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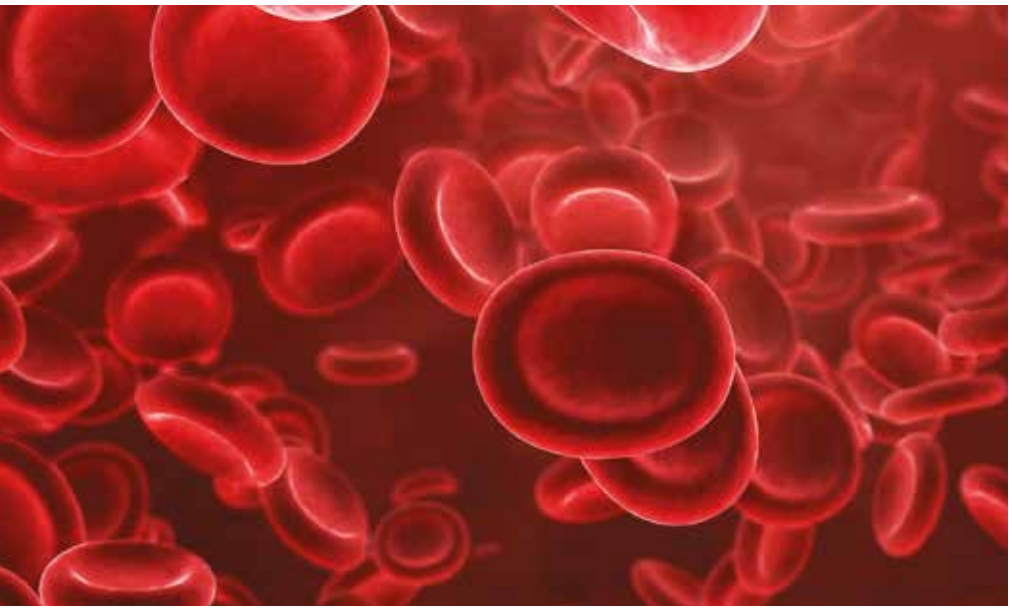

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Sanofi Builds Blood Disorder Specialty With Bioverativ Buy

KEVIN GROGAN & JESSICA MERRILL

Sanofi is making a big bet on blood disorders with the $11.6bn acquisition of **Bioverativ Inc.** The acquisition, announced Jan. 22, will position Sanofi as a leader in hemophilia, but the competition in the category is fierce and the prospect of gene therapy sits just on the horizon, raising questions about the steep premium Sanofi has paid.

In addition to two marketed drugs that are on track to generate more than $1bn in combined revenues in 2017, *Eloctate* (recombinant Factor VIII) for hemophilia A and *Alprolix* (recombinant Factor IX) for hemophilia B, Sanofi will gain a pipeline that includes a Phase III drug for the rare blood disease cold agglutinin disease (CAgD), a gene-edited cell therapy for beta-thalassemia that's ready for the clinic and a preclinical gene therapy for hemophilia. *(Also see "Bioverativ: More Than Just A Hemophilia Company" - Scrip, 22 Jan, 2018.)*

Much may be made about whether the deal represents a commitment to gene therapy on the part of Sanofi or, by bringing in the two marketed factor inhibitors, the opposite. In reality, it's probably just a bet that factor inhibitors like Eloctate and Alprolix will continue to dominate the market for the next several years.

For Sanofi, the deal adds some meat to the portfolio's bones in one of the company's core areas, rare diseases, where it leads with its Sanofi Genzyme unit. Investors have been anxious to see the French pharma move on the business development front to reduce its dependence on the challenging diabetes market, and particularly on the blockbuster *Lantus* (insulin glargine).

The company missed out on two high-profile M&A attempts. It lost out on a bid to buy the cancer specialist **Medivation Inc.** in 2016 to **Pfizer Inc.**'s $14bn offer and it also lost **Actelion Pharmaceuticals Ltd.** to **Johnson & Johnson**, which bought the Swiss biotech in a $30bn deal. *(Also see "Pressed Sanofi CEO Hopes For Positive Dupixent Launch, Praluent Ruling" - Scrip, 8 Feb, 2017.)*

With Bioverativ, Sanofi finally sealed the deal, agreeing to pay $105 per share in cash, a 64% premium over the company's closing price on Jan. 19. Bioverativ was only spun out of **Biogen Inc.** a year ago, on Feb. 1, 2017. *(Also see "Bioverativ Hits The Street Ready To Expand In Blood Disorders" - Scrip, 26 Jan, 2017.)* The company was tasked with growing the two marketed products and building out a hematology pipeline. Alprolix and Eloctate have been growing; Bioverativ generated $839.8m in the first nine months of 2017. However, Bioverativ only owns the rights to the products in North America and other select markets, while **Swedish Orphan Biovitrum AB** owns commercial rights in Europe, Russia and most Middle Eastern countries.

"Bioverativ is a pure play in the large and growing hemophilia market and brings an immediate leadership position for Sanofi," CEO Olivier Brandicourt said in a same-day conference call announcing the acquisition. "Second, it brings opportunities to leverage growth of a new platform including Bioverativ's pipeline of rare blood disorder assets and our novel hemophilia agent fitusiran."

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

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Walmsley Takes On Cancer
Can GSK be a power in oncology? (p10)

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Juno buy propels in cancer and hematology (p6)

from the editor

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As those of you who follow our coverage online will have seen, *Scrip* has now set off on the annual marathon of covering pharma sales conferences.

We've published our first results preview round-ups on www.scripnews.com, and will follow up with further expectation-setting pieces on Jan. 26 and Feb. 2, as the reporting period progresses. If you want to get ahead of the game, check out our website. By the time you read this, we'll have analyzed and digested the financial reports and associated executive pronouncements and general corporate updates from Johnson & Johnson, Novartis, Celgene, Biogen and AbbVie. More on those in next week's issue.

We're expecting US tax reform to be a hot topic this results season, and anticipate that the leaders of big US firms will tackle the question of how they might use freed-up cash. J&J's CFO Dominic Caruso has indicated that the diversified giant will repatriate a chunk of cash it had kept overseas, to spend on US operations and paying off debts. The company's executives minimized the prospects of it going on an M&A spree, however, something that many observers nonetheless believe will grip the pharma industry in general in 2018.

Deal-making activity failed to reach conflagration status at J.P. Morgan this year, but since the annual industry shindig in San Francisco ended a couple of deals have set pharma hearts racing: Sanofi's planned purchase of Bioverativ (the year-old spin-out of Biogen's hemophilia drugs and blood disorder R&D assets), and Celgene's announced acquisition of its CAR-T partner Juno Therapeutics. Get the lowdown inside this issue.

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Amgen Wins First EU Avastin Biosimilar Approval, But When Will It Launch?
http://bit.ly/2DwgV5V
Partners Amgen and Allergan have become the first biosimilar developers to win EU approval for a copycat version of Roche's Avastin; commercialization preparation is underway but predicting a launch date for the product is more complicated.

Astellas' ASP0113 Trial Failure Gives Merck's Prevymis Further CMV Boost
http://bit.ly/2rz2MDh
Merck's Prevymis should benefit from the failure of ASP0113 in a late-stage trial treating cytomegalovirus in certain kidney transplant patients.

Riding The Next Wave Of Biosimilars: Sandoz To Link Up With India's Biocon
http://bit.ly/2BozBTb
Pooling resources appears key to a major new collaboration in the biosimilars space, between Sandoz and India's Biocon, to develop the next generation of biosimilar immunology and oncology products.

Could Probiodrug Represent A New Era Of Alzheimer's R&D Progress?
http://bit.ly/2E57lIt
Probiodrug believes it can bring success to an Alzheimer's research community that has been hard hit by clinical failures in the last few years – but the company will need a partner or cash influx to take its first-in-class drug through late-stage trials.

Korea Stepping Up IO R&D To Catch Up With Global Players, Trends
http://bit.ly/2rwzLIz
Immuno-oncology deals and R&D by South Korean companies are picking up speed as they are put more focus on the hot sector in line with global trends.

Deal Watch: From The Sidelines Of J.P. Morgan, Lots Of Discovery Deals
http://bit.ly/2n43FPH
Strongbridge obtains rights from AEterna Zentaris to first drug approved for adult growth hormone deficiency. While the J.P. Morgan Healthcare Conference didn't have many major deal announcements, there was a flurry of announcements around discovery and development capabilities.

inside:

Bioverativ: More Than Just A Hemophilia Company

JESSICA MERRILL jessica.merrill@informa.com

Bioverativ Inc.'s two marketed hemophilia drugs, *Eloctate* and *Alprolix*, get most of the attention, but the blood disease specialist has been focused on diversifying beyond hemophilia in the year since it was spun out from **Biogen**.

Sanofi announced plans Jan. 22 to buy Bioverativ for roughly $11.6bn, gaining the two marketed hemophilia drugs, which are expected to have generated over $1bn in 2017 revenues, and an interesting pipeline that includes a Phase III drug for the rare blood disease cold agglutinin disease (CAgD), a gene-edited cell therapy for beta-thalassemia that's ready for the clinic and a preclinical gene therapy for hemophilia.

CEO John Cox talked to *Scrip* at the J.P. Morgan Healthcare conference Jan. 10 – before any buyout speculation emerged – about the company's pipeline and diversification strategy. At the time, Cox talked about how Bioverativ would be engaged in more business development to build out the pipeline even further with an eye on opportunities to address rare blood diseases beyond hemophilia.

"When we started this company we really didn't have a pipeline," Cox said. "We had a lot of positives. We had a great balance sheet. We had a lot of cash, and we had a terrific R&D organization."

"We built a pipeline," he added.

Bioverativ was spun out from Biogen as an independent company less than a year ago on Feb. 1, 2017. *(Also see "Bioverativ Hits The Street Ready To Expand In Blood Disorders" - Scrip, 26 Jan, 2017.)* The company's cash cows were two newly-launched and growing long-acting hemophilia factor inhibitors, Eloctate for hemophilia A and Alprolix for hemophilia B. Bioverativ generated $839.8bn in the first nine months of 2017, growth of 33% over what the business reported in the first nine months of 2016. The company markets the drugs in North America, but **Swedish Orphan Biovitrum AB** owns the rights in Europe and other select territories.

> 'I think the disease is underestimated,' Cox said of CAgD, pointing to Alexion's Soliris as a corollary for BIVV009

Given the competitive dynamics in the hemophilia market and the onslaught of drugs in development, including the first potentially curative gene therapies, Bioverativ has never intended to rest on its two marketed drugs. The goal was always to expand beyond hemophilia to become a rare blood disease specialist.

Bioverativ is developing its own gene therapy for hemophilia, but the product is only in preclinical development, roughly 18 months to two years from entering the clinic, according to Cox. The timeline puts it well behind rivals like **BioMarin Pharmaceutical Inc.** and **Spark Therapeutics Inc.**, which have already reported clinical trial data on their hemophilia gene therapies. *(Also see "Spark Plots Rebound For Hemophilia A Gene Therapy, As Rival BioMarin Surges" - Scrip, 12 Dec, 2017.)*

John Cox

Thus, gene therapy is not exactly on the near-term horizon for Bioverativ and Cox downplayed the company's reliance on gene therapy in the interview. He said a decision on whether or not to move the therapy into the clinic would depend on the animal data and that the treatment would need to offer something the competition does not at the time a decision is made. Bioverativ's gene therapy is based on a lentiviral vector approach, which he said could offer advantages over some of the other gene therapy approaches. Although some of the early data with gene therapies has been encouraging, it has also been highly variable.

Sanofi's decision to pay such a hefty premium to acquire Bioverativ suggests the French big pharma is betting on the durability of Eloctate and Alprolix over the near-term arrival of gene therapy. *(Also see "Sanofi Builds Blood Disorder Specialty With Bioverativ Buy" - Scrip, 22 Jan, 2018.)* Building a broad specialty in hematology, with Bioverativ's range of early technologies, could have more interest to Sanofi than just sticking to hemophilia.

A RARE DISEASE ASSET POISED FOR 2020 LAUNCH

"I think people were surprised we moved so quickly because we had just spun out," Cox said of the company's aggressive pipeline expansion. Bioverativ announced the acquisition of **True North Therapeutics Inc.** for $400m upfront plus $425m in future milestone payments in May 2017. *(Also see "Bioverativ Fills Gap In Pipeline With $400m True North Buy" - Scrip, 23 May, 2017.)* The acquisition gave Bioverativ a drug for CAgD that is now the company's lead pipeline asset.

