ionis-developed drug *Spinraza* (nusinersen) for the rare genetic disease spinal muscular atrophy (SMA), and secondly, Ionis is ramping up its own commercial organization – as the subsidiary Akcea – for the launch of volanesorsen in patients with severe hypertriglyceridemia. "It's a big transition for us because it is a final step for us toward becoming sustainably profitable," founder and CEO Stanley Crooke said of the Spinraza launch during an interview in January. While Spinraza is not the first drug developed by Ionis to reach the market, the company hopes it will be a lot more successful than the last foray. *Kynamro* (mipomersen) was approved by FDA for a rare familial hypercholesterolemia in 2013. Partner Genzyme Corp. launched the drug but it was a big disappointment commercially, and Genzyme ended up returning rights to the drug to Ionis, which it sold to Kastle Therapeutics LLC last year for $95m. Spinraza, approved by FDA in December, is an important achievement because it represents further validation of the ability of RNA-targeted antisense drugs to change the course of debilitating neurodegenerative diseases. While analysts expect the drug will become a blockbuster eventually, the launch appears to be off to a slow start because of pushback from payers, who are concerned about the exceptionally high price of the product even though it targets an ultra-rare population: $750,000 for the first year of treatment and $375,000 a year after that.

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Sandoz Eyes Doubling Of Japan Business

Japan is a priority market for Sandoz Inc. and the generics and biosimilars division of Novartis AG says it is aiming to roughly double its existing business in the country - currently worth "hundreds of millions of dollars" – by 2022, logging a compound annual growth rate of at least 11% over the period in the process. "New launches will be the key driver for our growth in Japan," country head Jason Hoffe told a media briefing in Tokyo. Sandoz KK is planning to roll out 70 generic molecules over the period and these new product introductions are expected to account for around 40% of sales by 2022, with oncology and CNS the main therapeutic areas, he said. "Cardiovascular is also a huge opportunity in Japan for us and we will be participating in all the major LOEs [losses of exclusivity] over the next few years," Hoffe declared. The expected launches include oncology injectables, biosimilars, and authorized generics, the latter being sees as attractive to both physicians and patients given their links to the original trusted brand, a factor than can carry particular weight in Japan. Biosimilars are seen becoming an increasingly important growth driver in Japan for the company, which just over a year ago entered into an alliance with Kyowa Hakko Kirin Co. Ltd. for the sale, distribution and promotion in the country of a biosimilar version of cancer drug rituximab. Sandoz has submitted an approval filing and will manufacture the product. Sanofi already has some presence in the sector, where it launched Japan's first biosimilar, somatropin, back in 2009 and also markets in Japan a biosimilar version of filgrastim.

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Gilead Needs M&A To Grow

Even though Gilead Sciences Inc. CEO John Milligan conceded during the firm's fourth quarter and full-year 2016 earnings call Feb. 7 that the company probably can't return to growth in the near term without significant business development activity, management kept quiet about M&A prospects and strategy. Gilead's presentations have featured the same underlying story for roughly the past two years. Analysts have been waiting for business development news as they watch the hepatitis C business mature and wonder how Gilead will manage to fill that void (or use its massive cash reserves, a reported $32.4bn at the end of 2016). Still, the virology titan surprised Wall Street with the extent of its lowered guidance for hepatitis C product sales. The day following the call, analysts reiterated, with mounting frustration, that Gilead unquestionably needs to rely on business development, possibly even a big-ticket acquisition, to return to growth. It's a dizzying turn in prospects for Gilead, which until last year seemed to be riding an HCV-fueled money train that might never slow down. But declining patient starts in the US, Europe and Japan, along with competition from rivals AbbVie Inc. and Merck & Co. Inc., have placed downward pressure on pricing and reduced duration of treatment; Gilead's HCV sales fell 35% globally during the fourth quarter and 22% for the full year in 2016. The Foster City, CA, firm acknowledged its new reality with its new 2017 sales guidance, which divides out HCV from the rest of the portfolio and notes that conditions around the HCV franchise are more variable than for the rest of its business. Gilead projected worldwide HCV sales of $7.5bn-$9bn for 2017, down substantially from the roughly $15bn realized in 2016.

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Pressed Sanofi CEO Hopes For Positive Dupixent Launch

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Sanofi's CEO Olivier Brandicourt's reassuring 2017 guidance relies on continued cost savings, a successful launch of its Dupixent biologic, and winning a US legal case that threatens its PCSK9 inhibitor Praluent.

Sanofi reported slightly better than expected fourth-quarter results and reassuring guidance for 2017 on Feb. 8 - but analysts said real growth remains elusive for the French drugmaker and that its immediate prospects largely hinge on launching its *Dupixent* (duplimumab) therapy for atopic dermatitis and also winning a pending patent infringement case that threatens sales of its PCSK9 inhibitor *Praluent* (alirocumab).

The Paris-based group – which Olivier Brandicourt has revamped since taking over as CEO in April 2015 – also faces pressure from investors and analysts to buy growth through M&A. But the French CEO played down that prospect when presenting the group's fourth-quarter update to analysts, stressing that any eventual acquisition needs to complement the group's core global business units.

Brandicourt, who lost out on two big biotech acquisitions last year, wouldn't be drawn on why, or how, he was rebuffed by Actelion Pharmaceuticals Ltd. late last year, a rejection that must have compounded the disappointment of losing the takeover fight for Medivation Inc. to Pfizer Inc. earlier.

DISCIPLINE M&A

Brandicourt insisted that any M&A deal would need to create shareholder value – and make sense for the company's overall strategy based five global business units, those being its Genzyme division, vaccines, diabetes and CV, general medicines and emerging markets, and consumer healthcare.

