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Reflections From J.P. Morgan: Challenges And Optimism

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The J.P Morgan Healthcare meeting wrapped up on Jan. 11 and as industry executives and investors departed San Francisco, the outlook for pharma appears bright in 2018, despite challenging fundamentals. The energy at the annual meeting, which drew more than 9,000 attendees, was more muted than in prior years, perhaps highlighting the transition point pharma has reached.

Industry is trying to balance increasingly innovative science against long-standing drug development, regulatory, reimbursement and management models. Navigating those two paradigms and modernizing to keep pace with the scientific breakthroughs may well be the biggest challenges industry faces as it moves into what feels like a potential new era for medicine.

Overall, drug makers and investors were optimistic about 2018, thanks to the big financial windfall poised to hit from tax reform, a sense that some of the biggest drug pricing threats have moderated and encouraging new breakthroughs in gene therapy and immuno-oncology.

Investors were underwhelmed by the level of deal news that broke in the opening days of the meeting, with **Celgene Corp.**'s acquisition of **Impact Biomedicines** for $1.1bn upfront being the big standout. *(Also see "Celgene's $1.1bn Impact Buy Is First Of More Deals To Come In 2018 And Beyond" - Scrip, 9 Jan, 2018.)* But the meeting also didn't have the undercurrent of tension it had in 2016, when big drug pricing scandals were in the headlines and executives were concerned a populist President Donald Trump might try to impose new pricing regulations on the industry.

Last year during J.P. Morgan, Trump said pharma was "getting away with murder," while this year the president's name was scarcely murmured at all. *(Also see "Trump Throws Pharma A Curve Ball On The Third Day Of J.P. Morgan" - Scrip, 12 Jan, 2017.)*

With the threat of sweeping policy changes out of the way and industry peer Alex Azar poised to be the next Health and Human Services secretary, some of the industry's most acute concerns seemed to be triaged.

But the industry is grappling with other challenges, most notably how to harness new scientific advances into medicines and how expensive medicines targeting small subsets of patients will be commercially successful and reimbursed by payers.

NEW LEADERSHIP LINING UP

The feeling of transition was also evident in pharma's leadership ranks. Even within big pharma, there are two CEOs in the midst of transitions. **GlaxoSmithKline PLC**'s new CEO Emma Walmsley debuted in the grand ballroom of the Westin St. Francis Jan. 9, while **Novartis AG**'s incoming CEO Vasant Narasimhan stayed offstage ahead of taking over from Joseph Jimenez on Feb. 1.

Those new leaders are poised to bring a refreshing perspective to their respective companies and the broader industry. Walmsley comes from a background in consumer healthcare and is the first woman CEO of a big pharma, while Narasimhan brings a scientific background,

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

Pfizer Exits Neuroscience
But door remains open for a return (p9)

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Not A Dry Eye In The House
Allergan and Shire battle it out (p16)

from the editor

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I promised last week that we'd have more insights from the J.P. Morgan Healthcare conference. The meeting finished a week ago but we'll be digesting the conversations, presentations, key themes and predictions from those hectic days in San Francisco for some time to come. This issue includes Jessica Merrill's wrap-up of the event (see cover story), highlighting talking points from the new generation of big pharma leadership to tax reform and the rebate system in the US.

J.P. Morgan is a rare crucible where the great and the good across the pharma and biotech industries gather in a spirit of loquacity that generates discussion and speculation for the year to come. Our reporters from the event bring you their executive revelations across the next few pages.

Meanwhile, those of you who access our articles online may have noticed that we're rolling out our Pharma Feedback survey to help us understand your needs and gather feedback on our content and its delivery. You can also access it here if you're reading this as a PDF, or type in the following URL if you're reading it in print: bit.ly/2yXash2.

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Decisions That Made A Difference: Wockhardt Chief On A Life In Business
http://bit.ly/2ELOwJr
Dr Habil Khorakiwala, Wockhardt's chair and group CEO, recounts his life and business journey, including an acquisition that went wrong, in an interview with *Scrip* as part of our ongoing executive profile series. Khorakiwala also outlines where he sees Wockhardt in the coming years, with the firm's R&D thrust in the antibiotics space expected to play a pivotal role.

Pharma Struggling To Assimilate Flood Of Clinical Trial Data
http://bit.ly/2D8f8Us
Big data may be prolonging development times for new pharmaceuticals, as companies struggle to cope with diverse digital applications and clinical trial protocol changes.

Oral Testosterone Therapies Face Clinical Practice Difficulties, Advisory Panels Suggest
http://bit.ly/2B52m7i
The FDA's advisory committee voted down Lipocin's Tlando and Clarus' Jatenzo based on concerns about off-label use, but if they do reach the market, Tlando's lack of titration could pose problems for physicians, while both drugs could raise difficulties with the types of tubing used to test testosterone concentrations.

Bharat Biotech Gets WHO Nod For 'Game-Changer' Typhoid Vaccine
http://bit.ly/2D8KRVj
India's Bharat Biotech has won WHO pre-qualification for a vaccine against typhoid fever that experts say will be a "game-changer" in preventing the bacterial disease, especially among children under two years - the age group most at risk.

Cipla Revs Up In US, Newer Markets To Cushion Against Volatility
http://bit.ly/2DkdVMX
US scale-up plans, cost optimization and a deeper push in certain other markets to garner volumes and as a buffer against volatility were some of the key strategies discussed by Cipla's CEO at the recent J.P. Morgan Healthcare Conference in San Francisco.

Deal Watch: As J.P. Morgan Waits For New Deals, Sanofi Takes Care Of Old Business
http://bit.ly/2FGHxTh
Alder ended a patent dispute with Teva with a deal that will enable it to take its Phase III migraine candidate forward, while Sanofi restructures pair of partnerships with Alnylam and Regeneron heading into the J.P. Morgan Healthcare conference.

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Lilly's CGRP Prospects, Juno On Track, Color From Alnylam's Greene, Shire's New CMO

MANDY JACKSON & EMILY HAYES

Eli Lilly & Co. CEO David Ricks attempted to allay investor concern during the J.P. Morgan Healthcare Conference about the likelihood of favorable reimbursement for the company's biologic galcanezumab, which is under review at the US FDA and is in a tight race with rivals to be the first calcitonin gene-related peptide (CGRP) inhibitor approved for the prevention of migraine headaches.

Amgen Inc. and its partner **Novartis AG** are talking to payers about reimbursement schemes that provide payment only when patients have a strong response to treatment with their CGRP inhibitor *Aimovig* (erenumab), which was the first biologic in the class submitted for approval. *(Also see "Novartis Floats 'Bold' Value-Based Reimbursement Idea In Migraine" - Scrip, 13 Nov, 2017.)* **Teva Pharmaceutical Industries Ltd.** also has a CGRP drug pending at FDA.

Ricks didn't appear to be particularly worried about coming to market in the US behind Aimovig, based on his response to a question about competition and reimbursement in the CGRP space, which was asked during the question and answer session following his Jan. 9 fireside chat – in lieu of a presentation – at the J.P. Morgan meeting.

"Competition may be good in generating awareness and that could make all boats rise," he said.

CGRP inhibitors represent the first new treatment in decades for migraine headaches and they will be the first biologics approved that target a mechanism specific to the debilitating condition. Migraine prevention is one of several indications for **Allergan PLC**'s blockbuster injectable *Botox* (onabotulinumtoxinA), but it wasn't the product's first approved use. Most patients are treated with the well-known class of generic triptans on an acute, not prophylactic basis.

All of those factors are why, for investors, the CGRP inhibitor market looks worryingly similar to the market for injectable PCSK9 inhibitors, a class of targeted biologics that do a good job of lowering LDL cholesterol, but compete against highly effective, generic oral statins. Amgen's *Repatha* (evolocumab) and **Sanofi/Regeneron Pharmaceuticals Inc.**'s *Praluent* (alirocumab) are robust for reducing cholesterol, yet payers have created hurdles for reimbursement.

"We understand, based on PCSK9, that people are worried," Ricks said, adding that he believes dosing convenience via an easy-to-use injector and education of treating physicians and consumers – including direct-to-consumer advertising – will help build a case for treatment.

> 'Competition may be good in generating awareness and that could make all boats rise'

He noted that efficacy seen in clinical trials will matter, such as the number of days that patients regained each month, because they were headache-free. The productivity boost could be important for employers, who ultimately drive private payers' reimbursement decisions, and Lilly hopes to supplement the efficacy of galcanezumab in the future with its acute migraine treatment – the Phase III oral drug lasmiditan. *(Also see "Phase III Lasmiditan Data Strengthens Lilly's Dual Migraine Strategy" - Scrip, 5 Aug, 2017.)*

With respect to the patient population and the productivity imperative for employers, Ricks said: "These are younger women; if I was an employer and it affects productivity in the workplace, I would be interested in supporting that."

JUNO HOT ON TRAIL OF BCMA/ CAR-T IN MYELOMA

Juno Therapeutics Inc. is keen to develop a chimeric antigen receptor T cell (CAR-T) therapy against the hot B-cell maturation antigen (BCMA) target in late-line myeloma, with plans to move fast this year.

An investigational new drug application for the company's BCMA-targeted JCARH125 has been cleared and a study will begin in myeloma this quarter, the company noted during a presentation at the J.P. Morgan meeting.

Striking data for **bluebird bio Inc.**'s BCMA-targeted bb2121, partnered with **Celgene Corp.**, in heavily pretreated multiple myeloma were presented at the American Society of Hematology meeting at the end of 2017 and were a major hit of the event. *(Also see "Celgene's CAR-T Leadership Goals Advance At ASH 2017" - Scrip, 12 Dec, 2017.)*

A dose-ranging study of JCARH125 will begin this quarter and the company may be in a position to start a pivotal trial in late-line myeloma this year, Sunil Agarwal, president of research and development at Juno explained in an interview at the meeting.

Juno plans to test JCARH125 in combination with a gamma secretase inhibitor to augment antitumor activity and ultimately to move into earlier lines of therapy.

Juno hasn't set the pivotal trial design yet, but it will likely be similar to the plan for bb2121 – an open label, single arm study of less than 100 heavily pretreated multiple myeloma patients, Agarwal said.

Salvage therapy is just the beginning though; bluebird is going earlier and so will Juno, the exec explained.

Development of JCARH125 will include combination studies with a gamma secretase inhibitor to augment efficacy.

JCARH125 will be in direct competition with bb2121, but Agarwal noted that Juno's partnership with Celgene only includes CD19 and CD22 directed CAR-T candidates, not BCMA.

Meanwhile, the company's lead CAR-T candidate JCAR017 (Liso-cel) is on track for a filing this year in relapsed/refractory diffuse large B cell lymphoma (DLBCL)

and Juno believes there's a chance that it may get approved this year. The CD19 targeted candidate will be ready for use in the outpatient setting starting on the first day of launch, management said during its J.P. Morgan presentation.

The company is emphasizing the ability to treat in the outpatient setting, due to the therapy's good safety profile, which it sees as better than the competition. *(Also see "CAR-T To Go: Juno Sees JCAR017 As Safer, Suited For Outpatients" - Scrip, 2 Nov, 2017.)* In the US, community hospitals and community clinics account for 80% of the US market.

Juno says it will initially aim to have the product manufactured for most patients in less than 21 days at the time of Lisocel's launch but hopes to get this timeframe down over time to from three to six days.

Meanwhile development of JCAR017 is progressing this year in other lymphoma indications, acute lymphocytic leukemia and chronic lymphocytic leukemia.

ALNYLAM'S GREENE ON RENEGOTIATED SANOFI DEAL

Scrip caught up with **Alnylam Pharmaceuticals Inc.** President Barry Greene while in San Francisco for the J.P. Morgan conference and spoke with him about the rationale for renegotiating some of the terms of the company's partnership with **Sanofi**. The annual conference seems to be the companies' favorite place to announce changes to their extensive partnership for the development of RNA interference (RNAi) drugs to treat rare and genetic diseases.

The collaborators first partnered in 2012 on the development of Alnylam's lead drug candidate patisiran, but they broadened their relationship in one of the most talked-about transactions at J.P. Morgan in 2014 when they announced that Sanofi would invest $700m in the RNAi specialist to gain expanded rights to patisiran in ATTR amyloidosis as well as rights to three other programs and an option to license development rights for additional candidates.