The firm is initiating two Phase III trials of BIVV009 now in patients with CAgD. Both studies are small, given the rare nature of the disease. One is an open-label trial enrolling 20 patients who are currently transfusion dependent, while the other trial is enrolling 40 patients who have not received recent transfusions. The company expects it could have data in early 2019 with a launch anticipated in 2020, Cox said. CAgD is an autoimmune hemolytic anemia in which autoantibodies target red blood cells, leading to

red blood cell destruction through complement activation by the C1 complex and resulting in chronic anemia, which can lead to fatigue, potentially fatal thrombotic events and a lifetime of blood transfusions. The disease is believed to affect about 10,000 people in the US and Europe combined.

"I think the disease is under-estimated," Cox said. He pointed to **Alexion Pharmaceuticals Inc.**'s *Soliris* (eculizumab), which also targets a different part of the complement pathway, as a corollary. Soliris has grown into a blockbuster based on approvals for three ultra-rare indications.

In Phase I testing, treatment with BIVV009 resulted in clear responses on multiple endpoints, according to Cox, including transfusion dependency and hemoglobin normalization.

Bioverativ also is moving forward with clinical testing of ST-400, a gene-edited cell therapy for the treatment of transfusion-dependent beta-thalassemia in development with **Sangamo Therapeutics Inc.** Beta-thalassemia is an inherited blood disorder caused by mutations in the beta-globin gene that leads to reduced or absent hemoglobin production. It can result in severe anemia and reduced oxygen transport to various tissues in the body.

"We are actually quite excited about that technology because we think it could be a best-in-class approach," Cox said. The company plans to initiate a Phase I trial in the first half of 2018 and is also filing an IND with FDA to begin testing in sickle cell disease.

A LONG-TERM BICYCLE RIDE

Bioverativ also partnered with platform company **Bicycle Therapeutics Ltd.** in September in a drug discovery deal to develop candidates for rare blood disorders, including hemophilia and sickle cell disease. Bicycle is developing bicyclic peptides that are a new therapeutic modality combining attributes of antibodies, small molecules and peptides. Bioverativ paid $10m upfront plus $4.2m in near-term R&D funding and offered up to $410m in milestone payments. *(Also see "Bicycle Partners With Biogen Spinout Against Rare Blood Disorders" - Scrip, 6 Sep, 2017.)*

Bicycle is responsible for leading initial discovery activities through lead optimization for the two programs that have not been selected but not disclosed. Cox said he viewed the partnership as a long-term play to potentially develop oral drugs for serious blood disorders.

"That one really points to our interest in really novel modalities," Cox said. And Bioverativ was still open for more business development before Sanofi made its intentions known.

"We certainly have the capacity to do more business development," he said. "So much of the key to this is really understanding the science and the underlying biology of these diseases, and then you can start to connect the dots. I think that is a competency we really have."

Whether the larger organization at Sanofi will have the same level of competency to develop a specialized hematology business remains unanswered for now.

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Celgene Seeks CAR-T Leadership, Hematology Diversification With Juno Buy

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Celgene Corp. will diversify its portfolio without really diversifying its focus with the $9bn acquisition of chimeric antigen receptor T-cell (CAR-T) therapy pioneer **Juno Therapeutics Inc.**, increasing its footprint in cell therapy and hematology while taking a step into new solid tumor territory.

The transaction announced Jan. 22 gives Celgene full ownership of programs that it is developing with Juno under a 2015 partnership agreement – a deal through which Celgene already has invested a lot of money in Juno, including the acquisition of a 10% stake in the CAR-T specialist. The buyout also diversifies Celgene's future revenue beyond sales of *Revlimid* (lenalidomide) with assets in indications where the company already is trying to grow, such as non-Hodgkin lymphoma (NHL).

Celgene based the acquisition cost for Juno on a peak sales estimate of $3bn for its lead product candidate JCAR017 in NHL and other indications, as well as on the value of the Seattle-based company's CAR-T technology platform, manufacturing capabilities and pipeline of additional candidates. The portfolio includes CAR-T therapies with the potential to treat solid tumors, but hematological malignancies are the main focus, at least initially.

"In our valuation model, the technology platform, as you might expect, was assigned significant value because, of course, this is one of the big drivers of the deal; we want to leapfrog from participating in CAR-T to shaping CAR-T and [the technology itself] would then have to be a value driver in the deal," Celgene CEO Mark Alles said during a Jan. 22 call to discuss the deal with investors and analysts.

ANALYSTS A LITTLE LESS BULLISH

Barclays analyst Geoff Meacham described the $3bn peak sales estimate for JCAR017 as "modestly aggressive" in a Jan. 22 note and estimated JCAR017's top sales as $2.6bn.

Evercore ISI's Umer Raffat polled investors and found an expectation of about $2.5bn in peak sales, while Raffat himself predicted $1.8bn in JCAR017 peak sales for the DLBCL indication. He noted on Jan. 22 that $2bn in annual sales would justify Celgene's $10bn investment (including earlier deal fees).

William Blair analyst Andy Hsieh said in a Jan. 22 report that he was not surprised by the acquisition of Juno based on the companies' existing relationship, noting that "we believe Celgene could leverage its global infrastructure and experience in developing novel therapies [for] hematological malignancies to efficiently make progress with JCAR017 and, in parallel, gradually optimize the manufacturing of cellular therapies."

The big biotech plans to aggressively pursue development of JCAR017, which is expected to win US FDA approval in 2019, and other Juno therapies, including JCARH125 targeting B-cell maturation antigen (BCMA). BCMA is the same target as bb2121, a CAR-T therapy in a pivotal trial for multiple myeloma with partner **bluebird bio Inc.** Interim results presented in December were among the highlights of last year's American Society of Hematology (ASH) conference.

Celgene's executives insisted during the company's Juno acquisition call that the deal changes nothing about its collaboration with bluebird. "The rapid advancement of bb2121 … remains one of our most important corporate priorities," Alles said, because data to date "demonstrate the potential to dramatically change the myeloma treatment paradigm." The company expects bb2121 approval in the US by 2020, which probably puts the bluebird-partnered program a few years ahead of JCARH125, which is expected to go into its first clinical trial early this year.

Both bb2121 and JCAR017 are projected to contribute more than $2bn in annual revenue each to Celgene's earnings at their peaks. They are among 10 late-stage R&D programs that are forecast to add $16bn in revenue in the post-2020 period, including a $1bn peak contribution from fedratinib, which the company is acquiring in its recently announced **Impact Biomedicines** purchase. *(Also see "Celgene's $1.1bn Impact Buy Is First Of More Deals To Come In 2018 And Beyond" - Scrip, 9 Jan, 2018.)*

JUNO DEAL BOOSTS NHL PIPELINE

New data for Juno's most advanced program, JCAR017 in diffuse large B-cell lymphoma (DLBCL, a form of NHL), also were presented at the ASH meeting, showing what Juno and Celgene believe to be best-in-class safety and efficacy relative to the first two CAR-T therapies approved in the US – **Novartis AG**'s *Kymriah* (tisagenlecleucel) and **Gilead Sciences Inc./Kite Pharma Inc.**'s *Yescarta* (axicabtagene ciloleucel).

All three target CD19, though Kymriah is approved as a third-line treatment for relapsed or refractory pediatric and young adult patients with B-cell precursor acute lymphoblastic leukemia (ALL), while Yescarta is approved in the third line for adults with relapsed or refractory large B-cell lymphoma, including DLBCL, primary mediastinal large B-cell lymphoma, high grade B-cell lymphoma and follicular lymphoma.

Non-Hodgkin lymphoma is an important indication for Celgene. The company's NHL portfolio includes Revlimid, for which data from two Phase III studies are expected this year. Results are due in the first half of 2018 from AUGMENT, testing Revlimid and **Roche**'s *Rituxan* (rituximab) versus Rituxan alone in relapsed or refractory indolent NHL. Data are anticipated from the ROBUST trial testing Revlimid plus Rituxan and CHOP chemotherapy (R-CHOP) versus R-CHOP alone in previously untreated DLBCL. The REMARC trial testing Revlimid in DLBCL as a maintenance therapy failed in 2016.

Celgene also has CC-122, a pleiotropic pathway modulator, in Phase I/II as an induction treatment for DLBCL and in Phase Ib as a treatment for second and later lines of therapy; CC-486, an oral formulation of the hypomethylating agent *Vidaza* (azacitidine), in Phase I for DLBCL induction therapy; and plans to develop JCAR017 in earlier lines of treatment for relapsed/refractory patients. CC-122 also is being developed as induction therapy for follicular lymphoma (FL) and in the third-line setting.

"JCAR017 represents an anchor molecule within our multi-modality approach to the

treatment of lymphoma, including protein homeostasis and epigenetics," Celgene President of Hematology/Oncology Nadim Ahmed said during the company's call. "And it also accelerates our strategy to build global leadership in this important therapeutic area."

JCAR017 also will be studied in third-line chronic lymphocytic leukemia (CLL) in the Phase I/II TRANSCEND-CLL trial. A Phase I/II study in the second line and a Phase II trial in combination with **AbbVie Inc.** and **Johnson & Johnson**'s kinase inhibitor *Imbruvica* (ibrutinib) are expected to begin in the second half of 2018.

"It is very exciting that Juno's efforts in translational medicine, focusing on how to understand their T-cell products and patients, add to our broader efforts in our Immuno-Oncology Thematic Center of Excellence in Seattle," Celgene Executive Vice President/Head of Business Development and Global Alliances Robert Hershberg noted during the company's call. "Here, we are integrating computational and data science with state-of-the-art immune monitoring and immune profiling. The combined efforts on this front in Seattle and Celgene-wide has the potential to define new products in combinations that will target the right immunotherapies, including cellular products, to patients that desperately need them."

JCARH125: SECOND-GENERATION BCMA

Multiple myeloma will, of course, remain a big market for Celgene due to Revlimid's dominance in that disease and its use as a backbone therapy for many combination regimens. That's why the company is also building a pipeline of BCMA-targeting therapies, now including bluebird's bb2121, its Phase I follow-on CAR-T therapy bb21217 and Juno's JCARH125.

"We think that BCMA is going to continue to be a very strong signal for this disease, so we're going to continue to make sure that our BCMA campaign is as broad as it can possibly be," Ahmed noted.

In addition to the three CAR-T therapies, Celgene has filed an investigational new drug (IND) application for the T-cell engager antibody CC-93269 and intends to file an IND with the FDA in 2018 for a BCMA-targeting antibody-drug conjugate, which is being developed with **Sutro Biopharma Inc.**

"In our view, Celgene has the industry-leading BCMA franchise, highlighted by five compounds targeting with three therapeutic modalities, which we believe could help the company maintain its leadership position in multiple myeloma," William Blair's Hsieh said. "The diversity of the targeted therapeutic modality, in our view, provides Celgene multiple shots on goal, and more specifically, allows the company to tailor therapeutics that maximizes the patient's chance of response (a move toward personalized medicine)."

But the early nature of JCARH125 and the other programs in Juno's pipeline mean that JCAR017 will be the main focus of investor attention in the near term, despite Celgene's insistence that its acquisition of the company is about much more than the CD19-targeting CAR-T.

"In the short term, the Street will debate whether pivotal Juno data coming will look better than Yescarta … and whether JCAR017 is truly differentiated; longer-term this is a deal hinged on Celgene's confidence in going 'all in' on cell therapy over the next 5-10 years. Like Gilead/Kite, this will be a smart deal if more than just JCAR017 plays out, which we think it will over [the] next few years," Jefferies analyst Michael Yee said in a Jan. 22 note.

A BIG DEAL, BUT SMALLER THAN GILEAD'S KITE BUY

Celgene's interest in Juno was rumored to ring in at $12bn – about as large as Gilead's purchase price for Kite. That deal, signed last August, was executed at $180 per share, or $11.9bn, just a few months before the US FDA approval of Yescarta.

Celgene's investment in Juno to date, including the companies' original licensing deal in 2015, tops $10bn. The collaboration was worth $1bn up front, including $150m in cash plus Celgene's purchase of 9.1m shares of Juno stock. *(Also see "Celgene shows CAR-T confidence with $1bn Juno investment" - , 30 Jun, 2015.)* Celgene owned 9.7% of outstanding Juno shares prior to its decision to acquire the CAR-T firm; it will use a mix of cash and new debt to acquire the rest from Juno's other shareholders. The transaction is expected to close relatively quickly – in the first quarter of 2018.