"We are centered around diabetes, cardiovascular, vaccines, rare diseases and emerging markets … I insist that all targets we look at have to make strategic sense and fall in these therapeutic areas … we solely look at deals where we strongly believe we tend to achieve a return on invested capital," he told analysts.

Olivier Brandicourt

The M&A caution went down well with observers. John Rountree of Novasecta, a pharma consultancy, applauded the fact Brandicourt doesn't seem to be in a hurry to make a big acquisition. "They should resist pressure to do M&A; I don't think that's what Sanofi need at the moment. M&A is very expensive, and Sanofi already have a lot of debt. It just increased by €3.7bn during the past year, bringing it now to just under €17bn." He doesn't think such a move would be consistent with investing for the future, which is what Sanofi needs. "They've really got to keep working on making their R&D engine deliver," Rountree told *Scrip*.

When presenting the full-year update, Olivier Brandicourt voiced optimism about the potential of Dupixent, its breakthrough-designated treatment for moderate-to-severe atopic dermatitis under FDA review with a March 29 user fee date, which could allow it to launch in mid-2017 to address an emerging therapy field that is attracting the attention of many pharma players.

Atopic dermatitis, a chronic lifelong condition that usually begins in childhood, is expected to become a blockbuster-sized drug market. Analysts at Datamonitor Healthcare expect the atopic dermatitis market to grow from around $579.2m in 2015 in the US, Japan and five European markets (France, Germany, Italy, Spain and the UK) to $2.1bn in 2024.

An interleukin-4/IL-13 inhibitor, Dupixent is the first biologic to treat the condition and has been granted a priority review by FDA. It is being co-developed by Sanofi and Regeneron Pharmaceuticals Inc. Sanofi is also developing Dupixent in multiple other inflammatory diseases, such as asthma and nasal polyposis. An ongoing Phase III study in adult asthma is due this year with a regulatory filing for that indication expected before year-end, Brandicourt said.

Another key topic of discussion at the results update was pending litigation over Praluent. Amgen Inc. last month won an injunction to halt Praluent sales based on the company's patent infringement claim, which Sanofi and Regeneron appealed.

Asked by analysts what the company's contingency plan was in the event that the US legal process goes against Sanofi and Regeneron – and they are forced to withdraw Praluent from the market – Brandicourt briskly replied: "We do not consider officially or detail any Plan B." Sanofi's global pharma head Elias Zerhouni added: "I'm very confident that in my view, the patent we're disputing is invalid, and we'll see that."

Later that day, the US Court of Appeals for the Federal Circuit ruled to stay the injunction pending the appeal, which allows Sanofi and Regeneron "to continue marketing, selling and manufacturing Praluent in the US during the appeals process," the companies said. The ongoing appeal challenges both the injunction and judgment on validity of Amgen's patent claims for antibodies targeting PCSK9.

SALES UP

In its fourth quarter update, Sanofi reported net sales of €8.87bn, up 3.3% on a reported basis and 3.4% higher measured at constant exchange rates from the same year-ago quarter. Sanofi's Genzyme Corp. specialty care unit grew sales by 12.6% from a year earlier, driven by multiple sclerosis products, while the Sanofi Pasteur vaccines operation grew 3.7% due to strong pediatric combination franchise sales. Diabetes and Cardiovascular sales were up 3.8% while the global diabetes franchise lifted sales 1.9%.

In terms of outlook for 2017, Sanofi said it expected its business EPS [earnings per share] to be stable to falling by as much as 3% at constant exchange rates. "This guidance is consistent with our previously announced expectation of no meaningful growth over the period of 2016 and 2017 and comes despite the challenging environment in which we operate," Brandicourt said.

ANALYSTS UNDERWHELMED

Analysts said the latest update from the company was underwhelming.

"We see the glass as half-full today with Sanofi. What is still missing is top-line momentum," analysts at Bryan Garnier said in a reaction note. Bernstein analyst Tim Anderson summarized: "Fundamentally, Sanofi's outlook remains mixed with little growth in 2016/2017, few positive catalysts, and a lead franchise in diabetes still in flux."

Analysts seemed in general to be relieved that there were no surprises in Sanofi's update.

Novasecta's Rountree said, "Looking at the positive side, they are stable, profitable, but that said, their overall performance is flat, posing the question: where's the growth going to come from?"

> Sanofi's outlook remains mixed with little growth in 2016/2017

He added, "There's a lot riding on Dupixent. And while Genzyme and vaccines are doing well, the bulk of the business, representing some 70% of it, aside from Genzyme and vaccines, is either flat or down from previous performances. That's a big chunk of their business. And it needs to be rejuvenated."

He said one priority should be increased spending in Sanofi's drug R&D, despite the group's need to contain costs.

"Sanofi's R&D as a percentage of sales in 2016 was 13.6%. That's pretty low compared with some of their peers. Compare it with AstraZeneca PLC, which okay it's a pure-play pharma but they're investing 26% of sales into R&D, while Celgene Corp. is investing 22% of sales into R&D, while GSK [GlaxoSmithKline PLC]'s proportion is 16.2%," Rountree said.

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GlaxoSmithKline Braces For Impact

Although it's not yet clear if an interchangeable version of the respiratory blockbuster will be approved by FDA, CEO Andrew Witty prepared investors to expect a hit, forecasting that a mid-year launch could significantly reduce revenues.

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GlaxoSmithKline PLC has enjoyed an extended life for its blockbuster respiratory brand *Advair Diskus* (fluticasone/salmeterol) beyond its patent expiry and transitioned patients to newer medicines in the interim, but the company might be about to hit the end of the road on Advair's exclusivity in the US.