The companies announced this year on the eve of the J.P. Morgan meeting that Alnylam regained global rights to patisiran – recently submitted for approvals in the US and EU – and ALN-TTRsc02 for ATTR amyloidosis, though Sanofi will earn royalties on sales. Meanwhile, Sanofi retained global rights to fitusiran for hemophilia A and B, which will pay Alnylam royalties on fitusiran products. *(Also see "Deal Watch: As J.P. Morgan Waits For New Deals, Sanofi Takes Care Of Old Business" - Scrip, 9 Jan, 2018.)*

Greene said there are three key benefits of the change for Alnylam. First, the company will be able to build up its global capabilities and retain more patisiran revenue to support commercialization for that drug and others in the pipeline, including the Phase III asset givosiran for acute hepatic porphyrias and the earlier-stage cemdisiran for complement-mediated diseases.

Second, the renegotiated deal terms give Alnylam a chance to build up the ATTR amyloidosis market, including all types of the disease, which could represent hundreds of thousands of patients. Third, by longer contributing funds to cover its half of fitusiran development costs, Alnylam can use the money to advance other programs.

"For Sanofi, they were a different company when we first did the deal," under prior CEO Chris Viehbacher, Greene noted.

He said Sanofi benefits from the new partnership terms by fulfilling goals under current CEO Olivier Brandicourt to develop more late-stage products internally and retain rights for drugs across more global markets. *(Also see "JP Morgan: Brandicourt Signals M&A Interest To Boost Sanofi's Growth" - Scrip, 13 Jan, 2016.)* The big pharma also can make sure it is spending the right amount of money on the development of the drug, Greene said.

For Alnylam, retaining its own commercial and global rights comes at a crucial time for its near-commercial pipeline. The company expects to have four drugs on the market by 2020, including patisiran, fitusiran and givosiran. *(Also see "Interview: Alnylam President On Patisiran Lift-Off Plans" - Scrip, 6 Nov, 2017.)*

"We will launch a new drug every 12 to 24 months," Greene said.

MAYER MOVES INTO CMO ROLE AT SHIRE

Howard Mayer took on the title of chief medical officer at **Shire PLC** at the start of 2018, but he's been with the company for six years, most recently as interim head of research and development after Phil Vickers left to lead a new start-up and before new R&D chief Andreas Busch came on board. *(Also see "Shire Tempts Busch From Bayer As It Eyes Top Spot In Rare Diseases" - Scrip, 1 Dec, 2017.)* Mayer is enthusiastic about the medicines Shire has in development, noting that "this is the most robust that we've ever seen our pipeline – particularly the late-stage pipeline."

Shire has 40 development programs, including 15 Phase III product candidates, such as lanadelumab (SHP643) in hereditary angioedema (HAE), which was acquired in the $5.9bn-plus purchase of **Dyax Corp.** in 2015. Submission of lanadelumab for US FDA approval was expected in late 2017 or early 2018, based on Phase III results for the monoclonal antibody targeting plasma kallikrein. *(Also see "Shire CEO Says Lanadelumab Results Vindicate Dyax Buy, M&A Strategy" - Scrip, 19 May, 2017.)*

Mayer, who was on the due diligence team that assessed the Dyax buy, said "we haven't stopped looking for the right opportunities in the areas we're in."

Recent transactions include a licensing deal in July with **Novimmune SA** for the development of a bi-specific antibody to treat hemophilia A with and without inhibitors. *(Also see "Shire Aims To Stay On Top In Hemophilia With Novimmune Pact" - Scrip, 18 Jul, 2017.)* That program remains in preclinical development, but a gene therapy for hemophilia A known as SHP654 has gone into human testing with expectations that the initial clinical trial participant will be enrolled during the first quarter of 2017.

Changes may be coming for Shire's management, however. CEO Fleming Ornskov said during the company's J.P. Morgan presentation on Jan. 8 that Shire will separate its business into two divisions – rare diseases and neuroscience. Mayer told *Scrip* that executive changes won't be made until the end of the first quarter of 2018. That means the R&D pipeline will maintain its status quo for at least a few more months.

"For right now, there aren't going to be any leadership changes, so there will be no changes to our programs," Mayer said.

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CRISPR's Not Worried; Theratechnologies' HIV Niche; And Is Moderna's IPO Coming Soon?

JESSICA MERRILL, MANDY JACKSON & EMILY HAYES

Alder BioPharmaceuticals Inc. was talking to potential partners at J.P. Morgan for its calcitonin gene-related peptide (CGRP) drug eptinezumab, which has shown promising efficacy in Phase III clinical trials. The company released positive Phase III data on the migraine treatment during the conference, which ran Jan. 8-11 in San Francisco, showing 15% of patients treated with the drug experienced a 100% response for three months following a single intravenous infusion; 61% achieved a 50% reduction in migraine days or greater from baseline.

The company is still awaiting some additional data readouts from the four studies that make up the clinical program for eptinezumab but Alder expects to be on track to file the drug with the US FDA in the second half of 2018.

The question is how Alder might commercialize eptinezumab if and when it is approved. The company has no commercial-stage products and would be going up against some deep pocketed rivals in what is expected to be an intensely competitive space. **Amgen Inc./Novartis AG** and **Teva Pharmaceutical Industries Ltd.** are in a tight race to be first to market with their respective CGRP drugs, which are both dosed subcutaneously monthly. Eptinezumab is dosed every intravenously every three months.

"We remain pretty confident in our ability to independently execute," Chief Business Officer Mark Litton said. "That said, we are always looking for opportunities that will add value and will accelerate the commercial side." The company is considering potential partners in the US and globally.

CEO Randall Schatzman noted deals outside the US could be particularly attractive, since the company doesn't have any expectations to build out in Asia or Europe. Alder reached an intellectual property settlement with Teva related to the CGRP antibodies, which clears the way for the drug's launch.

CRISPR THERAPEUTICS UNFAZED BY CAS9 CONTROVERSY

A new paper released on the Friday before the J.P. Morgan conference suggested the potential for high levels of resistance to gene-editing medicines, but **CRISPR Therapeutics AG** CEO Sam Kulkarni said that will not be a problem for the company's lead development program.

That's good news for CRISPR, which is preparing to be the first company to take a CRISPR/Cas9-based gene-editing therapy into the clinic. CRISPR's stock fell 2.8% after the paper authored by Carsten Charlesworth, *et. al.* from the Department of Pediatrics at Stanford University was published in the online preprint archive *bioRxiv*, which is operated by Cold Spring Harbor Laboratory. However, the share prices of other CRISPR specialists **Editas Medicine Inc.** and **Intellia Therapeutics Inc.** fell 10.6% and 11.8%, respectively, on Jan. 8 based on the *bioRxiv* preprint.

Because the Cas9 protein in CRISPR/Cas9 technology often is derived from the common bacteria *Staphylococcus aureus* and *Streptococcus pyogenes*, the authors looked at donor cells in an attempt to understand how much of the population may be resistant to Cas9-containing therapies. The researchers found antibodies against *S. Aureus* Cas9 (SaCas9) in 79% of the donor cells and antibodies against *S. pyogenes* (SpCas9) in 65% of the cells. There were no antigen-specific T-cells against SpCas9, but 46% of donors has T-cells against SaCas9.

However, CRISPR Therapeutics is developing its lead product candidate as an *ex vivo* therapy, meaning that cells are withdrawn from the patient, edited in culture, then delivered back to the patient.

"For *ex vivo*, I think [Cas9 resistance] is irrelevant," Kulkarni said in an interview with *Scrip*. "The Cas9 goes in to edit, then it gets chewed up before the cells go back in to the patient."

For *in vivo* therapies, where a drug is administered to the patient and cells are edited inside the body, he said Cas9 resistance may only be an issue when the therapy is designed to continually edit DNA rather than perform a one-time edit.

CRISPR's partner **Vertex Pharmaceuticals Inc.** apparently is not concerned about Cas9 resistance in patients treated with the gene-editing firm's technology, because Vertex had a 90-day period to opt in to the development of CTX001 in beta-thalassemia and sickle cell disease, but it waited only 10 days to flag its interest, according to Kulkarni.

CTX001 involves engineering hematopoietic stem cells so that they produce high levels of oxygen-carrying fetal hemoglobin in red blood cells, which may alleviate transfusion-dependence in beta-thalassemia and reduce acute pain crises in sickle cell disease. The therapy has performed as designed in healthy donor and patient cells in preclinical studies, increasing fetal hemoglobin to levels that correspond with transfusion independence or a reduction in sickled cells.

CRISPR filed a clinical trial application (CTA) with the European Medicines Agency in December and will file an investigational new drug (IND) application with the US FDA in the first half of 2018 so that the company can start a Phase I/II clinical trial for CTX001 in beta-thalassemia this year. If data from the first 12 patients enrolled is encouraging, the trial will be expanded and serve as a pivotal study to support approval.

THERATECHNOLOGIES SEEKS NICHE HIV DRUGS

Canadian biopharma firm **Theratechnologies Inc.** could have US FDA approval for its monoclonal antibody *Trogarzo* (ibalizumab) prior its April 3 user fee date, but the company is already looking ahead to what it could market alongside the treatment for multi-drug resistant (MDR) HIV-1.

Scrip spoke with Theratechnologies President and CEO Luc Tanguay and Senior Vice President and Chief Financial Officer Philippe Dubuc during the J.P. Morgan conference about the company's appetite for drugs serving subpopulations overlooked by the broader HIV market's major players.

The market for Trogarzo, which has shown impressive efficacy in patients who no longer respond to conventional oral HIV therapies, is estimated to be about 20,000 to 25,000 patients in the US. The CD4-directed therapy was licensed from **TaiMed Biologics Inc.** in March 2016 for $2m up front.

Trogarzo's original user fee date was Jan. 3, but that was extended to April 3 when the FDA requested additional chemistry, manufacturing and controls (CMC) information in late November. However, Theratechnologies believes approval could happen before April based on its ongoing dialog with the agency, Dubuc said.

The company has grown its small US sales force to about 70 representatives, who currently detail *Egrifta* (tesamorelin) for lipodystrophy in patients with HIV. Egrifta reaches an even smaller market than Trogarzo and its 2017 sales are expected to total about C$42m to C$45m.

"Having a commercial organization already in that field, to find another [niche product in HIV] makes sense," Tanguay said, noting that Trogarzo will hit the market as Theratechnologies prepares to lose patent exclusivity for Egrifta. The company also has rights to Trogarzo in Europe and other select countries, and it is expected to reach the market in the EU about 18 months after the US launch, he said.

"At this point, we are looking at HIV only and we're looking at patients who are left behind," Tanguay said. Products of interest may be commercial, but too small for a larger company to justify a significant marketing spend, or assets may be acquired from smaller firms with a candidate that could help Theratechnologies build out its research and development pipeline.

"Our sales force now could probably sell three or four products," Dubuc said. "There are not that many commercial products in HIV [for sale,] but there are some good products in development. There are some unmet needs in HIV."

2018 COULD BE A BIG YEAR FOR MODERNA

Moderna Therapeutics LLC continues to present at J.P. Morgan to keep investors interested, but the company still hasn't revealed when it will go public. CEO Stephane Bancel previously has said Moderna won't pursue an initial public offering until it has clinical data from multiple messenger RNA (mRNA) therapeutics – a strategy the private company can afford, because it's raised more than $2bn to date in venture capital, partnership fees and grants, and it had $910m in cash as of Dec. 31.

However, the time for an IPO may be coming soon, since Moderna now has 10 mRNA therapeutics in the clinic and disclosed during the J.P. Morgan meeting that of nine more candidates, at least three are expected to move into human studies in 2018. President Stephen Hoge told *Scrip* in an interview during the conference that clinical trials have been completed for three of the company's first 10 product candidates, but only one – for a flu vaccine – has been published to date.

However, clinical data from more programs will be revealed this year, including results for a vaccine candidate that should be published soon. While partner **AstraZeneca PLC** has not disclosed results from its Phase I study for the companies' heart failure program, the big pharma deemed the program successful enough to merit a Phase II study, which Hogue said AstraZeneca will initiate within the next few weeks.

Moderna's internal pipeline is focused on infectious diseases, immuno-oncology and rare liver diseases, but it is working with several partners in those and other therapeutic areas, including **AstraZeneca PLC** and **Merck & Co. Inc.** The company views its partnership with **Vertex Pharmaceuticals Inc.** "as a window into pulmonary" that can help Moderna determine whether it should develop its own mRNA medicines in that therapeutic area.