"We believe that adding Juno to Celgene now fits incredibly well into our strategic development and commercial priorities," Alles said. "We expect this acquisition to meaningfully contribute to revenue and earnings growth well into the next decade."

Celgene did not change its revenue guidance of $19bn to $20bn in 2020, but the company believes that JCAR017 and other Juno CAR-T candidates will be a meaningful contributor to sales between 2020 and 2030. The post-2020 period is crucial for Celgene, because Revlimid is expected to lose patent exclusivity around 2023 if ongoing legal challenges are unsuccessful.

The drug generated $6bn in 2017 sales through the third quarter, accounting for nearly two-thirds of Celgene's $9.5bn in revenue for the first nine months of last year. Investors are anxious for the company to buy assets that can add significant revenue in the near term in addition to the company's existing pipeline of research and development programs, a significant number of which come from partnerships and acquisitions.

JCAR017 and other Juno CAR-T candidates, excluding JCARH125, already were important programs in Celgene's R&D pipeline, but now the company will retain all revenue from those therapies. Celgene had only ex-US rights to JCAR017 under its partnership agreement with Juno.

"Operationally, this acquisition allows us to accelerate Juno's pipeline and capture 100% of global economics from JCAR017 and all future products," Alles said. "Our ability to immediately capitalize on current and future advances in cellular immunotherapy and to add new opportunities in this dynamic field is also significantly enhanced."

He and other executives implied that Celgene would continue to look for additive technologies in the CAR-T field. They also noted that the company has plenty of capital on hand to execute additional deals for assets that could boost Celgene's revenue in the future.

Alles noted at the end of the company's call that "we intend to continue to follow outstanding science and build our company through strategic transactions, be they bolt-on or transformational. We have the firepower to do it and we will look for those opportunities, like today, to be able to continue to build optionality and opportunity for our future."

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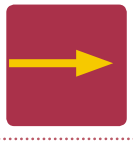

Better Together: BioCryst, Idera Merge To Improve Rare Disease Position: http://bit.ly/2DzGbMA

CONTINUED FROM COVER

A FIT FOR FITUSIRAN

The acquisition of Bioverativ is a strategic fit with Sanofi's own late-stage pipeline asset fitusiran, a Phase III RNAi compound discovered by partner **Alnylam Pharmaceuticals Inc.** in development for hemophilia A and B. The FDA recently lifted a clinical hold on the drug after deaths were reported, allowing Sanofi to proceed with the Phase III programs studying the treatment in hemophilia patients with or without inhibitors.

The two partners restructured the deal just ahead of the annual J.P. Morgan Healthcare conference in San Francisco, with Alnylam regaining full rights to patisiran and the follow-on ALN-TTRsc02 for transthyretin amyloidosis, while Sanofi got the global rights to fitusiran. Brandicourt said the new agreement "will simplify operations and enable both companies and parties to maximize the value of the alliance."

"There is some strategic logic to the deal," analysts at Berenberg said, noting Bioverativ would give Sanofi a significant footprint in the hemophilia market. Berenberg forecasts Alprolix and Eloctate will generate sales of $1.4bn this year. Nonetheless, reaction from analysts was largely lukewarm.

Leerink analyst Seamus Fernandez was more positive, calling the bolt-on deal "a strategically sound move," in a same-day research note.

"The biggest challenge for Sanofi management will be convincing investors that – much like **Shire PLC**'s acquisition of **Baxalta Inc.** – the current hemophilia market will not be disrupted by new technologies (gene therapies) and product launches."

One of the near-term threats to Bioverativ's commercial products is **Roche**'s *Hemlibra* (emicizumab-kxwh), which was recently approved by the FDA for use in hemophilia A patients with inhibitors. The inhibitor market does not make up a big part of Bioverativ's business at the moment, but Hemlibra could also be approved soon for the non-inhibitor population after the company reported impressive Phase III data, including superiority data versus prophylactic or on-demand Factor VIII clotting factors. Eloctate is designed to be administered every four days, versus every seven days for Hemlibra.

Brandicourt asserted on the conference call that Sanofi carried out an extensive assessment of the market before making the move.

"Despite potential future approvals, we're convinced that factor replacement therapy will remain the standard of care for many years due to excellent safety and its increasing superior standard half-life profile, and that Eloctate will retain the leading position in this category given its superior features," Brandicourt said. Potentially curative gene therapy is another threat. Bioverativ is developing its own gene therapy for hemophilia, but the product is only in preclinical development, roughly 18 months to two years from entering the clinic, Bioverativ CEO John Cox said in an interview at J.P. Morgan. The timeline puts it well behind rivals like **BioMarin Pharmaceutical Inc.** and **Spark Therapeutics Inc.**, which have already reported clinical trial data on their gene therapies.

Bernstein analyst Tim Anderson said the conference call didn't deliver any comfort that Sanofi really knows the hemophilia market well. "The majority of the feedback we have received from investors thus far is skewed towards the negative, given the shifting landscape in hemophilia … that could shift even further over the next few years due to advances made by competitors in gene therapy," he said.

Indeed, the franchise is one that is eventually expected to wane, with the big question being when. That can be a challenging sell to investors, but Brandicourt pointed to hemophilia as the largest rare disease market, worth $10bn at the moment and growing 10% per year. He expects Alprolix and Eloctate to keep flourishing, and expanding into China, Korea, Taiwan, Colombia, Brazil and Argentina, with the next-generation product fitusiran adding to that growth.

In addition, Bioverativ has been building out a pipeline of assets in other rare blood disorders, already focused on diversifying outside of hemophilia. The company has a late-stage asset BIVV009 for CAgD, a rare disease that can result in chronic anemia and a lifetime of blood infusions, that it acquired with **True North Therapeutics Inc.** for $400m upfront plus $425m in future milestone payments in May 2017. Bioverativ is also studying new technologies like gene editing and had its eye on more business development.

The acquisition represents an opportunity for Sanofi to build out a new blood disorder specialty within rare diseases. If it can do so successfully, the acquisition could very well pay off.

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Teva Falls Behind With SC Cinqair Failure

Two Phase III trials of a subcutaneous version of **Teva Pharmaceutical Industries Ltd.**'s asthma therapy Cinqair (reslizumab) have failed to meet their primary endpoints.

Teva is attributing the failures to a lack of efficacy in patients with a lower eosinophilic cell count and say they "reinforce the role of eosinophils in severe asthma disease biology and the importance of defining the right blood eosinophil cut-off point for patient selection." It is reviewing the full data to determine its next steps, the company said. No new safety concerns were identified.

Cinqair is currently approved as an intravenous formulation but an sc version is desirable to compete with rival therapies, **GlaxoSmithKline PLC**'s *Nucala* (mepolizumab) and **AstraZeneca PLC**'s recently approved *Fasenra* (benralizumab).

The two Teva studies included a 52-week registration study, which evaluated reslizumab (110 mg sc) in a pre-filled syringe every four weeks in 468 patients with uncontrolled asthma and elevated blood eosinophils (>300/mcL) but did not meet its primary endpoint of significantly reducing the frequency of clinical asthma exacerbations (CAEs).

However, a pre-specified a priori-powered subgroup analysis of 80% of the population with baseline blood eosinophil count of ≥400/mcL showed significant reduction in CAE risk ($p<0.025$).

Datamonitor Healthcare analyst Chris Mulligan noted that the pivotal clinical data that led to the approval of Cinqair IV pre-selected patients with a blood eosinophil count of ≥400 cells/mcL. "Given that the link between elevated eosinophil count and the efficacy of IL-5 inhibitors is well established, Teva's decision to target a wider patient population has likely contributed to this disappointing result. The pivotal trials supporting Nucala's application largely focused on patients with a blood eosinophil count of ≥300 cells/mcL, which has likely influenced Teva's decisions regarding the design of Cinqair SC trials."

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Novartis Pharma CEO Hudson On Leadership And Launches

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Novartis AG Pharmaceuticals CEO Paul Hudson is 18 months into the job running the Swiss company's pharmaceutical business, having joined from rival **AstraZeneca PLC** in July 2016. Now, he's got his footing and is preparing for seven new drug launches by 2020 at a transitional time for Novartis.

Hudson is one of a new generation of leaders at the Swiss drug maker. Incoming CEO Vasant Narasimhan will take over from Joseph Jimenez on Feb. 1, and the company recently announced the appointment of **Pfizer Inc.**'s Oncology President Elizabeth Barrett as CEO of Novartis Oncology, succeeding Bruno Strigni.

"I feel like I got lucky," Hudson said in an interview Jan. 9 at the J.P. Morgan Healthcare Conference. "We are putting together quite an impressive pharma story."

Hudson is invigorated by the leadership changes at the top of the company. Narasimhan, just 41 years old, brings a wealth of scientific expertise to the CEO role, having previously served as chief medical officer.

"The differences between Joe and Vas I think are just good for the company," Hudson said. "What Joe had got us to this point. Vas brings a lot of youth, vitality, progressive innovative thinking. He's from a generation [that believes] data is important, corporate social responsibility is a ticket eventually, and it's genuine."

Hudson oversees Novartis' non-oncology pharmaceutical business, including neuroscience, ophthalmology, immunology, dermatology, respiratory, cardio-metabolic and established medicines, groomed through a decade of experience at AstraZeneca, where he led the North American business. The company broke out oncology into a separate business unit reporting directly to the CEO in mid-2016.

A BIG LAUNCH FOR 2018

For 2018, Hudson's priorities are continuing the momentum behind Novartis' growth brands, mainly the first-in-class IL-17 blocker *Cosentyx* (secukinumab) for psoriasis and *Entresto* (sacubitril/valsartan) for heart failure, and preparing for the launch of erenumab, a potential first-in-class calcitonin gene-related peptide (CGRP) antagonist for migraine.

Both goals will require some prowess. Cosentyx is already on track to be a $2bn brand in 2017, and wringing more growth from the product in an increasingly competitive psoriasis market will require marketing savvy and smart negotiations with payers. Novartis believes access to Cosentyx is the same or better in 2018 compared to 2017, and the company sees substantial future growth coming from other indications like psoriatic arthritis and ankylosing spondylitis, for which it is also approved.

Erenumab, meanwhile, has the potential to be a blockbuster, but is also launching into what is expected to be a crowded category for the new class of medicines, one payers already are pushing back on because of cost concerns. Novartis partnered with **Amgen Inc.** on the drug, which is pending at the US FDA, with an action date of May 17. Both companies will commercialize erenumab in the US.

The CGRP drugs are expected to be an important and lucrative new class of medicines, given the high efficacy seen in clinical studies in migraine sufferers and the large number of migraine patients.

But the class is also going to be competitive, and payers will want to limit use of the drugs to the most serious patients who will get greatest benefit. Novartis and Amgen aren't expected to enjoy much of a head start. **Eli Lilly & Co.** and **Teva Pharmaceutical Industries Ltd.** are just behind with CGRP drugs galcanezumab and fremanezumab, respectively. Teva closed its gap behind Novartis by using a priority review voucher with its BLA filing for fremanezumab in October.

But Hudson is convinced that erenumab will stand out from the competition because it is the only one of the three CGRP drugs that is a fully human monoclonal antibody, which could result in fewer neutralizing antibodies and longer duration of response.

And despite Teva's priority review voucher, he said Novartis and Amgen will be first to market. He also thinks Novartis and Amgen will have an advantage when it comes to launch execution.

"The Teva story is well documented and very public right now. They have a lot going on," he said. "We are very focused on migraine. We have no distractions." Teva is in the early stages of a massive restructuring to stabilize the company, which includes cutting 25% of the workforce.

Beyond erenumab, Novartis could launch six more drugs through 2020 and important new indications for Cosentyx (non-radiographic axial spondyloarthritis) and Entresto (heart failure with preserved ejection fraction).

BROLUCIZUMAB: THE COMEBACK KID

Among the potential new launches is brolucizumab for neovascular age-related macular degeneration (nAMD). Investors have been enthusiastic after Novartis released positive Phase III data in November showing the drug was superior to **Regeneron Pharmaceuticals Inc.**'s *Eylea* (aflibercept) on key retinal health outcomes at fewer dosing intervals.

"It's absolutely in the sweet spot. We got what the retina specialist wants. We got what the patient wants," Hudson said of the clinical trial results.