During the company's fourth quarter earnings call Feb. 8, CEO Andrew Witty braced investors to expect a substantial hit to revenues from the potential launch of an interchangeable generic in the US later this year.

The quarterly financial update was the last financial call led by Witty, who will be succeeded by Emma Walmsley on April 1. Throughout his nine-year tenure at the helm of the UK drug maker, he was dogged by the risk posed by a potential generic launch and the resulting overhang on the company's stock. He spent much of his leadership run preparing the company for generic competition and trying to minimize the impact, with a focus on launching new respiratory drugs and diversifying outside of pharmaceuticals.

Walmsley, the former consumer health president, will be the one to see GSK through what could be a challenging period. Pricing pressure on Advair from payers and increased competition, as well as new respiratory launches, have reduced GSK's dependence on Advair in the last three years. Nonetheless, a generic launch will still have a significant impact on the company's sales and earnings in 2017.

A US generic launch mid-year could reduce Advair's sales in the US to £1bn ($1.25bn) from £1.83bn ($2.32bn) in 2017, the company said.

GSK forecast core earnings per share growth of 5% to 7% in 2017 at constant exchange rates – but that is without a generic entering the market. A mid-year launch of a substitutable generic competitor to Advair would result in flat to declining core EPS. Even if a generic doesn't reach the market, the guidance assumes a continued decline in sales of Advair in the US of 15% to 20%. "It's now a real possibility that a substitutable generic to Advair could be launched in the US during 2017," chief financial officer Simon Dingemons said. "While the timelines for the introduction of a generic are far from clear and its impact will depend heavily on the pricing strategy and supply capacity deployed, we've assessed a number of scenarios in our planning for this year."

The uncertainty around the availability of a generic is because it's not clear if FDA will approve a substitutable generic on a first-cycle review because of the complexity of developing respiratory drugs. Two drug makers, Mylan NV and Hikma Pharmaceuticals PLC, have confirmed they have ANDA filings pending at FDA, with action dates of March 28 and May 10, respectively. They and other generic manufacturers, including Teva Pharmaceutical Industries Ltd. and Sandoz Inc., are eager to fill the void in a high-barrier-to-entry space.

Teva recently received FDA approval of a competitor to Advair through the 505(b)(2) regulatory pathway, rather than the traditional generic drug pathway. Although AirDuo includes the two active ingredients in Advair – fluticasone and salmeterol – it isn't an interchangeable generic because it is delivered through Teva's own RespiClick device rather than the same device used to deliver Advair. As a result, the impact on the brand is expected to be muted, though Teva is developing what it hopes will be its own substitutable generic.

In 2016, sales of Advair declined 15% to £3.49bn ($4.38bn) on a global basis, GSK reported. Growth in new products, including Breo Ellipta, Anoro Ellipta and Nucala, offset the decline. New respiratory products generated sales of £1.05bn ($1.31bn). The once-daily, inhaled ICS/LABA Breo generated sales of £620m ($777m) for the year, while the LABA/long-acting muscarinic antagonist Anoro generated £201m ($259.1m).

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Biotech Execs Speak Out Against Trump

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Letter initiated by six CEOs drew 'absolutely overwhelming' response as 163 leaders of primarily small biotech and venture capital firms signed on; tech firms join court fight.

President Donald Trump's presidency is revealing political fault lines throughout the country – and the biopharma industry, as evidenced by participation in a recent public letter on immigration policy. The letter began to take shape after Ovid Therapeutics Inc. CEO Jeremy Levin was inundated with emails immediately after President Donald Trump signed an executive order barring individuals from seven predominantly Muslim countries from entering the country. Employees, others from the biotech industry and members of academia told him they were distressed by the ban and its "potential for harm to innovation and medicine," Levin said.

He drafted an initial letter objecting to the order and shared it with five other biotech CEOs. Together they revised the piece and sent it out to colleagues in the industry. "The response was absolutely overwhelming," Levin said. "I was taken aback by the number of people who wanted to sign."

A total of 163 leaders of primarily small biotech companies along with some venture capital firms signed onto the letter, which was published Feb. 7 on a Nature Biotechnology blog. Levin said more signatures have come in and may be added to the print edition. The co-authors include CEOs Steven Holtzman of Decibel Therapeutics, John Maraganore of Alnylam Pharmaceuticals Inc., Paul Hastings of OncoMed Pharmaceuticals Inc., Ron Cohen of Acorda Therapeutics Inc., and Bassil Dahiyat of Xencor Inc.

"We the undersigned, founders and leaders of biotech companies, write to express our deep concern and opposition to the executive order signed by President Donald Trump on January 27, 2017, barring the entry of citizens from seven countries into the United States," the letter states.

"Though the ban from the Trump administration is aimed at seven countries, our global employees interpret the underlying message as, 'America is no longer welcoming of any immigrants whatsoever.' They fear similar orders could be issued for other countries at a moment's notice. They fear being stigmatized and discriminated against, simply because of their religion, irrespective of the nation they come from," the letter says.

'NOT A POLITICAL STATEMENT'

Trump's executive order prohibits entry of immigrants and nonimmigrants from Iraq, Iran, Syria, Yemen, Sudan, Libya, and Somalia into the US for 90 days. It also suspends admission of all refugees for 120 days, and all Syrian refugees indefinitely.

The biotech execs say that if "this misguided policy is not reversed," the country is at risk of losing its leadership position in the biotech sector. "Indeed, it will harm an industry dominated by smaller companies and startups, the very kind of industry the administration has said it wants to support. It will slow the fight against the many diseases that afflict us, as well as carry negative economic consequences for the United States," the letter states.

Levin asserted that the letter "is not a political statement but a statement about science, medicine and innovation."