While the company has been slow to reveal specifics around its closely-watched mRNA therapeutics, Moderna has moved its programs forward quickly. Hoge noted that the company's first IND application was filed 25 months ago and now 10 programs are in the clinic with some moving into Phase II. "The next couple of years are the proving point," he said.

The company was built and funded on the idea that mRNA therapeutics should be judged based on the results of multiple programs rather than a single drug, so that Moderna's whole platform isn't tossed aside based on a single failure. "We could easily have done one drug at a time; that was never the vision the company was trying to accomplish," Hoge said.

With the kind of money and attention Moderna has attracted while maintaining a relatively slow drip of preclinical and clinical data, the company has a lot of critics, which its president describes as healthy in a science-based industry.

"Our ambition to do this is so disruptive, it's viewed skeptically," Hoge said. "We think it will work broadly. We have to go prove it, not just for the skeptics, but for ourselves."

TG'S EXPECTATIONS

TG Therapeutics Inc. is set to release top-line data in the first quarter from a Phase II study of its UNITY-CLL study of its ublituximab (G-1101), which has been bioengineered to target CD20, in chronic lymphocytic leukemia (CLL) and updated Phase II results in multiple sclerosis.

The company noted that the it expects to see a 15% improvement for ublituximab in combination with its PI3 kinase inhibitor umbralisib (GR-1202) over **Roche**'s next-generation anti-CD20 antibody *Gazyva* (obinutuzumab) plus chlorambucil, and an objective response rate ranging from 84% to 88% in treatment-naïve and relapsed/refractory (RR) CLL patients.

"If all goes as planned, the company aims to file for an accelerated approval in front-line and RR CLL in Q4 2018, however management was uncertain of when it could provide a mature PFS endpoint for full approval, citing 2019 as a possible time point when an adequate number of PFS events would be reached. The company gave no indication what their strategy would be if the estimated endpoint targets were not met," Biomedtracker analysts noted.

IMMUNOMEDICS LOOKS FORWARD TO LAUNCH

Immunomedics Inc. is looking forward to a first quarter FDA filing of the antibody-drug conjugate sacituzumab govitecan, which it hopes will get accelerated approval in metastatic breast cancer (mTNBC); the firm is mulling over a European filing.

The Phase III ASCENT study is enrolling patients and positive results from a single-arm, open-label Phase I/II study in mTNBC were reviewed at the conference.

Recently, Immunomedics announced a $250m deal with **Royalty Pharma** to fund operations through 2020.

That will provide sufficient cash to fund operations until 2020, enabling Immunomedics to prepare the drug for commercialization in mTNBC, and to further development in urothelial cancer, the company noted.

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CONTINUED FROM COVER

having previously served as the chief medical officer at Novartis.

"Vas brings a lot of youth, vitality, progressive innovative thinking," Novartis Pharmaceutical CEO Paul Hudson said in an interview. "I wonder whether this marks a moment for the future for many companies, but importantly for the big pharma companies, to have the next generation of leaders."

Walmsley too pushed for pharma to modernize more aggressively during remarks at GSK's breakout session. She said being a modern leader means working to improve gender and racial diversity in the industry, one of the other big themes that ran through the meeting. Her ability to bring on one of industry's preeminent R&D leaders, Hal Barron, as president of R&D to revive GSK's pharmaceutical pipeline has also renewed investor attention in the company.

TAX REFORM PAY OFF

US corporate tax reform is poised to be a big win for pharma, with some companies benefiting from the lower corporate income tax rate that will fall from 35% to 21%, as well as the opportunity to bring cash held overseas back to the US at a competitive rate. Some big pharmas and big biotechs have billions in cash stockpiled overseas.

For the most part, the industry is still largely digesting the impact of corporate tax reform on their respective bottom lines. Most US-based companies said they expect the impact of the legislation will be beneficial, but anticipate providing more details during their fourth quarter financial updates.

Biogen Inc. forecast a lower tax rate in 2018, and Chief Financial Officer Jeff Capello told investors to expect tax reform to be very positive for investors. "We have quite a bit of cash trapped off shore," he said.

The question is how drug makers will reinvest the extra cash, with most executives pointing to business development, R&D, share buybacks and dividends. **Regeneron Pharmaceuticals Inc.** CEO Len Schleifer said the company would reinvest the extra resources coming from a lower corporate tax rate in R&D. For smaller biotechs, the benefits of tax reform could be big. The blood disease specialist **Bioverativ Inc.**, for example, has been paying the full 35% tax rate and CEO John Cox said in an interview that tax reform could add $50m in cash to the company's balance sheet.

TIME TO SHAKE UP THE REBATE?

While industry had success last year pushing some of the drug pricing blame onto third-parties in the supply chain that absorb the discounts and rebates drug manufacturers offer on drugs, one of the issues that has emerged is whether or not those rebates should be given directly to patients at the pharmacy counter. Industry has been thinking about new ways to ensure the savings from rebates are passed onto the consumer, and the topic came up frequently at J.P. Morgan.

Third-party pharmacy benefit managers that currently negotiate the rebates with pharma companies say the savings do reach patients in the form of lower premiums, but patients with high deductible health plans do not get the benefit and pay full price at the pharmacy counter, which is in turn raising consumer frustration over drug costs. **Express Scripts Holding Co.** CEO Timothy Wentworth reinforced the PBM's talking point during the company's breakout session. He said all the data point to higher insurance premiums for patients if the rebate structure is changed, but said the company would have no problem administering the rebate at the pharmacy counter if changes to the practice are made.

Some pharma companies voiced support for change. **Merck & Co. Inc.** CEO Kenneth Frazier seemed open to new ideas on rebating.

"The challenge that patients are facing quite directly is that unlike in network hospital visits or physician visits those rebates don't get passed onto people at the counter," he said. "There is a lot of focus now on how do we ensure this robust set of negotiations that go on actually effect the people that need it. I think that is a very important issue on how do we proceed from here."

Mylan NV CEO Heather Bresch has been an outspoken advocate of changing the rebate structure ever since her company came under fire from consumers and legislators for substantially raising the price of the allergy rescue medicine *EpiPen* in 2016.

"Good or bad, I will take credit for starting that discussion," she said in an interview. "I don't think there was much discussion around that supply chain and that pain point for the consumer."

"I absolutely believe the first step has got to be that a patient should realize the rebates, or discount, being negotiated, at the point of sale," she added.

Novartis' Hudson seemed less convinced, pointing to the issue of insurance premiums. "I think long-term sustainability calls for a high-degree of transparency right through the chain. What is the real price, the net price? We take a lot of comments publicly about the net prices," he said.

J.P. MORGAN IN THE TIME OF GENE THERAPY

Despite the high-risk nature of drug development, all the pipeline setbacks and the many challenges commercializing drugs successfully, the FDA approval of the first gene therapy in December, **Spark Therapeutics Inc.**'s *Luxturna* for an inherited form of blindness, was heralded by industry as a landmark moment throughout the conference.

The excitement around Luxturna and other notable breakthroughs like the FDA approval of the first CAR-T therapies from Novartis and **Gilead Sciences Inc./Kite Pharma Inc.**, and antisense oligonucleotide-based drugs like Biogen's *Spinraza* for spinal muscular atrophy (SMA) was palpable, partly because serious medical breakthroughs give the industry a lot to be proud of.

"This is the time for gene therapy," Biogen's Chief Medical Officer Alfred Sandrock said in an interview. "We are very interested in gene therapy." The company said it plans to move its first gene therapy into the clinic this year, a new approach for SMA.

Bioverativ's Cox noted, "It feels like in biotech we are moving from slowing progression of disease to curing disease."

Constellation Pharmaceuticals Inc. CEO Jigar Raythatha summed up the industry's over-arching sentiment well. "It feels like years of hard work are coming to fruition," he said.

The trick now will be to turn the breakthroughs into commercial successes, and figuring out how health care systems around the world can pay for them. That's what 2018 is for – and beyond.

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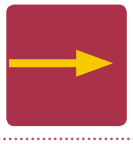

China Looms Large Seeking New Funding, Deals At J.P. Morgan: **http://bit.ly/2DFdBp0**

Pfizer Exits Early Neuroscience, But M&A Could Allow Later Re-Entry

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Pfizer Inc. has decided to call it quits in early neuroscience R&D in a move that analysts say was predictable and still leaves open the option of M&A as a return route if other players make a success of it.

Pfizer said on Jan. 5 it was ending its neuroscience discovery and early development efforts and re-allocate funding to those areas where the drug giant has strong scientific leadership. The US company, which has eight Phase I and Phase II programs currently active in neuroscience said it would seek to out-license those assets "where possible."

MOVE "UNSURPRISING"

Observers weren't surprised by the announcement given Pfizer's hitherto unsuccessful efforts in the area of neuroscience, notably in 2012 when Pfizer and partner **Johnson & Johnson** stopped Phase III trials on intravenous bapineuzumab after it failed to help patients with mild-to-moderate Alzheimer's Disease.

Datamonitor Healthcare Ali Al-Bazergan said "Pfizer has been trailing competitors in these CNS areas so it's hardly surprising that the company pulled the plug on early stage development. Pfizer was probably cognizant of its delayed penetration in other areas like immuno-oncology, deciding that the uncertainty in the return on these neuroscience assets would not balance the risk owing to later launches."

Datamonitor Healthcare lead analyst Dan Chancellor, who specializes in CNS, concurred, adding that "the projects that Pfizer is now discontinuing are all early stage, so it is speculative to say that any of these would have resulted in a breakthrough, so the near-term effect of this is very small. Pfizer announced it was reprioritizing away from depression back in 2009, while its work in Alzheimer's failed a long time ago."

The current state of Alzheimer's treatment development remains fractured. Recent years have seen several drugs have made it to Phase III only to be shown not to work. These have included gantenerumab from **Roche** and solanezumab from **Eli Lilly & Co.**

Still, companies continue to invest in amyloid and other hypotheses, including BACE, gamma secretase and other programs.

"Other companies continue to see opportunities in this field, with **Biogen Inc.**, **Roche** , **Eisai Co. Ltd.** and **Takeda Pharmaceutical Co. Ltd.** being recent examples of companies that are doubling down when it comes to Alzheimer's disease research," Chancellor said.

Chancellor said Pfizer's decision to focus on its strengths and exit neuroscience made sense. M&A also offers a re-entry point further down the road if necessary, he added.

"It is appropriate for companies to focus their R&D – and Pfizer certainly doesn't have a leadership position in neurology, so the move does make strategic sense. Should other companies translate promising science into medical breakthroughs, then Pfizer would likely have had to come to the deal-making table anyway, as it was already behind," the analyst said. But evidence of innovative progress in neuroscience remains elusive.

"The best barometer about whether the current Alzheimer's pipeline has any likelihood of succeeding is Biogen's anti-amyloid antibody aducanumab, which won't produce any new data until late 2019," Chancellor said.

He noted that Biogen and Eisai also have BAN2401, an amyloid antibody, and elenbecestat, a BACE inhibitor in their collaboration. "Roche also has two Phase III amyloid MAbs being conducted thorough clinical trial programs, and generating data from the second half of 2018." those therapies being gantenerumab and crenezumab.

Data on various other BACE inhibitors from pivotal Phase III trials should begin reading out in 2019 from J&J, **Merck & Co. Inc.**, **AstraZeneca PLC** and **Novartis AG**

300 JOB CUTS

Pfizer's exit from early stage neuroscience development will mean the loss of around 300 jobs spread evenly between sites in Cambridge and Andover, Massachusetts, and in Groton, Connecticut.

Pfizer has kept tight-lipped on the decision to leave neuroscience discovery and development.

Mikael Dolsten, head of global R&D at Pfizer said during his Jan 8 presentation at the 2018 J.P. Morgan Healthcare Conference in San Francisco that Pfizer "are exiting research and early development in neuroscience in order to focus and reallocate our resources into the other five areas where we think we can give them most value near to mid-term for shareholders and for patients. That's part of making sure you put your resources where you can make the biggest impact on where you can win."

Pfizer stressed however that the late-stage anti-epileptic *Lyrica* (pregabalin) programs and the tanezumab development program with Eli Lilly "will continue as planned."

Pfizer and partner Eli Lilly & Co. are developing tanezumab in six Phase III clinical trials for osteoarthritis and chronic back pain in roughly 7,000 patients. Tanezumab's mechanism of action is a nerve growth factor inhibitor.

Pfizer added that it plans to create a dedicated neuroscience venture fund to support continued efforts to advance the field and that more details on the fund will be forthcoming this year.