Brolucizumab represents a comeback of sorts for Novartis, which markets *Lucentis* (ranibizumab) for AMD and other indications outside the US, but lost ground to Eylea. **Roche** sells Lucentis in the US.

Now, with the latest clinical trial data in hand, Hudson said, "I think Regeneron have some things to think about." Indeed, Regeneron's stock price has fallen since the Novartis results were announced, given that Eylea is the big biotech's main revenue driver.

Novartis will need to build a US ophthalmology sales force since it doesn't commercialize Lucentis in the US, but that will be a small problem to overcome in exchange for potential blockbuster sales, according to Hudson.

"Nothing will give me greater pleasure than building it," he said. "It's a small infrastructure investment, and to go into the biggest retina market in the world to take on Eylea is going to be a great journey for Novartis."

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Walmsley Takes On Oncology: Can GSK Become A Power Player?

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GlaxoSmithKline PLC CEO Emma Walmsley's growth strategy for the big pharma calls for reversing course to reprioritize pharmaceutical R&D and innovation, with a particularly notable focus in a new potential growth area, oncology. Walmsley believes GSK can be a power player in the competitive field of oncology, where it lags rivals by a long shot.

Emma Walmsley

Walmsley is assembling a "dream team" to rebuild GSK's pharmaceutical pipeline, and the appointment of Hal Barron, a highly-regarded cancer specialist, as president of R&D has given the initiative some credibility on Wall Street. *(Also see "GSK Bags Barron As R&D Boss As Vallance Joins UK Government" - Scrip, 8 Nov, 2017.)*

Walmsley made her J.P. Morgan Healthcare Conference debut as GSK's CEO on Jan. 9 in the grand ballroom of the Westin St. Francis in San Francisco, where she outlined her strategy for recharging the company's growth outlook. Walmsley unveiled early plans in July, shortly after taking the helm from Andrew Witty, when GSK announced plans to slash more than 30 R&D programs and refocus on 10 priority geographies. *(Also see "Walmsley Shakes Up GSK; Cuts More Than 30 Drug Development Programs" - Scrip, 26 Jul, 2017.)*

"Our resources at GSK have historically been spread too thinly, and we need to bet bigger on fewer truly differentiated medicines with the potential for sizable peak-year sales," Walmsley said. The company will target 80% of its R&D spending to four areas: two where it has existing strengths – respiratory and HIV/infectious disease, where it already leads with drugs like *Advair*, *Breo*, *Anoro* and its **ViiV Healthcare** HIV subsidiary, respectively – and two emerging areas: oncology and immuno-inflammation.

GSK is prioritizing 16 pipeline assets, and Walmsley said the company already has increased spending on those programs by 30% since July. But, she also said she fully expects the priority assets will change as new data reads out and as the company's business development strategy evolves.

The CEO also noted that GSK will be much more proactive on pharmaceutical business development.

"The first priority is our pharma business and right at the heart of it is R&D, which is why I'm building this dream team to really work on finding what the pipeline is going to be," Walmsley said.

A LONG-TERM VIEW IN ONCOLOGY

While GSK isn't known as a cancer company, it has successfully brought some cancer drugs to market in the past. It currently has eight oncology drugs in clinical development and several more in preclinical development.

"Decisions are going to be made on how we may proceed here as new data reads out over the next few years and as Hal and his team review the portfolio in much more detail," Walmsley said. "What I can say is that we have an early and innovative portfolio."

Barron only officially joined the company on Jan. 1, so he wasn't prepared to provide any strategic R&D updates, but he did address investors in a breakout session about why he decided to join GSK, which largely came down to Walmsley's commitment to innovation.

The company's lead oncology asset is a potential first-in-class anti-BCMA antibody-drug conjugate, which attracted attention at the American Society of Hematology meeting in December, when GSK presented positive data from an early trial in heavily pre-treated multiple myeloma patients, showing a 60% response rate and median progression-free survival of 7.9 months.

Walmsley said GSK is prioritizing the development of BCMA, but acknowledged the R&D transformation is going to be a multi-year process. The company appeared to be backing off oncology in 2014 when it swapped its marketed oncology assets for **Novartis AG**'s vaccines business in a deal that was considered novel in terms of structure. *(Also see "GSK Swaps Cancer For Vaccines As It Sheds Legacy Products, Not R&D" - Pink Sheet, 22 Apr, 2014.)*

BARRON IS "A LEGEND," ONCOLOGY THERAPY HEAD HOOS SAYS

But GSK always kept a small R&D operation ongoing in oncology. Therapy Area Head-Oncology R&D Axel Hoos was GSK's oncology torch bearer for several years, and since he's well-respected in the field as an early pioneer in immuno-oncology and the developer of **Bristol-Myers Squibb Co.**'s *Yervoy* (ipilimumab), there remained the sense that something was brewing under the surface.

Hoos is energized about the R&D changes under the new leadership at GSK. He talked with *Scrip* in an interview at J.P. Morgan.

"Hal Barron is a legend in his space, and he will bring a lot of credibility, but also capability to GSK in terms of very senior leadership in R&D," Hoos said. "His background is largely oncology, not exclusively, but he has made major contributions to oncology in his time at **Genentech Inc.** and I expect he will bring some of that spirit and expertise to us in helping to bring oncology back to a much larger presence."

Hoos said he remained at GSK in the nascent years, because he believed in the molecules in the pipeline.

"R&D is a long-term business, so after investing yourself for four or five years, if you drop it, you start over and then you are faced with the same uncertainty somewhere else," he said. "Pharma goes through cycles, and we just had a low on that side and now are going back on a high."

The company's oncology pipeline is focused in three areas: immuno-oncology, epigenetics and cell therapy.

DRILLING DOWN IN ONCOLOGY

Hoos' top-priority is progressing BCMA through the clinic and regulatory process and onto the market, possibly as early as 2020, given that it has FDA breakthrough therapy designation and PRIME designation in Europe.

The 60% response rate seen in the multiple myeloma trial for patients treated with BCMA as a monotherapy was encouraging, he explained, given that the response rate in multiple myeloma trials for **Johnson & Johnson**'s *Darzalex* (daratumumab) as a monotherapy was about 30%. *(Also see "GSK's Oncology R&D Head: GSK2857916 'Proves We're Still Here And Serious'" - Scrip, 2 Nov, 2017.)*

"Now the parallel development that needs to follow to maximize what this drug can deliver is to continue with monotherapy as we have started, add on standard of care combinations in earlier lines, so that is lenalidomide/pomalidomide, the drugs that are commonly used in those lines, and then start investigating novel combinations," Hoos said. "Those novel combinations could possibly change the treatment landscape in myeloma quite dramatically." The first combination GSK plans to explore is BCMA in combination with **Merck & Co. Inc.**'s PD-1 inhibitor *Keytruda* (pembrolizumab). PD-1 has not been shown to be very active as a monotherapy in multiple myeloma, but it has boosted response rates in combination with **Celgene Corp.**'s *Revlimid* (lenalidomide), according to Hoos.

"I have the expectation that for BCMA, [which] is so active already on its own, that if you combine it with immunotherapy you might actually enhance the impact significantly and that would be different," he said.

Behind BCMA is a NY-ESO-1 cell therapy, developed under a partnership with **Adaptimmune Therapeutics PLC**, essentially a T-cell receptor genetically engineered to have a high affinity for a specific cancer target. *(Also see "$350m Adaptimmune deal shows GSK still does cancer R&D" - Scrip, 2 Jun, 2014.)* The therapy has shown encouraging response rates in early clinical trials in synovial sarcoma and multiple myeloma. GSK exercised its option on the drug last year.

"It is the first cell therapy that works in solid tumors," Hoos said. "We are now pushing that to go into different diseases."

Another clinical stage drug is an ICOS agonist in Phase I development as monotherapy and in combination with Keytruda, with data anticipated by the end of the year.

"Everybody is looking to what comes after PD-1. What is the next big checkpoint target," said Hoos. "I believe agonists like ICOS, OX40 or TLR4 could be important," he said, though their clinical properties are different so they may behave differently than a PD-1/L1 inhibitor. *(Also see "GSK Looks To Cross PD-1 Gap And Leap To Next-Generation IO Backbone" - Scrip, 4 Nov, 2015.)*

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Allergan Relying On 'Six Stars' To Blunt Restasis Blow

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One of **Allergan PLC**'s key themes in 2017 was its "six stars" – late-stage research and development programs seen as blockbusters in the making – and the company has expanded its focus in 2018 to include other mid- to late-stage assets that also could help offset the near-term loss of Restasis revenue.

Allergan CEO Brent Saunders told investors during the recent J.P. Morgan Healthcare Conference in San Francisco that the company expects generic competition for its blockbuster dry eye drug *Restasis* (cyclosporine) to hit the market after the second quarter of 2018. That means the pressure is on for new products to make up for declining Restasis revenue in the second half of this year, especially since it's not the only product losing patent exclusivity in 2018.

Saunders also informed investors at the J.P. Morgan meeting that Allergan expects this year's non-GAAP revenue to total from $15bn to $15.3bn versus last year's projected $15.88bn to $16.03bn in revenue (actual year-end 2017 earnings will be reported Feb. 6). The 2018 projection includes the impact of layoffs the company first revealed during its third quarter earnings call in November.

Allergan confirmed in early January that it will cut 1,000 jobs and 400 open positions to cushion the blow of declining revenue due to the loss of patent exclusivity for Restasis, *Estrace* (estradiol vaginal cream), the Alzheimer's drug *Namenda XR* (memantine extended-release), the ulcerative colitis therapy *Delzicol* (mesalamine) and the acne treatment *Aczone* (dapsone).

Saunders said in an interview during the J.P. Morgan meeting that one of the reasons the company so aggressively defended its Restasis intellectual property was to avoid job cuts. Allergan shifted ownership of its Restasis patents to the Saint Regis Mohawk Tribe to benefit from the tribe's sovereign immunity in an *inter partes* review (IPR) proceeding, but the patents still were invalidated in a separate court case with generic drug makers.

Scrip spoke with Saunders along with Allergan Chief R&D Office David Nicholson and Chief Commercial Officer William Meury about the company's six stars and emerging pipeline prospects in a joint interview.

SOME STARS MAY SHINE IN 2018

"Last year, one of the accomplishments that we're incredibly proud of is that all six stars moved into Phase III and one of the programs we filed the NDA for," Saunders said. "I think as we go into 2018 it's a combination of bringing those six programs closer to or over the finish line and replenishing them with additional programs."

Esmya (ulipristal) for uterine fibroids was submitted for US FDA approval last year and the agency's decision is expected in May. "We expect to launch Esmya in the middle of 2018, which could turn out to be a flagship product of our women's health business," Meury said.

In addition to Esmya, Allergan's six stars include the oral CGRP inhibitors ubrogepant, which is in Phase III for the acute treatment of migraine headaches, and atogepant, which is in Phase IIb as a prophylactic treatment for episodic migraines; results from both studies are expected in the first half of 2018.

Also, Phase III results in wet age-related macular degeneration (AMD) for the longer-acting VEGF inhibitor abicipar pegol, licensed from **Molecular Partners AG**, will be available in the second half of 2018. Phases III results in major depressive disorder (MDD) for the NMDA receptor modulator rapastinel (GLYX-13) – acquired in the 2015 purchase of **Naurex Inc.** – are due in 2019 and 2020.

"I view 2017 as a year of incredibly hard work. And in 2018 we're starting to get the data readouts from all the hard work that my colleagues in R&D have put in over the last few years," Nicholson said.

Allergan's other two stars sit in its gastrointestinal (GI) portfolio – cenicriviroc (CVC) for non-alcoholic steatohepatitis (NASH) and relamorelin for diabetic gastroparesis, both of which moved into Phase III in 2017. Topline results are expected in 2020 for the ghrelin agonist relamorelin, which comes from acquired partner **Motus Therapeutics Inc.** (formerly **Rhythm Pharmaceuticals Inc.**) *(Also see "'Open Science' In Action: Allergan Exercises Option For Motus After Gastroparesis Study" - Scrip, 28 Oct, 2016.)*

However, data from the CCR2 and CCR5 inhibitor CVC, acquired in the 2016 purchase of **Tobira Therapeutics Inc.**, aren't expected until after 2020. The drug will be tested in combination with FXR agonists, including a preclinical asset acquired alongside CVC and a mid-stage drug from **Novartis AG**.