The letter notes that many in the biotech sector are from other countries. It cites a recent study published in Nature that found that in 2014, 52% of the 69,000 biomedical researchers in the United States were foreign-born.

Holtzman noted that one-quarter of Decibel's workforce, 10 of 40 people, are in the United States on green cards or visas. He said they are concerned about being deported and afraid to leave the country.

Levin, who immigrated to the US 30 years ago, said everyone in his company has a parent or grandparent who is an immigrant. He noted that at least seven employees that Ovid is trying to recruit asked about how their visas would be treated.

ON THE SIDELINES

The letter stands out as the Pharmaceutical Research and Manufacturers of America and the Biotechnology Innovation Organization have remained silent about the ban. After it was announced, CEOs of a few companies made comments about it on social media, expressing support for their employees and advocating diversity.

PhRMA had no comment on the executive order, which was issued a few days before several pharma CEOs met with Trump at the White House to discuss drug pricing and tax and regulatory reform.

In response to questions about the Nature Biotech letter, BIO said its policy positions are determined by actions taken by its Board of Directors collectively, which includes more than 100 companies at any given time.

"While BIO has not taken an official position on the executive order in question, we have been gathering data from our membership on the real-world impact this executive order has had, or may have, on their businesses or institutions, so that BIO can engage appropriately in fact-based advocacy. We continue to collect that input," the association said.

Ron Cohen is the chair of BIO's board, but so far it seems the association is not ready to follow him on the executive order. Levin said the authors of the letter did not reach out to several larger companies, noting that it was the smaller companies who were primarily interested in it.

Other signatories include leaders of Amylin Pharmaceuticals Inc., Ironwood Pharmaceuticals Inc., the Massachusetts Institute of Technology, and Deerfield Management. Former Biogen CEO George Scangos, now CEO of Vir Biotechnology Inc., is also a signatory.

Holtzman said the authors felt the letter should come from them as individuals rather than from an organized voice. And he said they sought to publish it in Nature Biotechnology rather than a media outlet that could be impugned as being partisan.

The associations' silence on the issue isn't surprising. Being able to hire the best scientific and executive talent from around the globe is important, but Trump's executive order is polling a lot better than pharma's pricing practices are, and industry leadership understands the importance of trying to build good relations with the President in advance of the looming debate on healthcare reform.

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Amid Pricing Criticism, Marathon 'Pausing' Emflaza Launch

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Company plans to meet with caregivers and consider other options before moving forward.

Marathon Pharmaceuticals LLC has decided to hold the launch of its newly approved Duchenne muscular dystrophy treatment Emflaza before it even started.

Company CEO Jeffrey Aronin wrote on the CureDuchenne blog Feb. 13 that after hearing concerns from patients about the product's $89,000 annual cost as well as reimbursement details, the company decided it was "pausing" the launch of *Emflaza* (deflazacort).

> 'We have not sold any new product, and we will pause that process'

"We have not sold any new product, and we will pause that process," Aronin said in the blog post.

The move could be a major setback for privately-held Marathon. It had said Emflaza would be available in early 2017.

Aronin suggested a rethink of the marketing strategy will be needed. He said the company will meet with caregivers and explain its commercialization plans, "review their concerns, discuss all options, and move forward with commercialization based on an agreed plan of action."

"We hope this brings clarity and comfort to you and reassures you that your child's good health, access to Emflaza and an understanding of the clinical profile are our highest goals," he said.

CureDuchenne, a patient advocacy organization, tweeted that it was pleased the company was willing to listen to its concerns. The group also said Marathon has committed to conducting additional DMD research.

Emflaza was approved Feb. 9 for DMD treatment in patients five and older. It is not considered disease-modifying. DMD patients use the product off-label to help maintain respiratory function and ambulation.

But celebrations about FDA's approval of another DMD treatment were muted almost immediately by criticism of the price. Not only were problems potentially expected with payers, but members of Congress also aired their anger and will investigate the company.

Aronin also reiterated in the blog post that Marathon gained FDA approval for Emflaza "to improve access to this treatment" for a broader set of patients.

He said patients have asked how Emflaza reimbursement will affect coverage of Sarepta Therapeutics Inc.'s *Exondys 51* (eteplirsen), which was approved in September 2016 for treatment of DMD in patients amenable to exon 51 skipping.

Anthem Inc. announced shortly after the approval that it would not reimburse for the treatment because of a lack of efficacy.

EXPANDED ACCESS

Marathon will maintain its expanded access program, now with 800 enrolled patients receiving Emflaza for free, and will also allow new patients to join for free. Marathon said that patients "currently receiving deflazacort from other sources will continue to have that option."

In an open letter to the DMD community, Aronin also said that it expects patients to pay a standard $20 co-pay or less to obtain the medication and that Marathon's goal is for patients' costs to be "significantly less than they pay today if they were among the few who were importing it."

The corticosteroid has been available for years as an anti-inflammatory and immunosuppressant, but was not approved for any use in the US. Until its FDA approval, patients had been forced to import the product from other countries. About 7% to 9% of DMD patients import the product. Deflazacort can reportedly be imported from Canada or the UK for about $1,000 per year.

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India's 'Cautious' View Dulls Sanofi Hopes

An early rollout of Sanofi Pasteur's dengue vaccine in India is looking less likely with a senior functionary of the health ministry telling Scrip why India needs to take a "cautious view" on the product's licensure in the country, at least for now. Sanofi, though, has sought the "best regulatory solution" that can facilitate access to the product.

India is unlikely to clear Sanofi Pasteur 's dengue vaccine, Dengvaxia, in a hurry and the government would prefer a "cautious" approach given certain safety concerns in young children and the risk of indiscriminate use of the product in the country, among other issues.