Pfizer belongs to the Dementia Discovery Fund, a research initiative launched in March 2015 to boost investment to tackle dementia by bringing together major pharmaceutical companies, the UK government and Alzheimer's Research UK. At the time of the fund's launch, Pfizer's pipeline in neuroscience and pain included 14 programs in Phase I and II as well as a number of preclinical programs.

Programs set to be terminated are preclinical, early and mid-stage clinical programs mainly focused on Alzheimer's and Parkinson's, but Pfizer could license them out to interested parties.

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CSL Looks Beyond Organic Growth

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CSL Ltd. is not a typical biopharmaceutical company, given its plasma collection business and plasma-derived product expertise, but it has the same goal as many of its peers – to bring in more external innovation that augments the company's organic growth.

The Australian specialty pharma firm has an American CEO, Paul Perreault, who is based in Pennsylvania but spends most of his days on the road, traveling to CSL's dozens of office and manufacturing sites around the world. *Scrip* spoke with Perreault during the J.P. Morgan Healthcare Conference in San Francisco this month to talk about CSL Behring's global strategy.

The company reported $7bn in revenue for fiscal year 2017, which ended on June 30, representing a gain of 15% on a constant currency basis from 2016; its net profit after tax (NPAT) was up 24% year-over-year at $1.3bn. The company's NPAT forecast for fiscal 2018 is $1.48bn to $1.55bn and revenue is expected to rise 8% on a constant currency basis.

"Up until the last couple of years, most of what we've done is organic growth from hard-to-manufacture plasma proteins," Perreault said. "Now we have growth from new product launches and our specialty portfolio."

Its top sellers are *Privigen* (immune globulin intravenous) and *Hizentra* (immune globulin subcutaneous) for primary immunodeficiencies, which grew 14.1% year over year in fiscal 2017 to $2.8bn; hemophilia therapies, including the recombinant drugs *Idelvion* (coagulation factor IX) and *Afstyla* (antihemophilic factor VIII), which grew rose 4% to $1bn; and specialty medicines, such as *Kcentra* (human prothrombin complex concentrate) for warfarin reversal and *Berinert* (human C1 esterase inhibitor) for hereditary angioedema (HAE), which jumped 20% to $1.2bn.

The company's HAE portfolio grew in 2017 following US FDA approval in June for *Haegarda* (subcutaneous human C1 esterase inhibitor). CSL also sells albumin, for which revenue rose 7% to $840m, and vaccines through its Seqirus vaccine business, which primarily sells flu vaccines and saw revenue rise 23% to $900m in fiscal year 2017.

CSL employs about 21,000 people globally, including 8,500 people alone who work in plasma collection. More than half of CSL's employees are involved in raw materials and manufacturing. The company has about 1,500 people involved in sales and marketing with another 1,400 working in research and development. However, it's R&D operations have grown significantly in recent years.

CSL112 LEADS GROWING R&D COMMITMENT

The company will soon begin the largest clinical trial in its history – a $500m Phase III study known as AEGIS-II that will enroll 17,000 patients to test CSL112's ability to reduce cardiovascular events in the first 90 days after a heart attack. Patients will receive four infusions of the therapy in the hospital and rehabilitation center as they recover from a heart attack. The Phase IIb study AEGIS-I was able to confirm CSL112's mechanism of action, but it was not large enough to prove the drug's efficacy.

CSL112 is a novel formulation of plasma-derived Apolipoprotein A-I (apoA-I) that works to enhance cholesterol efflux capacity (CEC), the process by which cholesterol is removed from plaque and transported to the liver for elimination from the body. "Five or six years ago, I might've said we may partner this product. Back then we were only spending $300m per year on R&D. Now, we have grown so much we can afford it," Perreault said, noting that CSL's R&D budget now stands at $800m per year.

The company intends to retain the full economics associated with CSL112, which could address an unmet need in a reasonably large market. It's estimated that of the 800,000 people that have heart attacks in the US each year, one in five will have another cardiovascular event within a year and most of those will occur within the first 90 days.

"Nothing has reduced major adverse cardiac events in that first 90 days," Perreault said. "If we reduce that by even 15% it will be a blockbuster. It could have a great effect for patients, economically and for the company." But the CEO explained that CSL is looking to further diversify its portfolio beyond plasma-derived medicines, both internally and through partnerships.

SIGNING DEALS, BUYING NEW MODALITIES

The company signed a deal with **Momenta Pharmaceuticals Inc.** a year ago that was worth $50m up front and as much as $550m in milestone fees for a global license to develop M230, a recombinant immunomodulator of Fc receptors, which could improve on intravenous immunoglobulin (IVIG).

More recently, CSL paid $15m up front in early December to enter into a collaboration agreement with **Vitaeris Inc.** for the development of clazakizumab in the prevention of solid organ transplant rejection. CSL retained an option to buy Vitaeris, which acquired the interleukin-6 (IL-6) inhibitor from **Alder BioPharmaceuticals Inc.** in 2016.

The company also paid $91m up front and committed $325m in future payments in August to buy **Calimmune Inc.**, which is developing ex vivo hematopoietic stem cell gene therapies, including preclinical lead drug candidate CAL-H for sickle cell disease and beta-thalassemia.

Perreault said CSL's in-licensed or acquired therapeutic candidates should improve on the standard of care and provide savings for the health care system. The assets primarily will fall into the company's main therapeutic areas – immunology, hematology and coagulation, and specialty medicines – or adjacent areas, like transplant.

The Calimmune transaction checked a couple of boxes, because the lead product candidate is for rare, hematology indications and it's a combination cell and gene therapy.

"We're also interested in cell and gene therapy, because that's where everything's going," Perreault said, citing **Spark Therapeutics Inc.**'s newly approved gene therapy *Luxturna* (voretigene neparvovec-rzyl), hemophilia gene therapies in development by the likes of **BioMarin Pharmaceutical Inc.**, and novel cell and gene products from **Sangamo Therapeutics Inc.**

BioMarin and Spark both have gene therapies in development that could give CSL's hemophilia franchise a run for its money. The hemophilia space is facing potential upheaval following the entry of longer-acting intravenous clotting factors, such as CSL's Idelvion and Afstyla, and the recent approval of **Roche**'s *Hemlibra* (emicizumab), a weekly subcutaneous injection for hemophilia A.

Patients may be skeptical, as they're loyal to current therapies and wary about new products' safety, but payers are interested in less frequently dosed injectables rather than the current standard of care that requires frequent infusions.

Perreault said he has no doubt that gene therapies eventually will be approved as one-time treatments for hemophilia, but he noted that it could take a long time for the products to disrupt the global hemophilia market. He noted that in China, for instance, most patients don't receive treatment and those who do are treated on-demand with older plasma-derived clotting factors rather than prophylactically with recombinant factors.

"We're selling more plasma-derived factors than we ever have," Perreault said. "In a first-world country like the US or in Europe, gene therapies clearly will have an effect on the hemophilia market. It will take a long time elsewhere and there's a lot we can do in that time."

CSL is marketing the benefits of its recombinant factor Idelvion for hemophilia B, which can be dosed with up to three weeks between infusions versus competing longer-acting factors that can be dosed every two weeks, but sometimes need to be dosed once-weekly. The company continues to ramp up its promotion of both Idelvion and Afstyla, which is given once or twice weekly in hemophilia A, to help make up for the loss of revenue from **Bayer AG**'s recombinant factor VIII *Kogenate* for hemophilia A. CSL supplied the product as *Helixate*, but that contract ended, so the company is transitioning patients to Afstyla.

Perreault noted that the difficulty of developing and manufacturing cell and gene therapies is not enough to dissuade CSL. The company believes it can make inroads in those areas, because of its experience manufacturing plasma-based therapies and complex biologics.

"We have experience manufacturing tough stuff," Perreault said.

He noted that raw materials and manufacturing comprise 65% of CSL's costs, because of the company's plasma collection business and its production of complex products. That's why CSL is careful about what it spends on R&D and reviews the pipeline twice each year to determine which products should be accelerated, decelerated or stopped altogether.

"It's not so much how you spend, but what you spend it on," Perreault said. "You have to be thoughtful about where you spend the money."

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Novartis Finds All-Important Head Of Oncology Business At Pfizer

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With the development and commercialization of cancer therapies becoming ever more important to the success of pharmaceutical companies, the Swiss multinational **Novartis AG** has turned to its fellow big pharma, the US company, **Pfizer Inc.**, to recruit Elizabeth (Liz) Barrett as the head of its oncology business.

Barrett is currently global president of oncology at Pfizer, and has been appointed CEO of Novartis Oncology and a member of Novartis's executive committee effective Feb. 1, 2018. She will be based in Basel, Switzerland, and will succeed Bruno Strigini, who announced in mid-December 2017 that he was retiring from Novartis, and the industry, for personal reasons.

Barrett will be starting work at Novartis at the same time as the company's current chief medical officer and global head of drug development, Vasant (Vas) Narasimhan, succeeds Joseph Jimenez as CEO; she will become one of only a few female executives to reach the top echelons of the company, although the Novartis board is more balanced.

Barrett is joining Novartis at a key time for its oncology business, with the company having gained US approval for its groundbreaking CAR-T therapy, *Kymriah* (tisagenlecleucel) in August 2017. The Switzerland-headquartered company will be addressing patient access and commercialization issues with Kymriah on a worldwide basis for some time to come, and this will include the setting up of treatment centers and negotiating decisions on pricing and reimbursement.

Consequently, planning for the commercial positioning and success of Kymriah is likely to be near the top of Barrett's in-tray. The drug has been tagged a potential blockbuster, particularly if further studies in additional indications are successful. Another potential anticancer blockbuster being introduced by Novartis into markets worldwide is the cyclin-dependent kinase 4/6 inhibitor *Kisqali* (ribociclib), which is competing with Pfizer's commercially successful CDK4/6 inhibitor, *Ibrance* (palbociclib) and **Eli Lilly & Co.**'s abemaciclib.

Novartis also has checkpoint inhibitor, the PD-1 inhibitor, PDR001, in Phase III studies in melanoma and neuroendocrine tumors. Speaking at a meeting in the middle of last year, Barrett noted that combining multiple immune-oncology medicines and targeted therapies would likely be the winning strategy for the treatment of cancer.

Barrett is a "highly accomplished and recognized oncology and business leader, with an impressive record of building successful business organizations in the US, Europe, and globally," commented Narasimhan in a statement issued Jan. 11. "She has been instrumental in creating new commercial models, driving innovation in close partnership with R&D, and leveraged business development opportunities," he added. Before joining Pfizer in 2009, Barrett worked at **Cephalon Inc.** and **Johnson & Johnson**, and started her career at Kraft Foods Group Inc. in 1984.

Novartis chose the same day to announce that its head of global regulatory affairs, Robert Kowalski, would assume interim leadership of the company's drug development organization from Feb. 1, 2018, one of the positions to be vacated by Narasimhan. The definitive new head of global drug development will be announced in due course, the company said.

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Lynparza Gets First Mover Advantage In BRCA-Positive Breast Cancer

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Commercial prospects for the six-month-old global collaboration between **AstraZeneca PLC** and **Merck & Co. Inc.** to jointly develop and commercialize AZ's *Lynparza* (olaparib) got a big boost Jan. 12 when the FDA expanded use of the PARP inhibitor to include treatment of patients with metastatic breast cancer who have a mutated BRCA gene, the first such regulatory approval globally.

The okay was based on data from the randomized, open-label, Phase III OlympiAD trial which found olaparib monotherapy had a positive effect on progression-free survival when compared with "physician's choice" chemotherapy (capecitabine, vinorelbine, eribulin), in 302 patients with HER2-negative metastatic breast cancer with germline BRCA1 or BRCA2 mutations, which are predicted or suspected to be deleterious. It showed that Lynparza significantly prolonged progression-free survival compared with chemotherapy and reduced the risk of disease progression or death compared with chemotherapy by 42%.

Lynparza is also approved in the US for treatment of BRCA-positive ovarian cancer in patients who are in complete or partial response to platinum-based chemotherapy.

"This is the first time this class of drugs, PARP inhibitors, has been shown to work in a tumor other than ovarian cancer. This is encouraging as we work through other Phase III studies in prostate and pancreatic cancer," an AstraZeneca spokesperson told *Scrip*.

FIRST MOVER ADVANTAGE

The latest approval makes Lynparza the first personalized treatment option specifically for BRCA-mutated breast cancer patients, and gives the medicine a crucial first mover advantage in a field considered wide open and one that offers blockbuster sales potential.