BEYOND THE SIX STARS

Women's health, ophthalmology, central nervous system (CNS), GI, medical aesthetics, anti-infectives and urology are Allergan's seven key therapeutic areas. Within those areas, Nicholson noted that the company has 50 programs in development, from early-stage through registration.

He said Allergan came up with the "six stars" concept last year for Esmya, the CGRP inhibitors, abicipar, rapastinel, relamorelin and CVC, "because they were in or about to enter Phase III, they meet a large unmet medical need, and therefore they're going to be commercially successful when we get them approved. Now they're all in Phase III, so we're starting to say, 'OK, now we can spend a bit more time on a few more programs.'"

Allergan's emerging stars include *Vraylar* (cariprazine), which was approved for schizophrenia and manic or mixed episodes of bipolar I disorder in 2015. A supplemental new drug application (sNDA) will be submitted to the FDA this year for bipolar depression. The company believes that the drug's sales could grow from about $500m based for its two initial indications to more than $1bn with bipolar depression added to Vraylar's label, rising to a $2bn to $3bn product with additional indications, including MDD.

Allergan also is moving the selective Interleukin-23 (IL-23) inhibitor brazikumab into the spotlight in 2018, with plans to begin a Phase III program in Crohn's disease and a Phase II study in ulcerative colitis this year. Additionally, an unnamed RORγT modulator is in Phase II for psoriasis with Phase III studies initiating in 2020, while a sustained-release formulation of bimatoprost for glauco-

ma in Phase III with an expected launch in 2020. The company's two marketed bimatoprost products are *Lumigan* for glaucoma and *Latisse* for eyelash growth.

Allergan's executives are optimistic about the pipeline's prospects, particularly in some of the company's largest therapeutic areas, which could grow larger than aesthetics business dominated by the flagship product *Botox* (onabotulinumtoxinA).

"Between the products that we have today and our compounds in development, our CNS and GI businesses could be our largest product lines – and that's saying something given how large our aesthetics business is right now," Meury said.

Allergan reported $2.7bn in medical aesthetics revenue for the first nine months of 2017 and $2.7bn for eye care, both of which include US and international product sales. In its US general medicines business, the company reported $1bn in sales for CNS brands and $1.2bn for GI products during the same period.

Botox is Allergan's biggest seller and it's sold across multiple therapeutics areas. In addition to reducing forehead wrinkles and frown lines, the drug is approved to treat chronic migraine headaches, overactive bladder and several other conditions; in fact, therapeutic uses now exceed aesthetic sales.

The company faces competition from other neurotoxins – both marketed products and investigational therapies – but its executives aren't worried about a closely-watched product candidate from **Revance Therapeutics Inc.** Revance reported Phase III results in early December for RT002 (daxibotulinumtoxinA), which in some patients appeared to reduce wrinkles for a longer period than Botox. But with late-stage studies ongoing and an FDA submission planned for 2019, Allergan's product won't feel the impact from RT002 sales until 2020 at the earliest.

Saunders and Meury insist that Botox is so well known among consumers and physicians that it will take a long time for doctors to get used to injecting Revance's product and for patients to get comfortable with the new brand's name, efficacy and safety.

"In the meantime, we'll be expanding our Botox market," Meury said. Also in the meantime, however, **Evolus Inc.** is awaiting FDA approval for its neurotoxin product prabotulinumtoxinA (DWP-450) in the treatment of glabellar lines (wrinkles between the eyebrows) with a May 15 PDUFA date. *(Also see "Keeping Track Of New Drugs: US FDA Review Queue Adds Spark Gene Therapy, Amgen Migraine Antibody, Bayer Oncologic" - Pink Sheet, 21 May, 2017.)* The Irvine, Calif.-based company revealed in a Jan. 9 US Securities and Exchange Commission filing that it intends to raise up to $75m in an initial public offering to support commercialization of the product.

Evolus, via parent company **Alphaeon Corp.**, licensed DWP-450 from the Korean firm **Daewoong Pharmaceutical Co. Ltd.** for aesthetic indications in the US, EU and several other markets. *(Also see "Daewoong Strikes New Deal For Botox Rival" - Scrip, 29 Mar, 2015.)* The company has an option that expires at the end of 2018 to license the product for therapeutic indications in the same territories.

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Which Biotechs Enjoyed A 'JPM Jump' - And Which Lost Out?
http://bit.ly/2DChJJL

Mylan CEO Bresch On How Mylan Is Different Than Teva

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Mylan NV CEO Heather Bresch had a message for investors at the pharma industry's big J.P. Morgan Healthcare conference in San Francisco that was as much about what Mylan is not as about what it is. What Mylan is not is **Teva Pharmaceutical Industries Ltd.**

Bresch was as keen as ever to separate Mylan from the competition, not surprising given that Teva is in the first phases of a massive restructuring, cutting 25% of the workforce and talking about rationalizing its US generic drug portfolio in response to continuing pressure in the US generic drug market, among other challenges. *(Also see "Schultz Swings The Cleaver At Teva, Cutting 25% Of The Workforce" - Scrip, 14 Dec, 2017.)*

"You've got lots of companies, and we are not all painted with the same brush," Bresch said in an interview at the conference.

Indeed, while Mylan confronted its own challenges related to the branded rescue allergy medicine *EpiPen* (epinephrine) in 2016, including a Congressional probe into the drug's pricing and a significant financial hit, the company has largely cycled through that setback and has managed the US generic drug dynamics better than some competitors. *(Also see "EpiPen's Swollen Price May Trigger Patient Assistance Program Probes" - Scrip, 24 Aug, 2016.)*

"People are so familiar with the US generics, and I've said it is an important part of our business to be sure, but 50% of our revenues are outside the US and this diversification has allowed us to absorb the volatility," Bresch said. "I think that is resonating."

The company's stock price – which management has declared undervalued – began to pick up momentum late in 2017 and into the early part of 2018. The company's stock was $46.32 on its opening Jan. 18, which was up 28% from where it was trading Nov. 6, when the company released third quarter financials.

Mylan completed a $1bn stock repurchase program Jan. 9, which was all about putting "our money where our mouth is," Chief Financial Officer Ken Parks said during a breakout session with investors at J.P. Morgan.

What has been comforting to investors are signals that Mylan's complex generic drug and biosimilar strategy is starting to deliver. The company secured the first FDA approval for a generic version of Teva's multiple sclerosis blockbuster *Copaxone* (glatiramer) at the important 40 mg dose, as well as the 20 mg dose, in October, which further hobbled Teva.

In December, Mylan's first biosimilar was approved in the US under a collaboration with **Biocon Ltd.** *Ogivri* (trastuzumab-dkst) is the first biosimilar version of **Roche**'s *Herceptin* (trastuzumab) approved in the US for HER2+ breast cancer and gastric cancer. The timeline for a launch is uncertain but Mylan did reach a patent settlement and licensing agreement with Roche on trastuzumab in March.

Mylan is also hopeful that it will be the first to market a fully interchangeable generic version of **GlaxoSmithKline PLC**'s *Advair* (fluticasone/salmeterol) in the US this year, and anticipates launching a biosimilar version of **Amgen Inc.**'s *Neulasta* (pegfilgrastim). Success on either goal would be an achievement.

"Mylan has always gotten credit for its operating prowess, quality and manufacturing, but I think now [we can] add to that science capability," Bresch said.

A PLAN FOR SUCCESS

Turning approvals into commercial wins won't be as straightforward as Mylan's experience with small molecule drugs has been. Complex drugs and biosimilars don't have the same level of automatic switching that occurs with small molecule drugs, and early experience with the first biosimilars to launch in the US has demonstrated significant headwinds for biosimilars competing against well-entrenched brands.

"Copaxone has certainly gone as well, if not a little better, than we had anticipated," Bresch said. "Complex products by their nature are not going to have the same kind of uptake that small molecules did." For a drug like Copaxone, which patients can take for years, Bresch pointed out that it really comes down to new scripts as an indicator of performance.

The launch of a biosimilar Neulasta could be different, she said. "It will be interesting to watch because it's not a product that you get on and then are on for the rest of your life. It's a short period-of-time, where you see more turnover," she added. Mylan received a complete response letter for its biosimilar version of Neulasta in October, marking the fourth company to receive a CRL from FDA for a biosimilar version. But Mylan President Rajiv Mallik said the company has responded to the CRL and could see action on the application in mid-2018.

When it comes to commercializing generic drugs or biosimilars, Bresch said Mylan is well positioned because of its experience selling branded drugs like EpiPen. On the branded side of the business, Mylan has also filed a nebulized once-daily long-acting muscarinic antagonist (LAMA) for chronic obstructive pulmonary disease (COPD) with partner **Theravance Biopharma Inc.** The company has a respiratory/allergy sales force, as well as a sales force that sells to hospitals and institutions.

"Our infrastructure is really allowing us to be pretty nimble with our products and detailing from a specialty perspective," Bresch said. "We don't need to set up something new. How we direct or call on a different therapeutic category could alter."

Despite the positives working in Mylan's favor, the US drug pricing pressure is not expected to abate in the near-term. Customer consolidation and the launch of new third, fourth, or fifth-to-market small molecule generics, as FDA works through an ANDA backlog at the agency, are driving down prices of commodity-like drugs that are already priced at cents, not dollars.

Teva's new CEO Kare Schultz has said the company will reevaluate its US generic drug portfolio and could raise prices on some drugs or discontinue them altogether if they aren't profitable. At his inaugural J.P. Morgan meeting in his new role, Schultz said the review could affect about 10% of Teva's US generic portfolio.

But Bresch told investors in a J.P. Morgan breakout session that raising prices or rationalizing the portfolio is not something Mylan is going to be doing in any sort of strategic process.

"It's not about rushing in and rationalizing products that you don't necessarily make money on. That's not how we run facilities," she said. "We run facilities that are making 15 billion tablets and capsules a year, so it's about how you are managing this portfolio."

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Exelixis CEO Eyes Expanded Indications For Cabometyx

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With the recent launch of **Exelixis Inc.**'s multi-kinase inhibitor *Cabometyx* (cabozantinib) in first-line renal cell carcinoma on track, CEO Michael Morrissey is looking forward to expanding into hepatocellular carcinoma, as well as other tumor types.

Cabozantinib, which is partnered with **Ipsen** in Europe, cleared the US FDA on Dec. 19 for first-line treatment of previously untreated metastatic renal cell carcinoma (RCC), a filing supported by the Phase II CABOSUN study. This expanded use beyond the drug's FDA approval in April 2016 for patients with advanced RCC who previously received anti-angiogenic therapy.

In an interview at the Biotech Showcase meeting, held Jan. 8-10 concurrently with the J.P. Morgan Healthcare Conference in San Francisco, Morrissey noted that the company was ready to launch immediately in the earlier line of RCC therapy and that the launch is going well.

"We will see how that goes from the standpoint of market share growth, but obviously we are looking to compete for every customer in the first-line setting and second-line setting every single day," Morrissey said. The space is becoming more competitive, however.

COMBINATIONS

Bristol-Myers Squibb Co. reported positive results for *Opdivo* (nivolumab) with *Yervoy* (ipilimumab) in first-line kidney cancer in the CheckMate 214 study in November, including an overall survival (OS) benefit compared with **Bayer AG**'s *Sutent* (sunitinib) and is pursuing a broader label. Opdivo already is approved for second-line use.

Also, Roche's PD-L1 inhibitor *Tecentriq* (atezolizumab) used with its VEGF inhibitor *Avastin* (bevacizumab) and chemo demonstrated a benefit over Avastin plus chemo as first-line therapy in the Phase III IMmotion151 study in advanced kidney cancer.

Cabozantinib is being positioned for use in combination with checkpoint inhibitors in these and other tumor types (*see table below*).

The Phase III CheckMate 9ER study is evaluating cabozantinib in combination with Opdivo and Yervoy in first-line RCC. Cabozantinib also is being tested in combination with Tecentriq in a Phase Ib study.

Morrissey explained that a great deal of energy and focus is going into looking at combination approaches with checkpoint inhibitors. "There are lots of ideas, lots of biology and pharmacology and biology behind those approaches, combining these two orthogonal mechanisms can be a powerful way to go," Morrissey said.

CELESTIAL

The development program includes research testing cabozantinib with Opdivo, plus or minus Yervoy, in hepatocellular carcinoma as part of the Phase II CheckMate 040 study.

Full data for cabozantinib as a monotherapy in the CELESTIAL study of hepatocellular carcinoma were presented at the American Society of Clinical Oncology Gastrointestinal Cancers Symposium on Jan. 19, following a positive top-line release in November.