Dr Soumya Swaminathan, secretary, department of health research, Ministry of Health and Family Welfare and director general, Indian Council for Medical Research (ICMR), said that "better data" on dengue epidemiology in India would be required before Sanofi Pasteur's dengue vaccine can get the go ahead.

"If we know that above 70% of the population has dengue antibodies then it is likely that the vaccine would have protective effect but otherwise there will be no population level effect," Dr Swaminathan told *Scrip* at the sidelines of BioAsia 2017 in Hyderabad Feb. 6.

Dr Swaminathan also referred to certain safety concerns in children under nine, underscoring why the product cannot be given a license in the market immediately "because in India once you have something in the market it will be used indiscriminately."

"If there was no safety issue, even if the efficacy is poor, you can introduce the vaccine; you can say those who want to take it let them take it. But when you have a safety issue, the government has to take a much more cautious view on it," Dr Swaminathan said.

anju.ghangurde@informa.com, 9 Feb 2017

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Flat Is The New Black For Lilly And Sanofi

A lackluster fourth-quarter earnings season at least didn't get any worse with the reports of Merck, Lilly, Sanofi and GSK. Flat earnings guidance might be considered to be an improvement on guidance cuts, but financial guidance that depends on currency effects and the absence of generic competition may ultimately be unreliable.

ANDY SMITH

If fourth-quarter earnings reports could be weighted by market capitalization rather than by the number of companies reporting, after three weeks we would be over half way into earnings season. But they are not, and if the sales and guidance shortfalls from big biopharmaceutical companies from this earnings season are any guide, the losses to be reported from the long tail of smaller companies will almost certainly not rescue the sentiment lost.

There have, however, been some earnings season heroes, with Merck & Co. Inc. reporting fourth-quarter sales that were only $105m (or about 1%) below analysts' consensus estimates but which fell by about 1% since the same quarter of 2015. Merck's earnings were in-line with analysts' estimates. Merck's 2017 guidance for sales was ratcheted up 1.3% while their earnings guidance was ratcheted down 0.5%. This completed a financial report that stood out above most others from the early part of the season.

Propelling Merck's sales and sales guidance for last quarter and this year respectively, was the growth of its recently launched – and already blockbuster– anti-PD1 antibody *Keytruda* (pembrolizumab) for a range of oncology indications including non-small cell lung cancer (NSCLC). But Keytruda sales still trail those of Bristol-Myers Squibb Co.'s similar product *Opdivo* (nivolumab) despite Keytruda having far superior data in first-line NSCLC. This is not just counterintuitive, but counter to the virtually instant commercial transformation of two closely-related tyrosine kinase inhibitors – *Iressa* (gefitinib) from AstraZeneca PLC and *Tarceva* (erlotinib) from OSI Pharmaceuticals Ltd. – once the later demonstrated (and the former failed to demonstrate) a survival benefit in Phase III, ironically also in NSCLC. While the Keytruda-Opdivo anomaly could just be the current snapshot of the commercial dynamic between the two products it is emblematic of the topsy-turvy pharmaceutical world of 2017 where modest financial underperformance ranks as an earnings season success and the absence of a survival benefit outsells its presence.

Also inching out the sales and guidance disappointments of other big pharmaceutical companies was Eli Lilly & Co. when it reported what the analysts from J.P. Morgan suggested was a 'solid' fourth-quarter. Lilly reported fourth-quarter sales that were $211m or 3.8% ahead of consensus estimates but earnings that missed analysts' estimates by 3%. Fortunately, and unlike most companies that have so far reported, Lilly kept its 2017 guidance unchanged from the very bullish forecasts it issued after the failure of solanezumab in Alzheimer's disease just before Christmas.

Bringing some superficial European honor to redress the horror of the fourth-quarter earnings nightmare of Novo Nordisk AS, Sanofi reported fourth-quarter results that the analysts from Citigroup also described as being 'Solid'. Indeed, Sanofi beat analysts' consensus sales estimates by 2% driven by strong performances from its diabetes and vaccine franchises although the future performance of its diabetes business will turn on biosimilar insulin launches and further Medicaid rebates. What Sanofi terms 'business EPS' (earnings per share) also beat analysts' estimates by 2% and although it guided to business EPS growth of between 0% and -3% in 2017, in this topsy-turvy world where flat is the new black, this was between 3 and 5% higher than analysts' had expected. Sanofi's business EPS guidance for 2017 did count a 4% currency chicken from continued US dollar strength.

Playing a similar tune to Sanofi was GlaxoSmithKline PLC (GSK) when it reported quarterly sales and earnings that beat analysts' estimates by 2% and 5%, respectively, and were helped by royalties from the HPV vaccine Gardasil that were a whopping 50% or £39m ahead of analysts' estimates. On the other hand, I found GSK's 5% to 7% core 2017 EPS growth forecast to be opaque, or the antithesis of what Hemmingway called a clean, well-lighted place. This is because, like AstraZeneca's and Sanofi's 2017 guidance, it depended on moving parts that are outside of its control. In GSK's case these aspects will be currency exchange rates and limited generic competition to its respiratory blockbuster *Advair Diskus* (fluticasone/salmeterol). Similar limited generic competitive assumptions for big products have underestimated the threats to Johnson & Johnson and Teva Pharmaceutical Industries Ltd. but not at Celgene Corp. and Actelion Pharmaceuticals Ltd. where thanks to the protection of patented and unlicensed risk evaluation and mitigation strategies, generic competition has been significantly delayed. GSK's quarterly results were the last for its departing CEO and if the re-rating of the biopharmaceutical sector to one of lower growth has an obvious leading indicator, it is probably the departure of its CEOs.