"First-to-market status is crucial for Lynparza, as competing PARP inhibitors *Zejula* (niraparib) from **Tesaro Inc.** and **Medivation Inc.**'s talazoparib are currently in Phase III development for breast cancer patients and **Clovis Oncology Inc**'s *Rubraca* (rucaparib) is slated to begin Phase III trials in combination with **Bristol-Myers Squibb Co.** *Opdivo* (nivolumab) later this year," Datamonitor Healthcare analyst Zachary McLellan said.

The approval is important not only for Lynparza but the PARP inhibitor class as a whole, as the first approval in an indication other than ovarian cancer. Lynparza currently has a list price, or a whole acquisition cost (WAC), of $13,886 for a 30-day supply of the 150mg tablet. Sales of the product for ovarian cancer in the first nine months of 2017 were $197m. "Label expansions into other indications are important for companies developing PARP inhibitors as a way of increasing target patient populations and differentiating their products," McLellan noted.

Due to its relatively large prevalence, breast cancer is a potentially lucrative expansion opportunity for PARP inhibitors beyond ovarian cancer, particularly if subsequent expansions include patients regardless of mutation status."

AstraZeneca and Merck said the duo hoped to build quickly on Lynparza's latest regulatory success and advance their pact, entered last July, to jointly develop and commercialize AZ's anticancers Lynparza and selumetinib. The partnership with Merck & Co brought AstraZeneca an upfront payment of $1bn, with up to $750m payable in license options and up to $6.15bn in regulatory and sales milestones. The UK company will book sales of Lynparza and share the gross profits with its partner, recording this under cost of sales.

A spokesperson for Merck told *Scrip* the latest FDA approval "adds further impetus to our collaboration with AstraZeneca in developing cancer therapies."

AstraZeneca's spokesperson said that "together with Merck we have the broadest clinical development program of any PARP inhibitor – and we believe there is much more to look forward to from Lynparza in the coming years, not least into immuno-oncology combinations, as well as potential multiple cancer types."

In the US, approximately 155,000 women have metastatic breast cancer, the most advanced stage of breast cancer. Approximately 5-10% carry a germline BRCA mutation and these patients are often younger than other breast cancer patients.

"While there is no cure for metastatic breast cancer, today's approval makes a new targeted treatment available to women with gBRCAm metastatic breast cancer to further delay disease progression in an area of high unmet need," the AstraZeneca spokesperson said.

OTHER PARP PLAYERS

Clovis Oncology Inc.'s PARP inhibitor Rubraca was approved in the US in late 2016 for advanced ovarian cancer patients who have received at least two prior lines of chemo and whose tumors harbor the BRCA mutation. It's US marketing application as maintenance therapy for women with recurrent ovarian cancer who are platinum-sensitive, and in a complete or partial response to platinum-based chemotherapy, is currently under FDA review with an action date of April 6.

Tesaro's Zejula was approved in the US in March 2017 for the maintenance treatment of recurrent epithelial ovarian, fallopian tube and primary peritoneal cancers in patients who are in complete or partial response to platinum-based chemo regardless of their BRCA status. It was approved in Europe in November 2017 for the same indication.

BeiGene (Beijing) Co. Ltd. has a PARP candidate, BGB-290 (pamiparib), in Phase II development aimed at the China market. Other players include **Pfizer Inc.** with talazoparib, China-based **Zai Lab Ltd.**'s ZL-2306 and **AbbVie Inc.**'s veliparib.

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All Systems Go As Roche MS Drug Ocrevus Secures EU Okay At Last
http://bit.ly/2B5GwR5

Novartis' Cosentyx Goes Head-To-Head With Humira

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Novartis incoming CEO Vas Narasimhan

Shutterstock: Novartis

Novartis AG has begun two head-to-head trials looking to show superiority of *Cosentyx* (secukinumab) over the world's biggest-selling drug – **AbbVie Inc.**'s *Humira* (adalimumab) – for the treatment of ankylosing spondylitis (AS) and psoriatic arthritis (PsA).

Thanks to its success as a treatment for psoriasis, Cosentyx is already a big earner for the Swiss major, bringing in third-quarter sales of $556m, a leap of 83% on the like, year-earlier period. However, Novartis sees a lot of potential in expanding the other autoimmune indications it is approved for, namely AS and PsA, and taking on Humira forms a large part of that strategy. *(Also see "Novartis Champions Cosentyx With More Long-Term Psoriasis Data" - Scrip, 30 Nov, 2017.)*

EXCEED STUDY

First up is the EXCEED trial, evaluating Humira versus Cosentyx in over 800 biologic-naïve patients with PsA. The primary endpoint will assess statistical superiority for ACR 20 response rates at one year, while secondary endpoints, all at 52 weeks, include PASI 90 (a clearness of skin scale), ACR 50 and resolution of enthesitis, where tendons or ligaments insert into bone.

The second study, SURPASS, is a head-to-head superiority trial in AS patients of Cosentyx versus a Humira biosimilar developed by Novartis' Sandoz division which is currently under review by the European Medicines Agency. Slowing spinal bone damage is the primary endpoint in AS and Novartis noted in a statement that the "effect on progressive structural damage of the spine is one of the important attributes clinicians look for when assessing the performance of AS treatment options."

Novartis told *Scrip* that the use of its own proposed biosimilar of Humira is supported by strong data confirming that it matches the reference medicine's safety and efficacy profile, including 52-week data presented at the European Academy of Dermatology and Venereology congress in Geneva in September. 800 individuals will participate in the trial, meaning SURPASS will be the largest randomized, controlled study of a biologic in AS, the company added.

Novartis quoted Robert Landewé of Amsterdam Rheumatology and Clinical Immunology Center and the Zuyderland Medical Center, Heerlen, the Netherlands, as saying that the EXCEED and SURPASS trials "are addressing important clinical questions solving residual uncertainty for patients with PsA and AS." He added that "head-to-head trials deliver the most robust data helping to advance clinical practice and are key to clinical decision making. In this case, these data would add to the body of evidence to underline the benefit of different biologic pathways for physicians."

Vas Narasimhan, Novartis chief medical officer who will take over as CEO from Joe Jimenez later this month, pointed out that patients living with PsA and AS cannot enjoy a normal life as they are experiencing persistent pain and fatigue, and are at risk of long-term mobility loss. These patients "deserve the best treatment possible and we are hopeful that the EXCEED and SURPASS trials will provide valuable answers for doctors and patients in their decision-making."

EARLIER USE

The decision-making that Novartis will ideally want to see would involve Cosentyx, the only interleukin-17A inhibitor approved to treat AS, PsA and psoriasis, being prescribed earlier on the treatment pathway. In a recent note, Datamonitor Healthcare analyst Ines Mihel wrote that Cosentyx was displacing **Johnson & Johnson**'s *Stelara* (ustekinumab) as the preferred biologic option in the post-tumor necrosis factor (TNF)-failure setting for managing joint symptoms (Stelara is approved for PsA but not AS), but with EXCEED, Novartis is aiming to challenge Humira's status as the preferred first-line biologic.

However, Mihel expects that should Cosentyx demonstrate superiority over Humira, "patient and physician familiarity with the biologic alongside the increasing availability of anti-TNF biosimilars will limit the use of Cosentyx in the first-line biologic setting." On the latter point, she added that even if the trials go well, Cosentyx uptake will also be challenged by biosimilars of *Enbrel* (etanercept) and *Remicade* (infliximab).

FIERCE COMPETITION

Biosimilars of the latter two biologic blockbusters are already approved for PsA and AS which, along with copies of Humira, "are likely to generate fierce pricing competition" she added, and Novartis would need to offer similar discounts to the new versions of the anti-TNFs. *(Also see "Humira Biosimilar: Boehringer Faces Same Launch Hurdles As Amgen" - Pink Sheet, 28 Aug, 2017.)*

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Ferring Forges Fertility Pact With Chinese Academy Of Sciences

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Switzerland's **Ferring Pharmaceuticals AS** is looking to cement its place as one of the world's leading fertility companies by collaborating with the Chinese Academy of Sciences (CAS) to develop reproductive medicines.

As part of the agreement unveiled Jan. 10, a new jointly funded laboratory called the Ferring Institute of Reproductive Medicine will be created within the CAS research facility in Beijing. The partners said in a statement that the aim of the long-term pact was to find solutions to address global challenges in both male and female fertility and high rates of obstetric complications by exploring novel technologies in stem cell and regenerative medicine.

Ferring

In an interview with *Scrip*, Ferring's chief scientific officer Per Falk, noted that "about half of everything we do, both for what we sell and what we research, is about reproductive health, addressing the problem of infertility a global major global issue but one that is not highlighted as it is not considered a disease". Its societal impact is huge, however, he added, with one in six couples worldwide experiencing infertility problems".

Falk noted that in China, "there is a strong awareness of falling fertility rates in the country that it is going to hurt them and it is high on the national health agenda." However he stressed that the CAS link-up was not driven by a desire to expand Ferring's footprint in China but the opportunity to tap into the academy's expertise.

"We were looking for the strongest and most advanced research platform that addresses male and female infertility and pregnancy" and the CAS has led the way. "It is one of the biggest national research institutes on the planet with world-class researchers and world-class resources," Falk said, adding that a team of "hundreds of scientists" led by the CAS' Qi Zhou and Hongmei Wang, "have led scientific exploration in the area over several years."

As such, "the CAS is not just a China-leading research group but a world-leading research group, one of the top three in terms of publications and grants," he told *Scrip*. "It is a tremendous opportunity for us to be able to work with them".

Financial details were not disclosed but Falk stressed that it was a substantial investment on both sides in terms of cash and scientifically. "It is not a traditional public/private enterprise where pharma donates money in exchange for getting access to what comes out, we will shape the research program together."

Ferring's principal role will "be the translational part", he said, developing actual therapies from the excellent early basic research going on at the CAS in areas such as stem cells. In a statement, Wang, who is the director of the State Key Laboratory of Stem Cell and Reproductive Biology at the CAS, concurred, saying the collaboration would "expand our research base into the translational space and together we will rapidly expand our tool set to look at truly transformational ideas in reproductive medicine."

Ferring intends to be "the world's leading reproductive medicines company; at the moment we are one of the leading companies," Falk said, adding that in addition to the pact in China and the St Prex-headquartered firm's own pipeline, more partnerships will happen to achieve this goal. "We aspire to be the go-to company for others who have good ideas and we will invest heavily."

CHANGE OF STRATEGY

This represents something of a change in strategy for Ferring, which has grown organically over 68 years into a company with revenues of around €2bn with 7,000 employees. "We have realized that there is a big world out there and we need to become part of the innovation network, working with biotechs and being much more active in externally sourcing new products," Falsk said. "It is the only way any pharmaceutical company can survive these days."

Falk also spoke about Champion, a collaboration with the World Health Organization and Merck for Mothers, that began in 2014 to tackle post-partum hemorrhage (PPH) which claims the lives of 100,000 women each year.

Champion is the world's largest clinical trial in maternal health and aims to demonstrate the effectiveness of Ferring's heat-stable carbetocin in preventing PPH, compared with oxytocin, which is the current standard of care.

The CSO was equally enthusiastic about a research collaboration with the Karolinska Institute in Sweden looking at pre-term labor and infertility from the perspective of the microbiome. This should lead to new approaches to diagnose, treat and prevent pregnancy complications.

Privately-held Ferring is "a rare breed," Falk concluded, as it is one of the few companies, along with **Merck KGAA** and **Merck & Co. Inc.**, that is committed to fertility treatment and "while others come and go, we will be staying for the long-term."

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Forty Seven's IO Antibody Attracts Two Big Pharma Partners

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Californian biotech **Forty Seven Inc.** has caught the attention of two of Europe's biggest immuno-oncology players, **Merck KGAA** and **Roche**, both of which have signed deals to trial their approved PD-L1 inhibitors with Forty Seven's investigational CD47 antibody.

Forty Seven, a clinical-stage company focused on developing "next generation" IO treatments, announced both deals on Jan 11. The agreements cover various cancer indications and will see the launch of three new combination clinical trials.

Through its deal with Roche, **Genentech Inc.** (a Roche company) will sponsor two clinical trials combining Forty Seven's cluster of differentiation 47 (CD47) antibody, Hu5F9-G4, with Roche's programmed death-ligand 1 (PD-L1) antibody, *Tecentriq* (atezolizumab), in patients with acute myeloid leukemia and with urothelial cancer.