The median OS in the study was 10.2 months for cabozantinib and eight months for placebo, a 24% reduction in the risk of death and a highly statistically significant result (p=0.0049). Median progression-free survival (PFS) more than doubled at 5.2 months for cabozantinib versus 1.9 months for placebo, a 56% reduction in the risk of progression or death, also a statistically significant result.

Filings in liver cancer are slated for the first quarter in the US and the first half in Europe.

Published online 21 January 2018

Clinical Development Program For Cabozantinib

INDICATION	COMBINATION REGIMEN	DEVELOPMENT STATUS
Renal Cell Carcinoma		
First-line (intermediate or poor-risk)		Approved December 2017
First-line	With Bristol's *Opdivo* (nivolumab), plus or minus Yervoy (ipilimumab)	Phase III CheckMate 9ER pivotal study started in July 2017, co-funded with Bristol
Hepatocellular carcinoma		
Second-line		US and European filings set for 1H2018.
Advanced disease	With Bristol's Opdivo, +/- Yervoy	Phase II: Part of CheckMate 040
Non-small cell lung cancer		
EGFR wild-type		Phase II
Molecular alterations in RET, ROS1, MET, AXL or NTRK1		Phase II
Genitourinary Tumors, Including Bladder And Urothelial Cancers		
Genitourinary tumors	With Bristol's Opdivo, +/- Yervoy	Phase I: Through NCI's CTEP
Advanced solid tumors	With Roche's *Tecentriq* (atezolizumab)	Phase Ib study started June 2017

Click here to see full table including signal search opportunities to inform potential development.
http://bit.ly/2FdADE0

Merck Hits IO Bullseye With Keytruda Combo In First-line Lung Cancer

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Merck & Co. Inc.'s victory with its PD-1 inhibitor *Keytruda* showing an overall survival benefit in the KEYNOTE-189 first-line metastatic non-small cell lung cancer study shows once again that the company has a knack for getting it right in the most important immuno-oncology indications.

The KEYNOTE-189 study tested Keytruda (pembrolizumab) with **Eli Lilly & Co.**'s *Alimta* (pemetrexed) and cisplatin or carboplatin chemotherapy versus Alimta and cisplatin or carboplatin in 614 patients who had metastatic non-small cell lung cancer (NSCLC) with no EGFR or ALK genetic aberrations and no prior systemic therapy. The study took all comers, regardless of the level of expression of the PD-L1 biomarker.

Patients in the control arm who progressed underwent treatment assignment unblinding and were allowed to immediately cross over and get Keytruda.

Merck reported in a topline release on Jan. 16 that an interim analysis of the study showed that the test drug arm met the co-primary endpoints of progression-free survival (PFS) and overall survival (OS). The company confirmed a report in a Barclay's analyst note that the results were positive across all levels of PD-L1 expression.

Morningstar Research estimates that NSCLC will account for close to half of the total immuno-oncology (IO) market. Leadership in this indication means leadership overall.

Meeting the primary endpoints at the interim analysis means a hazard ratio below 0.70 is "more than believable," Bernstein Research analyst Tim Anderson commented in a Jan. 16 note.

BELIEVERS VINDICATED

The outcome vindicates analysts, like Anderson, who have had faith in the study, despite headwinds.

Merck suffered a market backlash in October when it said that it was changing the primary endpoint in the KEYNOTE-189 study from PFS alone to dual co-primary PFS and OS endpoints, with results expected in February 2019 – a year later than expected – though there was potential for an earlier release of interim analyses. *(Also see "Merck Stresses Overall Survival In Keytruda/Chemo '189 Trial Revamp" - Scrip, 27 Oct, 2017.)* At the same time, the company withdrew a filing for the combination in Europe, which was another disappointment.

"We argued that a delay (to capture OS as part of the primary analysis) made tactical sense. Today's news puts to rest an occasional bear-case concern that the delay may have signaled weakness in the conduct of the trial of some sort," Anderson said.

"Commercially, it secures a high price and brings forward the windfall that analysts had deferred following October's design change. As important, it restores MRK's leadership in IO," he added.

NEXT STEPS

Merck now plans to submit the KEYNOTE-189 results to regulatory authorities, although execs pointed out during a Jan. 9 presentation at the J.P. Morgan Healthcare Conference in San Francisco that the company does not need a supplementary approval and new labeling in order to promote the data, because the regimen already is approved in first-line NSCLC.

The Keytruda/Alimta combination won accelerated approval from the FDA in May 2017 for this indication, based on data for 123 treatment naïve patients enrolled in the "G" cohort of the KEYNOTE-021 study. In the trial, the objective response rate (ORR) was 55% for Keytruda/Alimta/carboplatin versus 29% for Alimta with carboplatin, a reduction in risk of 45%. Progression-free survival also was improved at 13 months versus 8.9 months for the control. *(Also see "Keytruda/Chemo Combo Approval Means Merck Holds Crown, For Now" - Scrip, 10 May, 2017.)*

At the time, Merck estimated that about one-quarter of the first-line market was getting Alimta.

KEYNOTE-189 will serve as a confirmatory study for full approval.

"This positive OS reading for KEYNOTE-189 comes well ahead of expectations, and should put to rest any skepticism surrounding the Phase I/II KEYNOTE-021G results that led to Keytruda's accelerated approval in first-line non-squamous NSCLC," Biomedtracker analyst Dustin Phan commented in a Jan. 16 report.

Keytruda won the first and still only immuno-oncology approval for use as a monotherapy in first-line metastatic NSCLC in October 2016 for treatment-naïve patients with a level of at least 50% PD-L1 expression. **Bristol-Myers Squibb Co.**'s competing PD-1 inhibitor *Opdivo* (nivolumab) failed in the first-line monotherapy space, a major stumble some chalked up to using different levels of PD-L1 expression for stratification compared to Merck. Data from Bristol's CheckMate 227 data for Opdivo in combination with *Yervoy* (ipilimumab) in first-line NSCLC are expected in the first half of 2018 and are eagerly awaited.

Keytruda previously was approved for second-line NSCLC.

Successes in NSCLC have allowed investors to be forgiving of Phase III confirmatory trial failures in smaller value markets like head and neck cancer and gastric cancer, especially since the drug did not lose approval for these indications. *(Also see "Commercial Fallout From Merck's Failed Keytruda Gastric Cancer Trial May Be Limited" - Scrip, 15 Dec, 2017.)*

During the company's J.P. Morgan presentation, Merck CEO Kenneth Frazier said that uptake of Keytruda in first-line NSCLC has been "very, very strong, particularly with respect to the high expressers in monotherapy, but also with others in monotherapy in first-line lung."

"With the chemo combination, we're seeing really good traction now that we've got subsequent data that shows what the trend is on overall survival. And in the long run, as you know, what really is important in these markets to patients and their physicians is, can you demonstrate overall survival? And that's why we decided to make a co-primary endpoint

out of overall survival in our '189 study. So we're very pleased with the uptake in the US and around the world, and we have many more opportunities to grow this going forward," Frazier said.

COMPETITIVE OUTLOOK

The timing of Merck's announcement is "critical" because pivotal data for competitors in the same setting is due in the first half of this year, Phan noted. On top of the interim analysis of CheckMate 227, the market is awaiting overall survival data for **Roche**'s PD-L1 inhibitor *Tecentriq* (atezolizumab)/chemo combination in the Phase III IMpower150 study, which already reported positive PFS data. *(Also see "Roche Powers Forward With First-Line Tecentriq In Advanced NSCLC" - Scrip, 7 Dec, 2017.)* Other important studies of Keytruda in lung cancer are due to report as well (*see chart*).

Jefferies analyst Jeffrey Holford said in a Jan. 16 note that the '189 news was positive for Merck, but added that "significant threats to the Keytruda NSCLC franchise remain with the key one being Roche's Tecentriq, in our view."

"We continue to expect positive data from IMpower studies across squamous and non-squamous NSCLC as well as in SCLC [small cell lung cancer] during H1'18. This would give Roche a powerful data set to take share in the larger community setting, where oncologists prefer a drug that they can use across a broad array of patients," Holford said.

Overall survival data for **AstraZeneca PLC**'s MYSTIC study for its IO-IO combo, including the PD-L1 inhibitor *Imfinzi* (durvalumab) with the CTLA-4 inhibitor tremelimumab, also are due in the first half. The study missed PFS, but could still prove an OS benefit. *(Also see "MYSTIC Misses: Devastation For AstraZeneca As Imfinzi Fails PFS Endpoint In NSCLC" - Scrip, 27 Jul, 2017.)*

"While Merck has already launched Keytruda in the first-line NSCLC setting in the US based on progression-free survival data from a smaller mid-stage study, the KEYNOTE-189 study will enable Merck to show the survival benefit of Keytruda in a large study based on a primary endpoint, which carries more significance with the medical community," Morningstar Research analyst Damien Conover said in a Jan. 16 note.

"We continue to expect Keytruda to gain close to 40% of the first-line setting, and the early KEYNOTE-189 data will help support that market share," Conover wrote.

The analyst explained to *Scrip*, however, that some doctors are still waiting for the OS results before more aggressively prescribing in this setting and that once these data are published, there will be more of a shift toward Keytruda.

VENUES FOR DATA RELEASE

Possible venues for release of the full data are two meetings in April – the American Association for Cancer Research meeting and the European Lung Congress – and the American Society of Clinical Oncology conference in June.

Howard (Jack) West has been one of the prominent lung cancer specialists to urge caution about acting on KEYNOTE-021G, without OS data.

The clinician commented to *Scrip* that many experts felt that the FDA's accelerated approval of the combination was "premature" as it was based on data for only 123 patients with only preliminary OS results at the time of approval.

"The report of statistically significant positive results for both PFS and OS with initial cisplatin or carboplatin with pemetrexed and concurrent pembrolizumab over the same chemo alone corroborates the KN-021G trial on a larger scale that we really needed to see," said West, medical director thoracic oncology at the Swedish Cancer Institute in Seattle.

West said that he expects several other trials of various chemo backbones with PD-1 and -L1 checkpoint inhibitors will also demonstrate at least a PFS benefit and most likely an OS benefit as well. However, he believes that the pemetrexed/carboplatin/pembrolizumab combination will be "the clear pace-setter for this population" and any "competing regimen would need to not just be comparable, but would need to be significantly superior to this one in order to provide a real incentive to change from carbo/pemetrexed/pembrolizumab," he said.

West added, however, that he would also like to see the rate of crossover from the control arm to immunotherapy in the KEYNOTE-189 study to make a real comparison – virtually all of the participants should have had that sequential immunotherapy option.

Merck has said in the past that because of the dramatic decline in PFS for the chemotherapy arm, everyone in the control arm was getting Keytruda pretty quickly and stressed that it was very important to understand Keytruda's performance as an early versus late treatment.

Furthermore, West noted, Keytruda monotherapy is the standard of care for the 30% of patients with high PD-L1 expression, based on the data from the KEYNOTE-024 study.

"It will be critical to assess whether the results of KEYNOTE-189 are still compelling once that subgroup is removed, because the most relevant question for 2018 is whether patients with low or no PD-L1 expression should receive concurrent chemo/immunotherapy or sequential chemo followed by immunotherapy." West said.

Bernstein's Anderson noted that Merck's decision to elevate OS was made in part so that it could answer questions about how to manage PD-L1 subgroups for practicing physicians. How these questions are answered "will determine how big is the opportunity, and thus how impactful is today's win for MRK over the competition," Anderson said.

Published online 17 January 2018

PharmaMar Endures Second Recent Setback With Phase III Ovarian Cancer Failure: **http://bit.ly/2E26pV6**

China In 2018: Watch Out For AI, CAR-T, Biotech Unicorns

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China's appetite for new technologies seems to be insatiable, and the arrival of the New Year is likely to bring profound changes to pharma and the overall healthcare sector, driven by the government's forceful policy pushes.

During the 19th Chinese Communist Party Congress held in October last year and the National Economic Work Conference held in mid-December, the ruling party's decision makers had set meeting the Chinese people's increasing demand for better lives as a final goal for every policy task.

Meanwhile, improving health service quality in tier three and tier four cities to appeal to rural migrant workers has been deemed a key work priority for 2018.

Already, the China FDA has issued a plethora of policies and draft regulations to streamline the clinical trial and new drug approval processes, and to allow certain foreign study data to be used towards an approval in China, leading to hopes for new drug approvals to take off in 2018 and beyond.