The departure of Teva's CEO last week after presiding over generic competition to its lead product, uncomfortable levels of debt, a lagging position in biosimilars and the sector-wide pressure of generic drug price deflation – exacerbated by big acquisitions of generic assets – was probably not the last for companies that similarly disappoint. Teva's CEO departure may also have been a prelude to disappointing fourth-quarter results that will lag its top management change by a week. While the CEOs of Mylan NV and Gilead Sciences Inc. remain in place despite their controversies and disappointments of sector-re-rating proportions, CEO turnover in the sector must surely now increase.

Andy Smith gives an investor's view on life science companies. He has been lead fund manager for four life science–specific funds, including 3i Bioscience, International Biotechnology and the AXA Framlington Biotech Fund, and was awarded the techMark Technology Fund Manager of the year for 2007.

Glioma A New Therapeutic Interest For GW Pharma

GW Pharmaceuticals has identified oncology as a potential new therapeutic area for its cannabinoid-based products, but such research is at an early stage and the UK company is currently focused on orphan neurology indications and the setting up of commercial operations in the US and Europe.

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A proprietary combination of tetrahydrocannabinol (THC) and cannabidiol (CBD) has been associated with increased survival in a small Phase II study in patients with recurrent glioblastoma multiforme, but it's too early to give a high-level view of what those findings mean for GW Pharmaceuticals PLC's business strategy, says company CEO Justin Gover.

That's not to say the company is uninterested. "These data are a catalyst for the acceleration of GW's oncology research interests, and over the coming months we expect to consult with external experts and regulatory agencies on a pivotal clinical development program for THC:CBD in glioblastoma multiforme," Gover said in a statement Feb. 7.

And other oncology indications are being targeted by GW's research. "Over the coming months, we will expand our research interests in other cancers," remarked R&D executive director Stephen Wright during a same-day earnings call with analysts.

The hope is that because cannabinoid-based therapies are believed to have a different mode of action to conventional anticancer drugs they may produce a synergistic therapeutic effect when used in combination with other types of anticancers. Cannabinoids are an active area of research for a number of pharmaceutical companies.

The top-line results from the THC:CBD study released Feb. 7 showed that, in a Phase II study in 21 patients with recurrent glioblastoma multiforme already being treated with temozolomide, treatment with GW's proprietary THC:CBD product was associated with a 83% survival rate at one year, compared with a 53% survival rate in those treated with placebo, a statistically significant difference (p=0.042). The median duration of survival was 550 days in those treated with THC:CBD, compared with 369 days in those treated with placebo.

But for now, GW Pharma is in the throes of setting up commercial operations in the US and Europe for its lead investigational cannabinoid product, Epidiolex (a liquid formulation of pure cannabidiol), having decided to take this route to market rather than the licensing route used for its first marketed product, the multiple sclerosis spasticity therapeutic Sativex (nabiximols).

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Concerned About Unsustainable Cancer Drug Prices?

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A group of leading researchers are suggesting that using academic centers to de-risk cancer drug discovery could tackle the problem of 'unsustainable drug prices'.

A commentary published in the journal *Cell* warns that the price of cancer drugs is now rising so fast it threatens the whole financial viability of cancer treatment – particularly as the increased use of drug combinations is multiplying costs.

Professor Paul Workman, chief executive of The Institute of Cancer Research, London, is joined on the commentary, entitled 'How much longer will we put up with $100,000 cancer drugs?' by co-authors from The Netherlands Cancer Institute and The University of Texas MD Anderson Cancer Center in the US.

They suggest that academic drug discovery teams could develop cancer drugs more cheaply by working with new forms of private enterprise as an alternative to the traditional pharmaceutical industry model.

The authors are not proposing that the new model replace the traditional pharmaceutical industry, but they argue that academics should take much greater control of the development of the drugs they discover. This way they can reduce costs, and also have more say in how new drugs are evaluated and used.

CALL TO ARMS

"This article is designed as a call to arms to the research community – both academic and commercial – to highlight the problem of unsustainable drug prices and suggest a possible solution," professor Workman told *Scrip*.

Under the authors' proposals, academic teams could partner with new forms of private companies to fund clinical trials and marketing. These new companies might specialize in partnerships with the non-profit sector, and would agree to cap the price of new medicines.

Another potential partner type might be generic companies. "Given that generic drug makers are used to working with lower profit margins, they may be one potential partner to develop highly innovative, but de-risked, drugs from academic drug discovery and development," the authors write in the commentary.

Professor Workman hopes that the commentary will generate interest from existing or potential companies. "We have already identified some interest," he revealed.

There are a number of reasons academic drug development tends to stall when it comes to the stage of clinical testing, but most of these could be solved with adequate funding, the authors believe.

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"I think this [idea] needs a combination of non-profit and commercial funding to make it work," said Workman. "We have identified interest from government and other non-profit funding sources and some models are already underway."

The authors believe that to start with, academic researchers could harvest "low hanging fruit" in the form of repurposing existing patent-expired drugs by funding new indications for them, or look at finding effective combinations of drugs that were abandoned for lack of single agent activity.

"There is a lot of interest in repurposing and combination studies from translational academics," Workman insists.

'SOMETHING MUST BE DONE'

Other experts are intrigued by the commentary but not fully convinced by all the ideas. Former vice president and head of biology at GSK Chas Boutra, now professor of translational medicine in the Nuffield Department of Clinical Medicine at the University of Oxford, agreed with some of the commentary but was wary about the potential of repurposing old drugs or combination drugs. "I certainly like the idea of trying to use academia to de-risk targets in the hope that we can get more affordable medicines in the future," he told *Scrip*. However, "We've been very much focused on trying to come up with completely novel therapeutics, because we think that's what patients need, not another me-too or a follow up – they want completely novel therapeutics."