A Roche spokesperson told *Scrip* that there is a need for new treatments in both indications, particularly for elderly patients or patients with compromised organ function who are not able to withstand chemotherapy. "Combining Forty Seven's anti-CD47 antibody's ability to engage both the innate and adaptive immune system with a T-cell checkpoint inhibitor represents a strategy to potentially enhance their efficacy in difficult to treat solid and hematologic tumors, such as bladder cancer and AML," they noted.

Genentech will supply atezolizumab and conduct both studies while Forty Seven will supply Hu5F9-G4 and share in the costs. Financial details of the deal were not disclosed.

Tecentriq is already approved as a treatment for urothelial (bladder) cancer and non-small cell lung cancer. The drug has not been approved for AML, but Genentech has other early-stage combination trials ongoing in this setting, in partnership with **BioLineRx Ltd.**

Hu5F9-G4 is Forty Seven's lead program; it is currently being evaluated in several clinical studies in patients with solid tumors, acute myeloid leukemia, non-Hodgkin's lymphoma and colorectal cancer.

Hu5F9-G4 engages the innate immune system and PD-L1 inhibitors engage the adaptive immune system, where most immuno-oncology drugs are looking to induce an immune response. CD47 is an immune modulator molecule overexpressed on cancer cells that sends inhibitory signals to macrophages. Binding of Hu5F9-G4 to CD47 takes the brakes off macrophages enabling them to phagocytose, or swallow, tumor cells.

"*In vivo* the adaptive and innate immune systems work together in concert. Forty Seven is pursuing an orthogonal and potentially complementary approach by attempting to incorporate the macrophage component of the innate immune system into the immuno-oncology armamentarium," Craig Gibbs, chief business officer at Forty Seven, told *Scrip*. He highlighted that Hu5F9-G4 is already being tested in five clinical studies.

MERCK ARRANGEMENT

Elsewhere, Merck (which in the US and Canada operates as **EMD Serono Inc.**) and Forty Seven will conduct a Phase Ib trial combining Hu5F9-G4 with *Bavencio* (avelumab), also a PD-L1 inhibitor, in patients with ovarian cancer.

Ovarian cancer patients have limited treatment options and are often diagnosed at a late stage in their disease.

Alise Reicin, head of global clinical development at Merck, noted that the company has two ongoing registrational studies exploring the role that Bavencio could play both as a monotherapy and in combinations in ovarian cancer. "This collaboration enhances our strategic approach to novel IO combinations in this disease setting. We are hopeful that through these efforts we will discover viable options to help patients with this hard-to-treat cancer," she said.

Bavencio is approved for bladder cancer and Merkel cell carcinoma.

Under this agreement, Forty Seven will conduct the clinical study for the combination therapy while Merck will provide avelumab. The two companies will share costs; no financial information was provided.

FORTY SEVEN'S BACKGROUND

Forty Seven, a spin-out company from Stanford University, raised $75m in venture capital funding through a series A round in March 2016 and a further $75m via a series B in October 2017. The series B financing was led by new investor Wellington Management Company LLP with participation from existing investors Clarus, Lightspeed Venture Partners, Sutter Hill Ventures and GV (Google Ventures).

"Forty Seven continues to make tremendous progress across multiple clinical trials," CEO Mark McCamish said upon the closing of Forty Seven's series B round. "The financing allows us to rigorously explore the clinical response of different tumors to Hu5F9-G4 mono- and combination therapy and determine the optimal pathway to rapidly bring this new treatment option to patients."

There are two monotherapy trials ongoing for hu5F9-G4 in solid tumors and AML; two combination studies with tumor targeting antibodies (rituximab and cetuximab) in non-Hodgkin's lymphoma and colorectal cancer; and one combination trial with azacytidine in AML. The three combination studies with Genentech and Merck will launch this year.

WIDER CD47 PIPELINE

CD47, also known as integrin associated protein (IAP), is a transmembrane protein in the immunoglobulin superfamily that partners with membrane integrins and binds the ligands thrombospondin-1 (TSP-1) and signal-regulatory protein alpha (SIRP-alpha). CD47 is commonly involved with immune and angiogenic responses and overexpressed in some cancers.

Forty Seven's founders, Irv Weissman and Ravi Majeti, were the pioneers that discovered CD47 as an oncology target; the company maintains leadership in the field with Hu5F9-G4. There are currently no CD47 antibody products on the market but there are a handful of drug candidates in the clinic. Hu5F9-G4 is the most advanced asset, with Phase I/II trials ongoing.

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Allergan, Shire Battle In Dry Eye As Generics Advance

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Dry eye disease was a relatively quiet therapeutic category with **Allergan PLC**'s *Restasis* (cyclosporine ophthalmic emulsion) the only approved drug in the US and Europe for many years, but now the area is poised for activity in the aftermath of the 2016 US approval of a second drug, **Shire PLC**'s *Xiidra* (lifitegrast). Allergan and Shire own the roughly $1.7bn market niche, for now, but that's about to change as new drugs and generics reach the field.

According to Biomedtracker's drug development database, 22 companies – including Shire and Allergan – have 27 drug candidates in clinical development for dry eye. **Kala Pharmaceuticals Inc.**'s anti-inflammatory approach, **Aldeyra Therapeutics Inc.**'s aldehyde trap drug and **Ocugen Inc.**'s steroid combination product are among the candidates that have advanced to mid- to late-stage development.

Besides potential new branded competition, the market is poised for further upheaval as generic competition to the blockbuster Restasis is expected in the US in 2018, following the US District Court for the Eastern District of Texas's ruling invalidating four Allergan patents for the drug on the ground of obviousness.

Allergan had attempted to stave off generic competition in September with a deal transferring rights to four Restasis patents to a Native American tribe, but that dramatic effort drew a lot of negative publicity and has not worked out as hoped. **Teva Pharmaceutical Industries Ltd.**, **Mylan NV**, **Akorn Inc.** and **InnoPharma Inc.** are among the companies that have been jockeying to bring a generic version of Restasis to market.

BOLSTERING RESTASIS

Restasis has been one of Allergan's most important growth brands in recent years. Knowing that external branded competition like Restasis was around the corner, along with the generic threat, Allergan had been bulking up its eye care sales force and bolstering the dry eye franchise with a multi-dose, preservative-free formulation of Restasis (approved in October 2016 and launched in March 2017), along with a planned pilot launch of *True Tear*, an intranasal stimulating device approved by FDA in April 2017 to temporarily increase tear production.

An Allergan spokesman told *Scrip* that the pilot launch to selected customers will help develop the training materials needed for a larger rollout of the product, which is a big change to the treatment paradigm by adding a device component. Allergan acquired True Tear in its $125m buyout of **Oculeve Inc.** in 2015.

Chief Commercial Officer William Meury said back in 2016, just after the Xiidra approval, that the specialty firm would back up the expanding eye care franchise with an increased sales force detailing to ophthalmologists and optometrists, along with extensive consumer advertising and education as it braced for more competition.

"We increased the size of our salesforce by 20%, essentially adding 60 more representatives," Meury said during the August 2016 earnings call. "We increased the investment in direct-to-consumer advertising. The sampling program both on Restasis as well as in our artificial tears has been increased."

But with Shire launching Xiidra with pricing at par with Restasis, Allergan hasn't been able to avoid the impact entirely, and now it's bracing for the even bigger blow of generics.

Sales of Restasis did moderate immediately following the launch of Xiidra, although Restasis continued to be a growth product, thanks in part to market expansion. Part of Shire's strategy entering the market was to grow the overall dry eye market through consumer education efforts, like the "Eye Love" TV commercials featuring Jennifer Aniston as a spokesperson. Restasis sales grew 13% year-over-year in the third quarter of 2016, after the entry of Xiidra, lower than the growth rate seen during the previous quarter, but still in line with the double-digit growth Allergan was projecting for the ophthalmic franchise overall.

Meury called Restasis' sales performance "durable" during the early launch of Xiidra. "Overall, the dry-eye market has expanded significantly since the launch of a second treatment option," he said during a Nov. 2, 2016, quarterly call.

Ultimately, Restasis sales totaled nearly $1.5bn in 2016, with more than 90% of that accrued in the US market, but sales have plateaued in 2017. Restasis generated $1.06bn in the first nine months of the year, a decline of 1.6% over the first nine months of 2016. Morningstar forecasts that sales of Restasis will be flat for the year. Shire's Xiidra is expected to make up some of the difference in 2018 as Restasis goes generic and eventually outpace Restasis sales in 2019 with its market share growing through 2021.

Allergan is preparing for the impact of generic competition to Restasis with models accounting for loss of exclusivity at the beginning of 2018 and at mid-year.

The company has said that Allergan's eye care portfolio represents more than $2bn in annual worldwide sales even without Restasis and anticipates that its LOE exposure due to that product will be felt mainly in 2018. After the Restasis patents were invalidated, Allergan took an impairment charge in the third quarter 2017 of $3.2bn related to Restasis.

BUILDING XIIDRA BY GROWING THE MARKET

Since its launch in mid-2016 as the first drug approved to treat the signs and symptoms of dry eye disease, lifitegrast – a lymphocyte function-associated antigen 1 (LFA1) antagonist – has ramped up gradually, partially behind a Shire strategy to grow the market through disease-awareness efforts. *(Also see "Shire's Xiidra Gets Advantageous Label Covering Signs, Symptoms Of Dry Eye Disease" - Pink Sheet, 12 Jul, 2016.)* Restasis, approved in 2002, is indicated to increase a patient's natural ability to produce tears.

Xiidra yielded $54m in sales in 2016 and brought in $173m during the first three quarters of 2017. Prescription demand increased 9% from the second quarter to the third quarter in 2017, Shire reported during its third quarter earnings call Oct. 27, 2017, with Xiidra capturing 23% of US market share to date. *(Also see "Shire Touts Ongoing Xiidra Growth, Targets Increased Medicare Access" - Scrip, 27 Oct, 2017.)* Overall, the dry eye market has increased 29% in 2017 compared to 2016, which Shire attributes both to Xiidra's broader label and its awareness campaign.

Morningstar projects that Xiidra will total $258m in sales this year and then begin growing more steeply as Shire adds international markets. The company obtained regulatory approval in Canada on Jan.3, 2018, expects approval in Israel in the near-term, plans a regulatory filing with the European Medicines Agency in 2018 and is progressing with a filing for Japanese approval, CEO Flemming Ornskov noted during the conference call.

Expansion in international markets will help Shire reduce its exposure to competition from generic versions of Restasis in the US.

Market analysts generally see the story playing out the way the two companies anticipate. In an Oct. 27 note, Morningstar analyst Karen Andersen pointed to Xiidra as one of Shire's stronger performers during a mixed quarter and predicted ongoing growth. "Double-digit dry eye market growth and a potential European launch in late 2018 bodes well for Xiidra's long-term strength, despite the prospect of generic Restasis," she wrote.

Credit Suisse analyst Vamil Divan has adopted a base case assuming generic competition to Restasis at the beginning of 2018, which would play a significant role in reducing Allergan's 2018 earnings per share to $15.25 from a previous estimate of $16.55. He anticipates "a relatively rapid erosion" in Restasis sales, with US revenues dropping to about $360m in 2018, Divan said in a Nov. 5 note.

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In Dry Eye, A Variety Of Mechanisms Pursue Established Therapies
http://bit.ly/2Dfo260

Truffle Primes BioMedtech Fund With $102m

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France-based **Truffle Capital** got its new BioMedtech venture fund off to a good start with an initial raising of $102m (€85m) from European and Asian institutional, corporate investors and wealthy individuals and aims to raise a further $138m in a similar way before the end of the year, one of the private equity firm's co-founders told *Scrip*.

2018 FINANCING PLANS

Truffle Capital CEO Philippe Pouletty said the initial closing met strong demand from investors who are attracted by the group's 'hands on' business model of nurturing start-ups in France that offer disruptive technologies in life sciences and information technology. "Truffle Capital attracts prominent investors, scientists, engineers, clinicians and entrepreneurs who share its vision," he said.

Based on other investments in discussion or already confirmed, Pouletty said he was confident Truffle would meet its $240m financing target for the BioMedTech fund in 2018. "It might take two more [finance round] closings to reach $240m but we're quite optimistic it will happen this year, with the next one probably before summer" Pouletty told *Scrip*.

FUND COMPOSITION

He said the BioMedTech venture fund's investment profile would be 70% medtech and 30% biotech, adding "our clinical pharmaceutical areas of focus are infectious disease, inflammation and dermatology."