The policy push is likely to catalyze the birth of healthcare giants comparable with that of China's "BAT" group (Baidu, Alibaba and Tencent), noted Wang Ran, CEO of the US-China venture capital fund, China E-Capital, in an article. Two promising areas singled out by Wang are new drug development and disease diagnosis and monitoring.

Several high-profile approvals of CAR-T therapies by the US FDA have bolstered the confidence of Chinese developers in the gene technology segment.

Seizing the opportunity of developing novel therapies quickly and cost-effectively, a new crop of Chinese biotech startups is blossoming, aiming to treat China-prevalent diseases with proven technologies.

One of these is Beijing **ImmunoChina Medical Sciences and Technologies Co**., a startup founded by three Tsinghua graduates in 2015. Among them, He Ting is one the founders who jumped on then new CAR-T gene engineering technology to treat a refractory and relapsed form of blood cancer, acute B-Cell lymphoma.

"Gene therapies' development has seen several breakthroughs in saving many patients' lives, so I decided to devote our business to it," He said in an interview with Tsinghua innovative incubator, where the company started.

The year 2015 proved to be crucial; the Beijing startup obtained angel investment from the Shenzhen-based Cowin Capital, and the capital injection propelled the company to start a Phase I clinical study.

In 2017, ImmunoChina obtained CNY50m ($7.8m) in its latest round of funding which allows the startup to actively recruit patients for its asset, IM19 CART for B-Cell ALL patients aged four to 65 years old.

With the fresh funding and large patient population, the plan is to complete the study by May 2018.

Meanwhile, on Jan. 8 the Beijing startup inked a collaboration with Shanghai-based **Harbour BioMed**, licensing Harbour's H2L2 transgenic mice antibody platform to develop CAR-T antibodies to treat blood cancer.

Another Chinese CAR-T developer, **Nanjing Legend Biotechnology Co**, surprised nearly everyone with a late-December multi-million dollar deal with **Janssen Biotech Inc.**, a subsidiary of **Johnson & Johnson**. Janssen agreed to pay an upfront of $350m and collaborate with Nanjing Legend for LCAR-B38M, a CAR-T therapy for multiple myeloma with B-cell maturation antigen (BCMA).

Additionally, Legend is eligible for milestone payments, and the two companies also agreed to share the cost and split the profits except in Greater China where Legend retains 70% profit.

Legend surprised the field with a late-breaking oral presentation at the ASCO annual meeting in June showing durable remissions with BCMA-specific CAR-modified T-cells.

AI+

As China vows to become a major player in artificial intelligence, the government On Dec.14 released a national Three-Year Plan in AI.

The plan prioritizes medical imaging diagnostics platform, along with video and imaging identification systems and service robotic devices for more policy support. New drug development aside, disease diagnosis powered by AI is another area poised to see increasing investment, noted China E-Capital's Wang.

Alibaba, for one, is developing an AI+health platform - the goal is to gather patient and medical data in a bid to get a deep understanding of diseases. The plan is to cover over 20 medical conditions.

Meanwhile, the e-commerce giants continue to work with pharma firms to digitalize disease management. Seeing the potential of reaching out to millions of smartphone savvy young users, both **GlaxoSmithKline PLC** and **Sanofi** have signed up deals with Alibaba's subsidiary **AliHealth** to promote HPV vaccines, diabetes treatment and blood thinner. The latest pharma leaping into the fray is **Merck & Co. Inc.** which inked a deal with Alihealth to provide information on its *Gardasil* HPV vaccine approved in late May.

BIOTECH UNICORNS

With the fast funding inflow, Chinese biotech companies including genome firms are seeing their valuations skyrocket.

One of them is **iCarbonX**, founded by Wang Jun, former CEO of China's largest genome company, **BGI-Shenzhen**. Started in 2015, Icanbox raised $154m in its 2016 round of financing, led by Tencent and putting the valuation of the company at $1.1bn.

There has been a rapid rise of the so-called unicorns, a term coined by Cowboy Ventures founder Aileen Lee in 2003 to describe these startups backed by private equity funds and valued at over $1bn but not publicly traded.

Icarbonx's goal is to digitalize human lives to improve their health, and other leading investors include domestic cell therapy developer **Vcanbio** and software developer UEC Group.

Another notable biotech unicorn is **Innovent Biologics Inc.** Based in Suzhou, InnovetBio raised $260m in its D round financing in 2016. While developing biosimilars of some big-selling biologics, Innoventbio is also betting on novel biologics, with an ongoing Phase III study for its PD-1 checkpoint inhibitor IBI308.

The company recently started its first-in-human study in the Beijing PUK Hospital for a PCSK9 inhibitor to treat hyperlipidemia. Innovent Bio is reportedly a subject being considered for investment from Capital Group Cos., one of the largest investment firms in the US.

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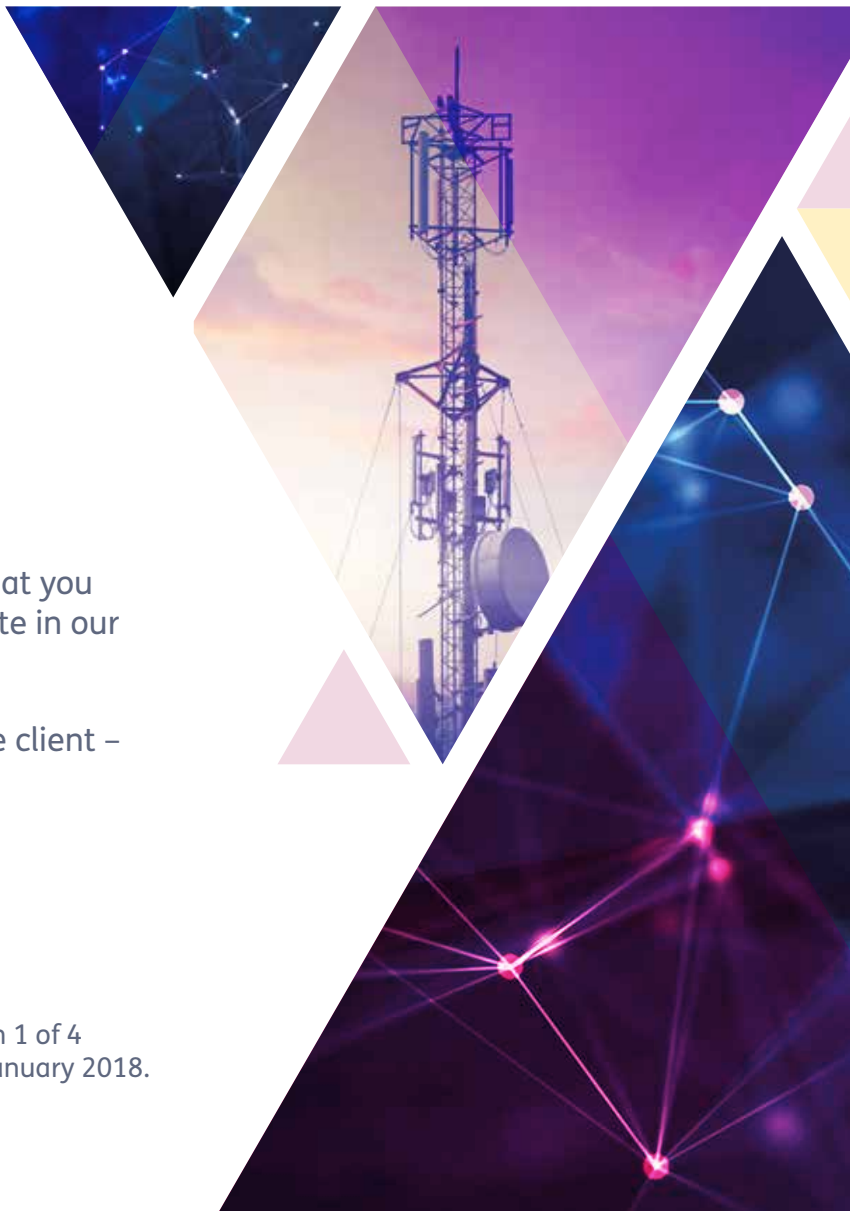

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AstraZeneca's Pangalos On How He Turned Around R&D Productivity

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Mene Pangalos

Source: AstraZeneca

When Mene Pangalos first joined **AstraZeneca PLC** as head of its Innovative Medicines and Early Development Biotech Unit in 2010 he was charged with turning around a pipeline that had become a byword for unproductivity. He embarked upon a root and branch reform of R&D that has now produced a pipeline viewed by some analysts as one of the most exciting in the industry. And what's more, he's spending less money.

Pangalos revealed the first details of his prescription for the company's ills –a five dimensional framework for decision making that is now the cornerstone of the company's R&D strategy – in a highly cited 2014 paper in *Nature Reviews Drug Discovery* that surprised many with its candour about what had gone wrong, and what it would take to put right. Four years later, he has the data to demonstrate his remedy's efficacy and he's back in the same journal with a much more cheerful sequel that he admits was a "bit more easy to publish" (Jan. 19, 2018).

The framework he and his small team devised – dubbed "5R" – aims to challenge scientists to validate or invalidate their scientific hypothesis at a project's inception and throughout its lifetime. The new paper details how implementing it has made AstraZeneca's project success rate from candidate drug nomination to Phase III completion shoot up from 4% in 2005-2010 (compared with an industry average of 6%) to 19% between 2012-2016, while the average for the industry (between 2013-15) still languishes at 6% for small molecules. When they began, AstraZeneca's ambition had been to improve project success rates from preclinical to launch from to at least 8%.

The number of products progressing into Phase III trials has been maintained at 2010 levels despite the number of candidate drugs in development having halved.

Pangalos told *Scrip* the "warts and all" tack he took in the first paper, highly unusual for a big pharma company, was positively received externally and this spirit of openness still runs through the new paper. Though being careful not to reveal commercial details or anything that would compromise its IP or programs, the paper goes into specifics about what AstraZeneca learnt during the process. He said his hope was that it would prove useful for other companies, particularly smaller firms, that may also be having productivity issues, and help the industry as a whole.

Meanwhile, Pangalos has seen a change in the way the company is viewed externally. At the start of the decade it faced a steep patent cliff and declining revenues. "When I first joined the company, I would say AstraZeneca was viewed at least externally as having a very poor R&D organization – it was unproductive and the $5bn we were spending wasn't a good return on investment," he said. "The conversations I would have with investors were 'Please don't spend any more money. We think you're a nice guy Mene, you're smart, but you won't turn a company like that round', and the trajectory that people had the company on was one of a downward spiral with no uptick.

> 'I was surprised when I joined at how bad it was'

"Today when you look at the investor sentiment and the number of buy and overweight ratings, you know, it's very, very different to where it was in 2012 or 2010 and the nice thing is that it is not just the pipeline that's full of promise, there are drugs that have come out of it… drugs like Tagrisso, Lynparza, Fasenra, Imfinzi, and that is what's driving the improvement in productivity."

A NEW DIRECTION

Arriving, via Pfizer, from Wyeth in 2010, Pangalos said he was keen to join a European company determined to change its R&D direction. "It was a fantastic opportunity doing a very big role across therapy areas and it was a big step up for me from what I was doing at Wyeth," where he had been head of research. But he admits to having been a little taken aback at the situation he found at AstraZeneca. "I was surprised when I joined at how bad it was."

His remit was simple: "I had to fix R&D – that was the reason they brought me in, to try and transform the company."

The first step was to understand what had gone wrong. Like many of its peers, Pangalos said, AstraZeneca had been playing a numbers game. Without a clear idea of how to predict successful R&D programs, firms were just moving more projects into the clinic and hoping that their success rate held steady. "The attitude was: 'We are putting 10 things into the clinic and we are getting a drug out – let's put 100 things in and we'll get 10 things out.' And AstraZeneca was very much following that philosophy: 'Let's just put lots and lots of things in and something will stick.'"

The problem was this approach required much investment in infrastructure, people and buildings but did not lead to an increase in

What are the 5Rs?

