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Novartis CEO-Designate Vasant ('Vas') Narasimhan

Novartis AG

Novartis: Jimenez Passes CEO Baton To Narasimhan

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With **Novartis AG**'s root-to-branch revamp a reality, its American CEO Joseph Jimenez is passing the leadership baton to the Swiss group's chief medical officer Vasant Narasimhan – another American who has been increasingly at the center of its drug development and commercialization strategy and who is a big proponent of automation and artificial intelligence in future discovery.

JIMENEZ: CORPORATE RESTRUCTURER

News of Jimenez's departure - effective Feb. 1, 2018 - came as a surprise to the industry, and comes after eight years at the helm of Europe's biggest medicine maker, during which time he restructured the Swiss group with asset swaps and prepared the sale of underperforming divisions. It is the second-largest cancer drug maker today after Swiss rival *Roche* and has six main therapeutic areas of interest: oncology, cardiology, neuroscience, immunology and dermatology, respiratory, and ophthalmology.

NARASIMHAN: THERAPY SCIENTIST

Vasant ('Vas') Narasimhan has been overseeing Novartis's pharmaceutical development since 2014, prior to which he had worked in different roles at the company over 10 years, including as global head of development at Novartis Vaccines. He has been a key proponent of targeting drugs to patient populations and identifying patient populations that can best benefit.

Neither Jimenez nor Narasimhan were available immediately for comment. But a Novartis spokesperson told *Scrip* that Narasimhan's appointment "should be seen as a confirmation of the group's current strategy."

"We continue to improve the efficiency and effectiveness of the company to further free up resources to keep Novartis at the forefront of medical innovation and create long-term value for shareholders and society," he added.

In announcing Narasimhan designation as Jimenez's successor, Novartis board of directors chairman Joerg Reinhardt in a statement said: "Vas is deeply anchored in medical science, has significant experience in managing the interfaces between research and development and commercial units and has strong business acumen with a track record of outstanding achievements."

He went on to note that as a physician, Narasimhan has a strong patient focus "and a genuine humane perspective and care for the mission and values of Novartis. As a result, the board of directors is confident that Vas is the right choice to lead Novartis on our expected next growth phase, driving innovation and further strengthening our competitive position."

The Basel, Switzerland-based group recently made history by achieving the first FDA approved CAR-T treatment for its *Kymriah* (tisagenlecleucel) chimeric antigen receptor T cell therapy.

Novartis recently reported unexpected good news from the 10,000-patient CANTOS Phase III study of its IL-1β inhibitor antibody *ACZ885* (canakinumab) apparently confirming the hypothesis of target-

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

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ESC Barcelona Meeting
COMPASS, CANTOS and REVEAL steal the show (p18-23)

from the editor

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It's part of the core navel-gazing repertoire of the pharma industry to reflect on its public trust deficit, and discuss how to build and maintain that trust. Just such a debate was held at the Royal Institution in London this week, in a Roche-sponsored event looking at the future of healthcare with panellists' experience ranging from surveying public opinion to representing patients' voices to communicating science to the public, and from working in pharma to founding a disruptive healthcare business.

The discussion circled around the need for transparency and credible information filters, but a few more radical remarks cast the perennial quest to improve pharma's reputation in new light.

First, one panelist posited that distrust is actually a good thing, in that it is part of a virtuous circle that sees patients' questioning practices and behaviour (including in the courts and media), which ultimately leads to reforms and better regulation. I wonder if industry should indeed embrace distrust, focusing on responding honestly and constructively, rather than aspiring to winning public trust as an end in itself.

Second, an audience member turned the debate on its head, pointing out that trust (or lack of it) goes both ways, and that some industry players are reluctant to sign up to AllTrials because they don't trust the public to interpret the data. Does our industry have a trust problem of its own, and if so, do we need to address it? Is it possible to improve our understanding of "the public" and work more constructively with it? Food for thought.

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Dr Reddy's Faces US Class Action Case Heat
http://bit.ly/2gBrla5
Pressure builds on Dr Reddy's Laboratories after at least two US law firms press ahead with a class action case against the company. Analysts appear unperturbed, however – at least for now – about the possibility of any material implications.

AZ Partners Parkinson's Compound With Takeda
http://bit.ly/2eCMQdz
The deal, worth up to $400m, will see the companies develop an early-stage alpha-synuclein antibody, a hot area of research in Parkinson's disease.

Deal Watch: CSL Behring's Calimmune Buy Builds On Its Base & Adds Platform Tech
http://bit.ly/2vYKOXK
Acquisition of gene therapy company Calimmune expands on CSL Behring's hematology franchise and fits rare disease business model, plus adds platform tech with wide application for CSL's portfolio.

Teva Set For Immediate US Launch Of Austedo In Tardive Dyskinesia
http://bit.ly/2exm9U7
FDA-approved labeling includes boxed warning for depression and suicidality, though this is specific for Huntington's disease patients, who are prone to these conditions.