He said Truffle's entrepreneur-investor business model had worked well in the past, as demonstrated by recent successful start-ups such as **Vexim SAS, Carmat SAS**, **Symetis SA,Pharnext SA, Carbios** and **Abivax**, all founded or cofounded by Truffle Capital, alongside highly qualified and experienced management and research teams.

"The way we work is we screen early stage IP both in the US and Europe with some 40 top-notch universities and either license on an exclusive, worldwide basis technologies that we believe are of strong medical potential."

Truffle BioMedTech aims to create start-ups in France, each with the ambition to become a global leader thanks to a disruptive and life-changing medical device, drug or healthcare product.

For each start-up, Truffle Capital sets up an ambitious R&D team, an experienced management team, and attracts co-investors to promote growth to advanced clinical, manufacturing and commercial stages."

"We create the companies in France, firstly because France today is the best start-up environment in Europe, with a lot of available non-dilutive financing, and secondly because we are a very 'hands-on' group and it would be very difficult to oversee startups from a long distance and its best to operate in an ecosystem you know best."

"Regarding clinical trials, we like to take a broader approach and conduct them in the US, Europe and in China."

12 STARTUPS PLANNED

The first thing Truffle did upon the fund's first closing was set up and finance three companies in France and overseen by the private equity group's partners: **HoliStick Medical**, chaired by Antoine Pau; **ArteDrone,** chaired by Alain Chevallier; and **Nanosive**, chaired by Pouletty, the latter being a biotech.

"We like to be very much involved, structuring the management team, the organizational plan while have an independent board of directors."

Pouletty declined to give details of Nanosive's business and therapeutic focus, saying only that it was based on technology invented at a US university that offers a novel way to deliver cardiac-related medicines. "Its product offering would be classified midway between biotech and medtech," he said without elaborating.

In total, a dozen companies are expected to be financed by the new fund once the targeted $240m has been raised. "We have already started three new companies this year and will probably launch a further three or four by the end of the year, and then in 2019 the remainder, either five or four, to make up an even dozen," Pouletty said.

Previous Truffle Capital funds have founded or co-founded and financed 20 medtech and biotech companies, 10 of which have been listed on stock markets and three of which have been acquired by corporate partners.

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Stock Scan December 2017: Teva Stick, Valeant Carrot Spur Generics Revival

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Big Pharma* Stock Trading Trends - December 2017

-25%

Planned cuts in staff at Teva

+27.9%

Increase in Teva stock after staff cuts announced

+2.9%

Average increase in stock value in December across Top 50 pharma

+$1,594

Winnings from daily pharma bets starting with a $1,000 stake ...

*Top 50 Companies By Annual Prescription Drug Sales

Yet again the volatile nature of generics stocks comes to the fore but, in December, that volatility was a force for good. Or, at least, a force for economic gain.

Valeant Pharmaceuticals International Inc. stock gained over 24% in the last month of 2017 as the company continued to demonstrate that it was actively dealing with its debt. In December, Valeant sold back its **Sprout Pharmaceuticals Inc.** subsidiary to former Sprout shareholders in exchange for royalties on the female libido-drug *Addyi* (flibanserin). More significantly, however, it extended the period of $1.5bn worth of its substantial debt by another five years to 2025, reassuring investors that it now actively managing its prevailing crisis.

Meanwhile, at **Teva Pharmaceutical Industries Ltd.**, CEO Kåre Schultz struck again.

> Valeant Pharmaceuticals International Inc. stock gained over 24% in the last month of 2017 as the company continued to demonstrate that it was actively dealing with its debt

The mere announcement of his arrival from **Lundbeck Inc.** back in September bumped Teva's market capitalization 17% *(Also see "Teva Lands A CEO: Can Schultz Replicate Lundbeck Success?" - Scrip, 11 Sep, 2017.)*. This time Schultz announced wholesale restructuring involving the loss of 14,000 jobs, a reduction of 25% across the Israeli company. The markets loved the prospect of the carnage, adding nearly 28% to Teva's market value in the month.

In effect, Schultz increased the value attributable to each future Teva employee by 37.5% in this one market-charming move.

SCRIP ANALYSIS

In general, December was a positive month for pharma. Across the top 50 pharma companies (ranked by drug sales), valuations grew 2.9% in the month. Thirteen companies' stock value grew more than 5% in December: only two – Sanofi and Allergan – shrank by 5%.

Allergan PLC was hit early in the month by the news from **Revance Therapeutics Inc.** that its Phase III trial had shown that its drug RT002, a rival to Allergan's *Botox*, reduced the severity of frown lines for almost twice as long as Botox did. RT002 is not yet approved, of course, and Revance still has to sign up a major pharma partner to help it market the treatment, but investors already discounted Allergan's stock nearly 6% in December.

Sanofi was hit by the suspension in the Phillippines of programs using its dengue vaccine, *Dengvaxia(Also see "Sanofi's Dengue Vaccine Gets WHO Backing In People Previously Infected" - Pink Sheet, 13 Dec, 2017.)*.

SCRIP ANALYSIS

The revival of the generics sectors is reinforced by December's day-trading simulation (see below). Either Teva or Valeant were the best bet on seven out of 19 trading days in December, with **Mylan NV**, **Fresenius SE &**

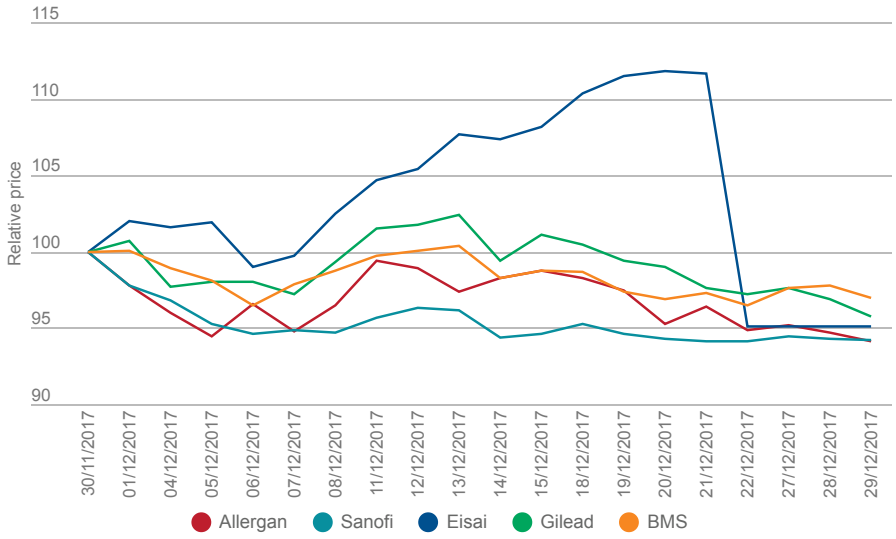
Why Stocks Changed

Company	Monthly rise	What happened
Teva	27.9%	Announces 14,000 (25%) staffing reduction across company
Valeant	24.1%	Refinancing debt removes uncertainties
Mylan	15.8%	Herceptin biosimilar approved by FDA
Hikma Pharmaceuticals	10.1%	Analysts back company after moves in biosimilars with Celltrion
Alexion	8.9%	Recovery following sharp decline in October/November
Lupin	8.2%	Recovery after regulatory setback at start of November

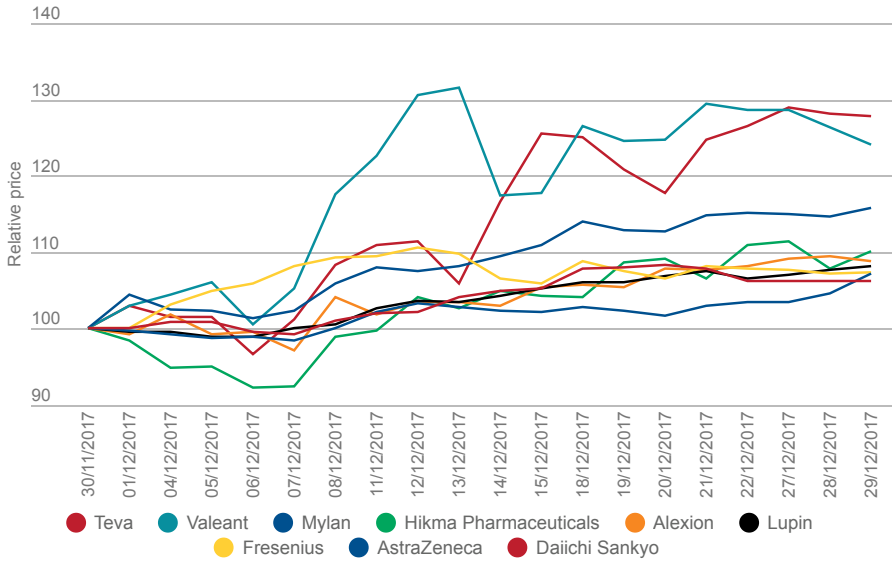
Company	Monthly fall	What happened
Allergan	-5.9%	Hit by positive Phase III for Revance Therapeutics' Botox competitor
Sanofi	-5.8%	Dengue vaccine withdrawal in Philippines
Eisai	-4.9%	Anti-amyloid antibody BAN2401 misses Phase II endpoint in Alzheimer's Study 201; partner Biogen marginally affected
Gilead	-4.2%	Erosion following immuno-oncology setbacks at ASH
BMS	-3.0%	Erosion following immuno-oncology setbacks at ASH

Winners and Losers In December

Losers



Winners



Co. KGAA, **Endo International PLC**, **Hikma Pharmaceuticals PLC**, **Sun Pharmaceutical Industries Ltd.** and **Dr. Reddy's Laboratories Ltd.** being the best bet on another eight days. Of course, its never as easy as all that, however. Generics companies – the big winners listed above, plus Cipla and Aspen – were also the biggest losers on 12 days in December. Day-trading is all about timing!

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Pharma Struggling To Assimilate Data

The time it takes to develop a new pharmaceutical is getting longer because of the sheer volume of data that is collected in clinical trials, despite the use of new data management technologies, claims a new US analysis.

The increase in drug development times is being blamed on the rising scope and complexity of clinical trial protocols, which has led to a growing volume of clinical data being collected from numerous and disparate data sources, says the lead author of the analysis, Ken Getz of the Tufts Center for the Study of Drug Development, in Boston, Massachusetts.

There are also concerns that clinical trial protocol changes, compatibility issues between different electronic applications, and the still relatively common use of paper case report forms, are also holding back progress, say the US researchers.

Finding ways to reduce the R&D data mountain have already been suggested by commentators, including advocating the use of machine reading and machine learning technologies, and other aspects of artificial intelligence.

The president of the EFPIA, **Merck KGAA**'s Stefan Oschmann, has targeted the better use of health data as one of the aims of his tenure at the association.

Industry regulators are also evaluating the use of big data, with a joint EMA/EU Heads of Medicines Agencies taskforce working on a strategy on the use of big data to support the development and assessment of medicines.

The time from the end of a study to completing data collection, referred to as the time from last patient, last visit to database lock, has increased from an average of 33.4 days in 2007 to 36.1 days in 2017, the Tufts analysis estimates.

Nearly a third of the 257 drug developers surveyed still use paper case-report forms.

john.davis@informa.com 10 Jan 2018

A Different Approach To Corporate Venture: An Interview With AbbVie Ventures' Scott Brun

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Before launching its own effort less than two years ago, **AbbVie Inc.** leadership gave significant thought to how it wanted to be different from other biopharma corporate venture arms, according to Scott Brun, a corporate vice president and head of AbbVie Ventures.

Brun moved to AbbVie Ventures after two decades in R&D for AbbVie and its predecessor **Abbott Laboratories Inc.** He recently spoke with Scrip about AbbVie Ventures' goals and strategy, and how it operates differently from the corporate venture arms run by other big pharma companies.

When AbbVie opened for business in 2013, it inherited a handful of venture investments from Abbott, but didn't hatch AbbVie Ventures until mid-2016. Current AbbVie CEO Richard Gonzalez headed Abbott Ventures before the spinout, and Chief Financial Officer William Chase "gave us the freedom" to prioritize access to "optimal science" rather than focusing on hitting a certain return on investment, Brun said.