Right Target
- Strong link between target and disease
- Differentiated efficacy
- Available and predictive biomarkers

Right Tissue
- Adequate bioavailability and tissue exposure
- Definition of PD biomarkers
- Clear understanding of preclinical and clinical PK/PD
- Understanding of drug-drug interactions

Right Safety
- Differentiated and clear safety margins
- Understanding of secondary pharmacology risk
- Understanding reactive metabolites, genotoxicity and drug-drug interactions
- Understanding of target liability

Right patient
- Identification of the most responsive patient population
- Definition of risk-benefit for given population

Right commercial potential
- Differentiated value proposition versus future standard of care
- Focus on market access, payer and provider
- Personalized healthcare strategy, including diagnostics and biomarkers

Source: AstraZeneca

the number of successful drugs. "And that was a very painful, difficult lesson. So, I did the analysis, we looked at the data, we looked at the things that we thought were predicting improved probability of success versus not having an impact and those were the things that we focused on in terms of the framework."

Pangalos drew from his experience at Wyeth and looked at what was going on at other firms (proof of mechanism work at **Pfizer Inc.** and patient stratification at **Novartis AG**, for example), but the main impetus was AstraZeneca's own data.

"What I was really dissatisfied with was that we didn't understand why we were failing. I was asking the question, 'We've done this Phase II study, the molecule failed, did we test the right hypothesis?' and people wouldn't know the answer. They wouldn't know if it had engaged the target in the brain, for example, or the heart or the kidney – we didn't know the PK properly, we didn't have any target validation that was in the right patient population so it wasn't a satisfying failure."

Having done his assessment of all the research projects, and made his diagnosis, his prescription was to focus the process of deciding which projects to take forward on five technical determinants – to improve the quality of the drug candidates earmarked for clinical development and to help develop a culture where "truth-seeking" is prized. These were: Right target, Right tissue, Right safety, Right patient, and Right commercial potential – the 5Rs (See box for more details.)

Distilled on paper, the 5Rs might look self-evident, and indeed in the paper they are described as "intuitive", but just how easy were they for Pangalos and his team to codify?

"You look at those things and you think that they are reasonably obvious and for goodness' sake why has nobody been doing it? But what was very interesting was how few people were doing it… putting it all together is the piece that hadn't been done before," Pangalos said. "What made AstraZeneca different was that the company put the principles into a framework and got the whole company behind them… We'd seen snippets of things before but I'd never seen it done holistically like this."

This very "intuitiveness" helped when Pangalos presented his 5R framework to his colleagues. Then, two things happened, he said: "The first thing was there was a little bit of a gulp: 'I didn't realise we were this bad'… and then they were inspired.

"We went through it with data because they're scientists and showing them that the data is wrong and then telling them that we are moving away from volume and are going to focus on quality and science and patients – they loved it. In all honesty, they loved it."

But the changes did not come without challenges – job losses and site closures ensued. In 2013, AstraZeneca announced its small molecule and biologics R&D activities would be concentrated in three strategic centers: Cambridge, UK; Gaithersburg, Maryland and Mölndal, Sweden, and that its UK research activities in Alderley Park, Cheshire would cease. *(Also see "AstraZeneca tired of life? Leaves London and reorganizes global R&D" - Scrip, 18 Mar, 2013.)*.

"We had to close sites and all those difficult things that people didn't love as much, but the principles of what we were doing, how we were going about making decisions focusing on the science-based decisions, that to the R&D organization, to my organization, was music to their ears," he said. "People actually bought into it very quickly."

The arrival of the science-focused Pascal Soriot as CEO, who added science and R&D-delivery metrics into the company's incentives program, also helped foster the new climate, Pangalos added.

> 'You can have the best molecule in the world but if you are working on the wrong target it's still not going to be a drug'

AstraZeneca scientists now work in fewer disease areas – the three major ones being oncology, cardiovascular and respiratory – with a focus on a deeper scientific understanding of disease biology and mechanisms. The company has also made substantial investments in its capabilities for target selection and validation, lead generation, pharmacokinetic/pharmacodynamic (PK/PD) modelling and patient stratification and biomarkers.

"What we tried to do was say, 'Let's make sure we understand the biology of what we are doing and let's make sure we design the preclinical research work and the clinical work in a way that helps us either prove or disprove whatever our hypothesis is, and then, if we do fail then at least we have moved forward because we understand that that pathway or that target or that patient population isn't the right one.'"

The result has been a marked reduction in the number of projects in the discovery portfolio. Between 2005 and 2010 (before the initiation of the 5R framework), 287 small-molecule discovery programs

CONTINUED ON PAGE 23

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 12–18 January 2018

LEAD COMPANY/PARTNER	COMPOUND	INDICATION	COMMENTS
Phase III Results Published			
Amgen Inc.	*Kyprolis* (carfilzomib)	multiple myeloma	ASPIRE; the *Journal of Clinical Oncology*, online Jan. 17, 2018.
TiGenix NV	darvadstrocel (Cx601)	perianal fistula in Crohn's disease	ADMIRE-CD; in *Gastroenterology*, online, Dec. 22, 2017.
Phase III Interim/Top-line Results			
Merck & Co. Inc.	*Keytruda* (pembrolizumab) plus chemotherapy	metastatic non-small cell lung cancer (NSCLC), first-line	KEYNOTE-189; met overall survival and PFS dual primary endpoints.
Novartis AG	*Cosentyx* (secukinumab)	plaque psoriasis	CLARITY; superior to ustekinumab.
PharmaMar SA	*Zepsyre* (lurbinectedin)	ovarian cancer; platinum resistant	CORAIL; missed PFS primary endpoint.
Japan Tobacco Inc./Torii Pharmaceutical Co. Ltd./ Leo Pharma AS	JTE-052, topical (LEO124249)	atopic dermatitis	Effective and well tolerated.
Kissei Pharmaceutical Co. Ltd./JCR Pharmaceuticals Co. Ltd.	JR-131 (darbepoetin alfa biosimilar)	renal anemia	Equivalence shown to darbepoetin.
Updated Phase III Results			
Exelixis Inc./Ipsen	*Cabometyx/ Cometriq* (cabozantinib)	advanced liver cancer, second line	CELESTIAL; improved overall survival, PFS.
Neos Therapeutics Inc.	*Comtempla XR-ODT* (methylphenidate)	attention deficit hyperactivity disorder	Symptoms improved, well tolerated, in children aged 6 to 12 years.
Phase III Initiated			
Eddingpharm International Holdings Ltd./Amarin Pharmaceuticals Inc.	*Vascepa* (icosapent ethyl)	hypertriglyceridemia	In China.
ImmuPharma PLC	*Lupuzor* (rigerimod)	systemic lupus erythematosus	Open-label extension study.
Phase III Announced			
GC Pharma (formerly Green Cross Corp.)	GC1102 (Hepabig-gene)	hepatitis B infection after liver transplant	A monoclonal antibody.
Kite Pharma Inc. (Gilead Sciences Inc.)/Pfizer Inc.	*Yescarta* (axicabtagene ciloleucel) plus utomilumab	diffuse large B-cell lymphoma	In patients with refractory disease.
Phase II Suspended			
Eiger BioPharmaceuticals	ubenimex	pulmonary arterial hypertension	LIBERTY; Lacked efficacy, studies in lymphedema continue.
Updated Phase II Results			
Castle Creek Pharmaceuticals LLC	CCP-020 (diacerein) ointment	epidermolysis bullosa	Cleared lesions.
ValiRx PLC	VAL401	NSCLC, late stage	Signs of efficacy, improved quality of life.
NLS Pharma Group	NLS-1 (mazindol), controlled-release	attention deficit hyperactivity disorder	Effective and well tolerated.
MacroGenics Inc.	margetuximab plus pembrolizumab	esophageal, gastric cancer	Preliminary signs of antitumor activity.

Source: Biomedtracker

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were initiated, and this was reduced to 76 programs initiated from 2012 to 2016. In addition, there was a reduction in the number of back-up programs from around 28% to less than 7% of the portfolio.

"We are spending less as well – this is on a backdrop of half the number of people and probably half the budget roughly as when I first joined," Pangalos noted.

RIGHT TARGET

But there is still much room for improvement. Of the 5Rs, the most difficult to get right is the first: target. "Because the biology is complex, the diseases are complex, and we fail 80% of the time and the reason we are failing most now is efficacy – which means we are testing the hypothesis but the hypothesis is wrong." The amount of times a project fails for safety or PK has dropped, he said, but now failures are more often because the understanding of the biology isn't deep enough. That is an area in which the company intends to continue to improve.

"You can have the best molecule in the world but if you are working on the wrong target it's still not going to be a drug. That's the most important decision we make: what target, what projects do we start and ultimately what experiments do we do to prove or disprove that scientific hypothesis. What we want is to do that as fast and as thoroughly as you can."

The question of how much of AstraZeneca's improvement can be attributed to the framework is one that is hard to answer especially given scientific advances such as CRISPR, but the company believes that the improvements it has seen across the phases are more than coincidental. Pangalos said: "It's down to people ultimately, not the framework, the framework is something that helps guide people and their mindset in terms of the way they work and the way they make decisions and what's important in terms of driving their projects and programs."

One example of where the framework came into its own is with the PARP inhibitor *Lynparza* (olaparib). The product was not deemed to have enough commercial potential in a company that at the time still had a primary care sales mentality, Pangalos said. "Lynparza was written off, but we had the 5Rs. We said we don't agree and we carried on working on it because we thought absolutely this is going to be a drug." Once Soriot joined and saw the product's potential the product swiftly progressed into late-stage development, he noted.

PEAK OR TROUGH

The next test for Pangalos and his team is to maintain these improvements, especially since they were coming from an all-time low. A raft of approvals last year for AstraZeneca suggests that the trajectory is still upwards in 2017, which is outside the timeframe of the paper. "Our industry does tend to go in peaks and troughs and the key for us is: can we keep it going as a peak? Or at least as a slightly increasing plateau?"

He added: "The bit I worry about is that we are still failing 80% of the time – so what's the next level of improvement we could see across our industry? We are in the top quartile now, one of the top two or three performers, productivity-wise. How do we get ourselves to a 30% success rate or 40% success rate? Those are the questions I ask myself and my leadership team now. What else would it take?"

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APPOINTMENTS

Sanofi has appointed ***Dominique Carouge*** executive vice president head of business transformation, effective Feb. 15, 2018. He will join the executive committee and take charge of accelerating the French company's transformation. Carouge has served as deputy chief financial officer and head of finance operations and group controlling since the beginning of 2016, and has held other leadership roles at the company, which he joined in 1991.

Fiona Marshall is to lead **MSD Research Laboratories**' new discovery research facility in London. MSD Research Laboratories is known as Merck & Co. Inc. in the US and Canada. Marshall was previously executive vice president and chief scientific officer at Sosei Group Corp., which in 2015 acquired the company she had co-founded, Heptares Therapeutics Ltd. An expert in G-Protein Coupled Receptor (GPCR) biology, she has more than 25 years' experience in drug discovery, and formerly headed the department of molecular pharmacology at GlaxoSmithKline PLC.

Pandion Therapeutics Inc. has been launched with new leadership and a $58m series A financing. The company, which develops bispecific antibodies for localized immunomodulation to treat autoimmune and inflammatory diseases, has appointed co-founders ***Anthony Coyle*** CEO and ***Jo Viney*** as chief scientific officer. Coyle was previously senior vice president at Pfizer Inc. and vice president and global head of inflammation biologics at MedImmune. Viney was previously senior vice president of drug discovery and vice president of immunology research for Biogen Inc. Fellow co-founders of Pandion include Alan Crane, partner at Polaris Partners, and David Sachs, a clinician and expert in transplantation and immunology. Joining Crane and Coyle on the company's board of directors are Carlo Rizzuto, partner at Versant Ventures, Mitchell Mutz, investment director at Roche Venture Fund, and Vikas Goyal, principal at SR One.

Gene therapy specialist **Orchard Therapeutics** has appointed ***Frank Thomas*** to the newly created position of chief financial officer and chief business officer. Until recently, Thomas served as president and chief operating officer of AMAG Pharmaceuticals Inc.

Redx Pharma PLC has appointed ***Andrew Saunders*** as chief medical officer, as the company prepares to take its lead compound, the oral small-molecule porcupine inhibitor RXC004 for cancer, into its first Phase I study. Saunders joins from Lytix Biopharma AS, a Norwegian immuno-oncology firm, where he was also CMO. He was previously medical director at Bioenvision Limited, later acquired by Genzyme, and global clinical science leader for rituximab at Roche.

Robert Lutz has been appointed chief scientific officer of ***Glythera Ltd.*** of the UK, which is developing antibody drug conjugates aimed at difficult to treat tumors. Lutz was responsible for all early-stage ADC development programs at ImmunoGen Inc., where he was vice president of translational research and development.

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