GeNeuro, Servier 'Disappointed' With Mid-Way Phase IIb Multiple Sclerosis Study
http://bit.ly/2vYmd5I
GeNeuro and partner Servier voiced disappointment over results seen midway through a Phase IIb trial studying a potential cause of multiple sclerosis - but insisted the trial will continue for the final 6 months.

Jazz Raising Hematology/Oncology Reach Further With ImmunoGen Deal
http://bit.ly/2wxXJnk
Ireland-based Jazz Pharma is extending its shift away from specialty pharma with an option-based deal with ImmunoGen involving three antibody-drug conjugate programs.

inside:

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Novo Nordisk: There's More To Victoza's Outcomes Benefit

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Novo Nordisk AS is stressing unique attributes of its GLP-1 receptor agonist *Victoza*, including its consistent and broad cardiovascular effects, in its promotional activities with specialist prescribers, following approval of a claim for an outcomes benefit in the US and Europe.

The US FDA cleared Victoza (liraglutide) on Aug. 25 for reducing major cardiovascular (CV) events in patients with type 2 diabetes and established cardiovascular disease. This followed approval in July by the European Commission for preventing cardiovascular events in patients with diabetes.)

As part of the launch related to the new outcomes claim, Novo Nordisk is increasing the size of its sales force and has been raising awareness of the risks of cardiovascular mortality related to type 2 diabetes through the unbranded HeartofType2 campaign.

Novo Nordisk has also been reaching out to prescribers. The company featured a thorough review of the pivotal LEADER results supporting the new claim, as well as analyses of CV outcomes trials for diabetes drugs across the board, during an Aug. 26 satellite symposium at the European Society of Cardiology (ESC) meeting in Barcelona.

Up to now, only one other diabetes drug has enjoyed a cardiovascular benefit claim in labeling. **Boehringer Ingelheim GMBH**/**Eli Lilly & Co.**'s SGLT2 inhibitor *Jardiance* (empagliflozin) has an indication for prevention of CV death in the US and in Europe.

Jardiance's indication is for CV death alone because the drug showed mixed results on other aspects of the major adverse cardiovascular events (MACE) composite endpoint in the pivotal EMPA-REG outcomes study. The drug demonstrated a 14% significant reduction in the risk for MACE overall, but while there was a reduction in CV death, there was no significant reduction in the number of heart attacks and there was a numerical increase in the number of strokes.

Johnson & Johnson's competing SGLT2 inhibitor *Invokana* (canagliflozin) recently showed a reduction in CV events in the CANVAS study on par with the one shown by Jardiance in EMPA-REG, but researchers also reported double the risk of amputations compared to placebo. **Sanofi**'s GLP-1 inhibitor *Lyxumia* (lixisenatide) failed to show an outcomes benefit in the ELIXA study, though safety was established.

Novo Nordisk's investigational once-weekly GLP-1 inhibitor semaglutide has demonstrated an outcomes benefit in the SUSTAIN-6 study, but the company does not intend to file for a labeling claim based on that trial.

During the ESC symposium, Lars Rydén, senior professor of cardiology at the Karolinska Institute in Sweden, noted that the outcomes benefit in the EMPA-REG study of Jardiance was driven mostly by heart failure, and that the benefit for Victoza in LEADER was driven mostly by mortality. The benefit for semaglutide was driven by stroke and myocardial infarction rates.

Rydén also noted that lixisenatide's half life is short, whereas liraglutide's is medium/long and semaglutide's is very long.

"In principle, you cannot trust class effects - that something belongs to GLP-1 or SGLT2 inhibition doesn't say it is efficient, just because one other drug in the class is efficient. Each drug needs to be tested. They are all different," Rydén said.

GLP-1 agonists affect multiple organs and the mechanisms behind the outcomes benefit seen for some members of the class are yet to be understood, Rydén added.

The next "piece of the jigsaw," he noted, will come in September with the release of full data from **AstraZeneca PLC**'s study of the Phase IIIb EXSCEL outcomes study of once-weekly *Bydureon* (exenatide extended-release). In May, AstraZeneca announced that Bydureon had not met the primary endpoint for reducing a MACE composite, but the cardiology community and analysts alike are eager to see a full rundown of results to understand what they mean for other GLP-1 receptor agonists.

Rydén advised choosing empagliflozin or liraglutide for patients with type 2 diabetes and established heart disease in need of additional glucose lowering in order to "protect people from dying too early and getting too many myocardial infarctions."

When asked during a question and answer session why he did not include canagliflozin as an option for these patients, Rydén noted the higher rates in the CANVAS study of bone fractures and amputations, which were not seen in EMPA-REG. DPP-4 inhibitors have not demonstrated a cardiovascular benefit in outcomes studies to date but have demonstrated noninferiority and are safe, oral treatment options, whereas the GLP-1 drugs are injectable.

BROAD CV BENEFITS

Compared to Jardiance, Victoza has a broader label for preventing major adverse cardiovascular events, based on the LEADER results. In that trial, Victoza reduced the risk of cardiovascular death, non-fatal heart attack or non-fatal stroke by 13% compared to placebo, both on top of standard-of-care therapy. For the cardiovascular death component, risk was significantly reduced by 22% while non-fatal heart attack and non-fatal stroke were reduced numerically.