But as a newer organization, AbbVie Venture's investments are less mature than those of peer companies' venture groups, although AbbVie made a splash in October by paying $205m up front to **Alector LLC** in a partnership around the start-up's portfolio of antibody candidates for Alzheimer's and other neurodegenerative diseases. *(Also see "AbbVie Goes Boldly Into Immuno-Neurology With Alector" - Scrip, 24 Oct, 2017.)* AbbVie had invested in Alector's Series D financing in 2016. To date, Alector is the only AbbVie Ventures' investment that has contributed something to the AbbVie pipeline.

An edited version of *Scrip*'s discussion with Brun follows:

Shutterstock: Sveta71

JOSEPH HAAS: *This is one of the newer corporate venture groups in pharma, since AbbVie was spun out in 2013. (Also see "Abbvie: A Glimpse Of What The New Biopharma Will Look Like" - Pink Sheet, 17 Oct, 2012.) When was it founded and what is its strategy?*

SCOTT BRUN: A little more than 18 months ago, we decided to really revitalize and re-energize our venture investing efforts at AbbVie. Part of it comes down to, fundamentally, we've got very productive laboratories and discovery efforts in AbbVie that resulted in therapies like *Mavyret* (glecaprevir/pibrentasvir) for hepatitis C or *Venclexta* (venetoclax) for the hematological oncology space, but when we look at our pipeline, more than half of it comes from external sources of innovation. And as science begins to move more and more rapidly, we acknowledge that while we have many bright and hard-working scientists, most breakthroughs aren't going to occur our labs. So our question is how do we best position AbbVie to be exposed and working with these innovators, these technologies, in order to ensure that we have novel opportunities for our own pipeline in our areas of interest?

What that translates to is that our corporate venture group is strategic in nature. We are not investing primarily to make money off of our efforts. We do not have a specific financial target. What we're looking to do is invest in early-stage biology, technologies and, frankly, people for projects that have the opportunity to complement our internal [focus] areas of R&D within oncology, neurodegenerative and autoimmune/inflammatory diseases.

So, unlike some other corporate venture groups – like I said, our primary remit is not financial – we are not agnostic. Some groups will use venture investing to explore white space, in areas where their companies are not active – but that's not what we're doing. We're using it to find the most innovative technologies in areas where we already have deep expertise.

JH: *What are AbbVie Ventures' goals for the companies it invests in?*

SB: We want to be able to provide value to the companies that we invest in, so we'll make minority equity investments – a less than 20% stake in a company – but through that, we want to have an ability to work with the board. That could be voting board seats or that could be as a board observer, because beyond the money, which companies can receive from many sources, what we want to do is provide connections to the broader AbbVie organization. Obviously, we've got R&D, commercialization, market-access expertise, and we would like to help companies to progress their technologies by giving them access to that expertise. We find that companies more often than not will take us up on that proposition.

So we're building relationships with entrepreneurs, with other institutional venture capitalists, with university tech transfer of-

fices, which even beyond the investments we make allow us to gain broad exposure to a range of opportunities. We don't have a dedicated fund – this year we did six new specific investments just on our own, and we did some more through Accelerator Corporation, in which we're a limited partner. We want to maintain that momentum moving forward.

Right now, our active portfolio consists of about a dozen companies – it's only been about 18 months since I came over from R&D to really focus our efforts, but we're looking to grow that portfolio. And what we hope will happen is that some of these investments will allow for evolution into business development opportunities.

We had a great example recently with a company called Alector, which started out as an AbbVie Ventures investment and has now turned into a business development partnership on two novel targets within neuroinflammation applied in Alzheimer's disease. That's the kind of evolution that we'd like to see coming out of our portfolio – but when we invest, we don't put any special rights on, such as rights of first refusal or options. We really invest for standard rights of the kind that any institutional investor would look for.

JH: *For your portfolio companies, is AbbVie Ventures the sole investor or do you put together syndicates?*

SB: We absolutely syndicate, be it in the earliest seed investments where we've done two this past year or when we're involved with Series A. There's been some where we've led, there've been others where we were invited to join the syndicate. We want to syndicate – we feel that institutional as well as other corporate venture groups have a lot that they can bring into these companies in terms of expertise, as well as leveraging risk through investment syndication. So, we're happy to invest with other corporate groups as well – we do not need to be the sole strategic investor.

JH: *With AbbVie Ventures not having a dedicated fund, how do you figure out what its investment bandwidth is for a given year?*

SB: In terms of our process, we try to keep things very streamlined. We have an investment committee that we meet with once a month, which includes Bill Chase, the chief scientific officer, the chief strategy officer and our general counsel. So it's four people and we will bring opportunities forward to them, and we're essentially trying to do about half-a-dozen new deals a year, to get us to a particular steady state with appropriate follow-on reserves. We've done some modeling and we track how much we're committing to in any given year. It equates to roughly half-a-dozen new investments a year with follow-ons and we're typically investing off the balance sheet.

JH: *What is the total volume of investments AbbVie Ventures has made so far, in terms of dollars?*

SB: We're in building mode right now. As we amass more investments, we're going to be getting to the point where our follow-on commitments are going to increase, so I think the number we've done [in 2017] would be a bit of an undercall. We want to be roughly in line with what some of the other leading [biopharma] venture groups do, somewhere on the order of $50m a year. Targeting a range like that should keep us amongst the most notable and active corporate VCs.

JH: *With no requirement to provide a certain return on investment and with the ability to "blue sky" your investments a little bit, how does that affect the decision-making in what you invest in?*

SB: What it allows us to do is focus on some of the innovation that is the most creative and has the greatest potential of markedly transforming care. If I'm talking about a personal investment portfolio, once I get to a certain point, I'm going to balance it with more risky plays – maybe emerging market stocks – but then I'll also have some fixed-income investments. We don't have to focus on more incremental opportunities – in other words, a reformulation of a drug or an existing target that is just being refined. We have other ways to access that with business development. With AbbVie Ventures, we're really on the frontier.

JH: *In situations where AbbVie Ventures leads the creation of a portfolio company, what is the ultimate goal? Might it differ from company to company, or are you looking to advance them to a certain inflection point, followed by an exit?*

SB: If a company feels it is in its best interests to go public, we will certainly support that. What our hope would be certainly is that we would get to the point where some form of partnership or other business development activity would make sense. And that's kind of varied depending on the stage of the company.

Provided that the science is progressing and the opportunity is moving forward, we absolutely are ready and excited to invest in follow-on rounds. A lot of it depends on the therapeutic area and how much information one needs to feel comfortable with a transaction. Again, that's going to vary.

At AbbVie, we've demonstrated our willingness to do business development activities on preclinical opportunities – we've done deals in oncology for assets that are in the preclinical stage with companies like **argenx SE** or **Dong-A Pharmaceutical Co. Ltd.**, so a lot of it is going to depend on the particular opportunity and how we feel about the ability to translate the science from where the company has progressed it to the clinic and to approval, and that's going to depend on specific circumstances. *Published online 11 Jan 2018*

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

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

Selected clinical trial developments for the week 5–11 January 2018

LEAD COMPANY/PARTNER	COMPOUND	INDICATION	COMMENTS
Phase III Completed			
Ardelyx Inc.	tenapanor	irritable bowel syndrome	With constipation symptoms.
Phase III Interim/Top-line Results			
Alder BioPharmaceuticals Inc.	eptinezumab	migraine prophylaxis	PROMISE 2; met primary endpoint.
Kala Pharmaceuticals Inc.	KPI-121	dry eye disease	STRIDE 1, 2; met primary endpoints.
Santen Pharmaceutical Co. Ltd./ Ube Industries Ltd.	omidenepag isopropyl (DE-117)	glaucoma	Met primary endpoint.
Merck & Co. Inc.	*Keytruda* (pembrolizumab)	advanced melanoma, post-resection	KEYNOTE-054; effective as adjuvant therapy.
Flexion Therapeutics Inc.	*Zilretta* (triamcinolone) injectable suspension	osteoarthritis, knee	Clinical benefits after repeat administration.
Ohr Pharmaceutical Inc.	squalamine, topical	wet age-related macular degeneration	MAKO; missed primary endpoint.
Updated Phase III Results			
Otonomy Inc.	*Otividex* (dexamethasone) sustained release	Meniere's disease	AVERTS-2; achieved additional endpoints.
Kala pharma	KPI-121	ocular pain and inflammation	Reduced symptoms.
Phase III Initiated			
Ardelyx Inc.	tenapanor	hyperphosphatemia	Its second Phase III study.
Novartis AG	*Cosentyx* (secukinumab)	ankylosing spondylitis	SURPASS; head-to-head with biosimilar adalimumab.
Novartis AG	*Cosentyx* (secukinumab)	psoriatic arthritis	EXCEED; head-to-head with *Humira*.
Bioverativ Inc.	BIVV009	complement deficiencies	Cadenza, Cardinal; a monoclonal antibody.
Semnur Pharmaceuticals Inc.	SP-102	lumbar radicular pain/ sciatica	CLEAR; a viscous gel injection.
Phase III Announced			
Agios Pharmaceuticals Inc./ Celgene Corp.	ivosidenib, enasidenib	acute myeloid leukemia	Combined with standard chemotherapy.
Agios Pharmaceuticals Inc.	AG-348	pyruvate kinase deficiency	ACTIVATE/ACTIVATE-T; plus a global registry.
Dova Pharmaceuticals Inc.	avatrombopag	thrombocytopenia	In patients undergoing invasive surgery.

Source: Biomedtracker

Scrip Awards Winner 2017

Best Company in an Emerging Market

Bangladesh's Beximco Pharmaceuticals enjoyed an increase in sales and profits as it launched eight new products on the domestic market and began selling carvedilol to the US, making it the first Bangladeshi firm to export pharmaceutical products to the American market.

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Winner: Beximco Pharmaceuticals

"I am honoured and excited that Beximco Pharma has been selected as the 'Best Company in an Emerging Market' at the prestigious Scrip Awards. As the only Company in Bangladesh to export pharmaceutical products to the US, we are setting a high standard for the pharmaceutical industry in Bangladesh. I look forward to our continued advancement as we strengthen our research and development capabilities, create new partnerships and build our presence in both domestic and international markets."

Beximco Pharma Managing Director, Mr Nazmul Hassan MP

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APPOINTMENTS

Hikma Pharmaceuticals PLC has appointed ***Surendera Tyagi*** chief scientific officer and global head of R&D. Tyagi will focus on Hikma's non-injectables business during the first year and will become a member of the company's executive committee. Tyagi joins the Jordan-headquartered company from Fresenius Kabi AG, where he most recently led its US innovation and development center. Prior to joining Fresenius, Tyagi he was chief scientific officer for Dabur Pharma.

French pharma **Ipsen** has named ***Richard Paulso***n executive vice president and CEO of Ipsen North America, responsible for commercial operations throughout the region – effective from Feb. 5, 2018. He will report to CEO ***David Meek***, and will become a member of the Ipsen executive leadership team. Paulson joins Ipsen from Amgen Inc. where he was vice president and general manager of the oncology business unit. Prior to joining Amgen, he held international positions at Pfizer Inc.

Sinclair Pharma PLC, an international aesthetic dermatology company headquartered in London, has appointed ***Kamal Abbasi*** head of the Middle East and Asia Pacific regions. Abbasi was previously head of Galderma SA's Asia business and is a qualified doctor.

Japan's **PeptiDream Inc.** has named ***Kiyofumi Kaneshiro*** to its management team as executive vice president. Prior to joining PeptiDream, Kaneshiro was a partner and managing director at The Boston Consulting Group. At PeptiDream he will work side-by-side company president Patrick Reid and executive vice president Keiichi Masuya to manage and direct all scientific, strategic and business efforts.

Targovax ASA, a clinical-stage company developing immuno-oncology therapies to target solid tumors, has named ***Michael Bogenstaetter*** chief business officer. Bogenstaetter previously held senior business development and strategy positions at Sanofi and Novartis AG. He has also worked as a consultant with The Boston Consulting Group and acted as an independent corporate and business development advisor to some of the world's top pharmaceutical and biotechnology companies.

Nicox SA, an ophthalmic company, has appointed ***Tomas Navratil*** vice president and head of development. In this newly-created position, Navratil will be responsible for leading the company's non-clinical and clinical development activities. He will report to ***Michael Bergamini***, executive vice president and chief scientific officer of Nicox.

Moderna Therapeutics LLC, a clinical stage biotechnology developing messenger RNA (mRNA) therapeutics and vaccines, has named ***John Mendlein*** president of corporate and product strategy. Mendlein will be responsible for corporate strategy, product advancement, partnering and product protection. He will report to CEO ***Stéphane Bancel***.

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