'TRAGEDY'

But Boutra firmly agrees that something needs to be done about the way cancer research is being conducted. "The challenge we've got is that most pharma and biotech companies are all working on the same few ideas, in parallel and in secret, and the reason they all work on the same ideas is because everybody reads the same literature, they go to the same conferences, they talk to the same opinion leaders. So you've got 20 companies, they work on the same target, they spend six or seven years coming up with a proprietary molecule, they test it in patients and then of course 80% to 90% of the time, that idea fails in the clinic. So if one company fails, the other 19 companies fail as well," he explained.

"That is a tragic waste of money and a tragic waste of people's careers, but it's also a devastating waste of patients. Frankly, the way we are doing drug discovery today, we are exposing patients to molecules that other groups already know are destined for failure. Ethically and morally, that is wrong."

He has proposed pooling resources, working with companies and patient organizations and philanthropic bodies "and do the

experiment once, do it well, identify the nine targets out of 10 that are garbage, find the one out of 10 that has the potential to be a new drug. Once it is clinically validated, de-risked, then let all the companies concentrate their resources on it and take it into large-scale clinical trials and eventually launch it. That's good for industry of course, it's good for patients and it's good for society."

Boutra's group has been given funding from eight pharma companies, five patient organizations and from philanthropy. The Wellcome Trust has put in nearly £60m into his laboratory.

"We only work on completely novel targets. I'm not interested in targets where there are already 5000 publications and people have been working on them for 20 years. I want to open up completely new areas of biology, because that's where the big step changes are going to happen." He says payers "don't want just incremental innovation, they want transformative innovation, transformative therapeutics."

Professor Workman's warnings are correct, according to Boutra. "If we keep generating a load of new medicines that each cost more than £100,000 each, the NHS can't afford it, and you end up upsetting the pharma companies which then say 'we're not going to do any R&D in the UK.'"

> 'The way we are doing drug discovery today, we are exposing patients to molecules that other groups already know are destined for failure. Ethically and morally, that is wrong'

However, he warns against 'low hanging fruit', although admits not everyone has his inhibitions. "A lot of my clinical colleagues here are desperate to come up with new treatments for their patients and so as long as we can present a strong scientific rationale, they will do those studies. And as long as the molecules are safe."

Boutra himself is not excited by re-purposing. "I know a lot of people are doing it and some pharma companies are making their compounds available. But those pharma companies – after spending £15-20m generating that molecule and maybe having done some clinical studies with it, you can be sure that they've trawled the literature, they've spoken to all the opinion leaders, and they've decided there is no value in it, and then they make it available. So I'm not convinced there are loads of opportunities there. I'm sure there will be some, but I'm not there will be loads."

He also has concerns about combinations of drugs. "All the pharma companies are doing combinations," he notes. "You could argue cynically that if you're not coming up with enough new drugs, then it's easy to put together the ones you already have into some sort of combination.

"Now we've got lots of cancer drugs out there. How do we rationally pick which are the best combinations? If there are 50 different cancer drugs out there, who can tell me that if you combine number 1 and number 39, that's the best combination? That's what I want to know."

But he believes in the importance of the initiative. "This is a process that is incredibly costly, incredibly slow, incredibly inefficient, incredibly risky. It just makes sense that you pool your resources."

ABPI CAUTIOUS

Head of science policy at the ABPI, Dr Rebecca Lumsden, had this to say: "The biopharmaceutical industry is always looking for faster and better ways to deliver medicines to patients, and we welcome the development of any new competitive models that could achieve this. The pharmaceutical industry routinely collaborates closely with partners in academia, the NHS and charities, particularly for early drug discovery. By working together, we share expertise and risk as potential new medicines move through the stages needed to bring it to patients. However, the reality is that drug discovery and development remains a considerable scientific challenge, even with our increased understanding of disease. Robust regulation to protect public health establishes quality, safety and efficacy of new medicines but also drives up the cost. All these steps require considerable investment and expertise."

Published online 9 February 2017

Prexton Turns mGluR4 Fortunes Around

Prexton Therapeutics has the only mGluR4-targeting drug candidate in clinical testing, after a number of big pharma dropped preclinical programs. The company has just secured €29m to fund two Phase II trials.

Parkinson's disease is caused by the degeneration of dopaminergic brain cells, and most current treatments aim to replace dopamine or mimic its effects. Prexton Therapeutics' approach, however, is to stimulate a separate, compensatory neuronal system unaffected by Parkinson's. Its drug candidate Foliglurax (formerly known as PXT002331) activates a specific target of the glutamatergic system (mGluR4). The aim is to treat the motor symptoms of Parkinson's.

Merck & Co and Bristol-Myers Squibb both had mGluR4 programs that stalled in preclinical development.

Merck & Co returned rights to a program to Addex Pharmaceuticals in 2011.

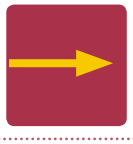
BMS partnered with Vanderbilt Center for Neuroscience Drug Discovery on a mGluR4 program in Parkinson's in 2012, but no progress has been reported since then.

Forbion Capital Partners and Seroba Life Sciences co-led the €29m series B financing round, which includes current investors Merck Ventures, Ysios Capital and Sunstone Capital. Marco Boorsma from Forbion and Alan O'Connell from Seroba will join the board of directors at Prexton.

Scrip asked Forbion's Boorsma why he expected Prexton to succeed where other mGluR4 projects had failed.

"The management team, the advisory board and the data pack at Prexton are really excellent," he said. "Our experts were very impressed with the data, especially."

sukaina.virji@informa.com, 7 Feb 2017



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

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

Selected clinical trial developments for the week 3–9 February 2017

LEAD COMPANY/PARTNER	COMPOUND	INDICATION	COMMENTS
Phase III Suspended			
Lundbeck Inc.	idalopirdine	mild to moderate Alzheimer's disease	STARBEAM, STARLIGHT; well tolerated but lacked efficacy.
Phase III Results Published			
Synergy Pharmaceuticals Inc.	*Trulance* (plecanatide)	chronic idiopathic constipation	In the *American Journal of Gastroenterology*, online Feb. 7, 2017.
Merck KGAA	cladribine	brain atrophy in multiple sclerosis	CLARITY post-hoc analysis in the *Multiple Sclerosis Journal*, online Jan. 31, 2017.
Allergan PLC/Gedeon Richter Ltd.	*Vraylar* (cariprazine)	schizophrenia	Negative symptoms. *The Lancet* online, Feb. 6, 2017.
Phase III Interim/Top-line Results			
Bayer AG/Janssen R&D LLC	*Xarelto* (rivaroxaban)	prevention of major cardiac events	COMPASS; met primary endpoint ahead of time.
Acorda Therapeutics Inc.	CVT-301	Parkinson's disease	SPAN-PD; met primary endpoint .
Biofrontera AG	*Ameluz* (BF-200 ALA) plus daylight phototherapy	actinic keratosis (additional indication)	Met primary endpoint on lesions clearance rate.
Phase III Initiated			
Novo Nordisk AS/Emisphere Technologies Inc.	semaglutide, oral	type 2 diabetes	PIONEER; all 10 Phase IIIa trials now underway.
AstraZeneca PLC	durvalumab	first line in small cell lung cancer	CASPIAN; with tremelimumab and chemotherapy.
Kiadis Pharma Netherlands BV	ATIR101 (treated donor T-cells)	acute myelogenous leukemia	HATCY; a transatlantic study.
AbbVie Inc./Enanta Pharmaceuticals Inc.	glecaprevir plus pibrentasvir	hepatitis C	M16-126; in genotype 5 or 6 infected patients.
Sumitomo Dainippon Pharma Co. Ltd.	napabucasin	pancreatic cancer	CanStem111P; plus nab-paclitaxel and gemcitabine.
Seikagaku Corp.	SI-613	osteoarthritis	Injected directly into the joints.
Phase III Announced			
Flexion Therapeutics Inc.	*Zilretta* (FX-006)	knee osteoarthritis	A formulation of triamcinolone acetonide.

Source: Biomedtracker

Alzheon Inc., a company focused on Alzheimer's disease and other neurological and psychiatric disorders, has appointed ***Neil Flanzraich*** chief business officer. Flanzraich joins the company with over 30 years of executive leadership, operational and legal experience. Previously, he was CEO of Cantex Pharmaceuticals, where he is now executive chair. He is the founder and principal of Leviathan Biopharma Group, LLC., a venture capital firm. Flanzraich was also vice chair and president of IVAX Corporation, before its sale to Teva Pharmaceutical Industries Ltd. in 2006.

Arena Pharmaceuticals has named ***Jayson Dallas***, ***Oliver Fetzer*** and ***Garry A. Neil*** to its board of directors. Current directors Harry F. Hixson Jr. and Donald D. Belcher will be retiring from the board. With over 20 years of experience in the pharma industry, Dallas is chief commercial officer and executive vice president of Ultragenyx Pharmaceuticals. Previously he was general manager of Roche UK; and prior to this he held senior positions at Genentech, Novartis AG, Pharmacia and Roche. Fetzer is currently CEO at Synthetic Genomics and previously he was CEO at Cerulean Pharma. He is also on the board of Tecan Group AG. Neil is chief scientific officer of Aevi Genomic Medicine and has previously held senior positions at various companies including Johnson & Johnson, Merck KGaA /EMD Pharmaceuticals, AstraZeneca plc and Astra Merck. He is the founding chair of the pharmaceutical industry consortium, TransCelerate Biopharma and is on the board.

Medical oncology expert ***James Griffin*** has joined **RXi Pharmaceuticals Corporation**'s scientific advisory board. He is a professor of medicine at Harvard Medical School and director of medical oncology at Brigham and Women's Hospital. Griffin received his medical degree from Harvard Medical School and joined the staff of Dana-Farber, where he is chair of the department of medical oncology. Previously, Griffin was editor-in-chief of the hematology journal *Blood*. He sits on the scientific advisory boards of the Lombardi Cancer Center at Georgetown University, the Johns Hopkins Cancer Center and Case Western Cancer Center.

Ligand Pharmaceuticals Incorporated has appointed ***Christel Iffland*** vice president of antibody technologies. Iffland joins the company from Merck KGaA/EMD Serono, where she was group leader of antibody display technologies. Iffland is an author of various scientific publications and patents and is a prior recipient of the Merck Award for Patent and Inventorship.

The biotech company, **Therachon AG**, has appointed ***Hans Schikan*** to its board as non-executive director, ***Richard Porter*** chief operating officer and ***Jeffrey Stavenhagen*** vice president of biology. Schikan is chair at Asceneuron, Complix and InteRNA, and is a non-executive director at Hansa Medical, Swedish Orphan Biovitrum, Wilson Therapeutics and Dutch Top Sector Life Sciences & Health. Previously, he was CEO of Prosensa and before this, he held senior strategic and commercial positions at Genzyme and Organon. Porter spent over 14 years at Roche, most recently as global head of operations management for neuroscience Ophthalmology and Rare Diseases. He was also product general manager in the emerging business unit at Shire Pharmaceuticals. Stavenhagen brings over 20 years of scientific experience in both the US and EU and most recently was senior director at Lundbeck. Before this, he was director, molecular immunology at Amplimmune and held various roles at MacroGenics.

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