During the Novo-sponsored symposium at ESC, Neil Poulter, professor of preventive cardiovascular medicine at the Imperial College of London, noted the consistent benefits on a wide range of cardiovascular endpoints. Commenting on the non-fatal heart attack, stroke and CV death results, he pointed out that "all three contributed beneficially to that significant outcome," for an "all-around benefit."

According to an analysis that was not pre-specified, on almost any important cardiovascular outcome, the hazard ratios for the results are going in the right direction and there was no harm in terms of heart failure, he said.

The new FDA prevention claim is a victory for Victoza, but not a complete victory. The sponsor had wanted a broad label for primary prevention, not just for use in patients with type 2 diabetes with established cardiovascular disease.

However, the FDA's Endocrinologic and Metabolic Drugs Advisory was uncomfortable with a broad claim for primary prevention – there was a trend toward a worse result in a small subgroup of patients without cardiovascular or renal disease.

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View LEADER's Primary and Secondary Cardiovascular Outcomes here: **http://bit.ly/2xIzJMP**

What's Gilead Getting From Kite For Nearly $12bn?

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Gilead Sciences Inc. executives enthusiastically advocated for the company's $11.9bn acquisition of **Kite Pharma Inc.** on Aug. 28, but investors had mixed feelings about the $180-per-share price tag, despite overwhelmingly positive efficacy for Kite's lead chimeric antigen receptor T cell (CAR-T) therapy to date.

President and CEO John Milligan and other Gilead executives praised Kite's clinical trial results as well as its manufacturing preparations and reimbursement negotiations in advance of a potential late-2017 launch for lead CAR-T candidate axicabtagene ciloleucel (axi-cel; KTE-C19). In fact, Foster City, Calif.-based Gilead is so impressed that it will build its oncology portfolio around the cell therapy platform and hopes to keep most of Kite's 500-plus employees in Santa Monica and El Segundo, Calif. to keep the positive momentum going for axi-cel and the firm's follow-on CAR-T and T cell receptor (TCR) therapies.

The US FDA is reviewing Kite's biologic license application (BLA) for axi-cel as a treatment for relapsed or refractory aggressive non-Hodgkin lymphoma (NHL) patients who are ineligible for autologous stem cell transplant (ASCT), including patients with diffuse large B cell lymphoma (DLBCL), transformed follicular lymphoma (TFL) and primary mediastinal B cell lymphoma (PMBCL). The BLA has a Nov. 29 PDUFA date, which is nearly two months after the PDUFA date for **Novartis AG**'s competing CAR-T therapy (see story on page 10).

"Kite has been preparing for this historic event for quite some time and is ready for a successful commercial launch in the United States," Milligan said during an Aug. 28 conference call to discuss Gilead's acquisition of the company. He also noted that "preparations are ongoing in Europe," where Kite filed a marketing authorization application before Novartis and expects approval in 2018. *(Also see "Kite First Off The Blocks For EU CAR-T Filing" Scrip, 1 Aug, 2017.)*

Evercore ISI analyst Umer Raffat wrote in an Aug. 28 note that Kite has the shortest manufacturing time of the three top competitors in the CAR-T field. The firm's process of taking T cells from a patient, reengineering them to target CD19 on cancer cells, then sending them back to the oncologist to infuse the cells back into the patient takes 16 to 18 days versus 29 days currently and 22 days in the future for Novartis's tisagenlecleucel and 24 days for **Juno Therapeutics Inc.**'s lead product candidate. *(Also see "Much Anticipated JULIET Data Show Novartis Playing Catch-Up On CAR-T Manufacturing" Scrip, 7 Jun, 2017.)*

GILEAD'S CAR-T RELUCTANCE VANISHED THIS YEAR

Any reluctance that Gilead might have had about CAR-T therapies disappeared in 2017 after several de-risking events for the field and for Kite, Milligan said. He explained that "it was really a transformative year for the whole field as BLAs

Kite's Clinical Product Pipeline And Upcoming Milestones

PRODUCT CANDIDATE	STATUS	UPCOMING MILESTONES
Axi-Cel (KTE-C19); CAR-T therapy targeting CD19	BLA filed for third-line treatment of NHL (DLBCL, TFL, PMBCL); Phase II/III ZUMA-2 trial ongoing in mantel cell lymphoma (MCL) and ZUMA-9 (expanded access) for aggressive NHL; and Phase I ZUMA-3 through ZUMA-8 trials under way in adult ALL, pediatric ALL, indolent NHL, DLBCL (combination with a PD-L1 inhibitor), second-line DLBCL and CLL.	Axi-cel PDUFA date in relapsed (third-line) NHL is Nov. 29. Data are expected at the European Society of Medical Oncology (ESMO) meeting in September from the ZUMA 3 and 4 studies in adult and pediatric ALL. The company will report one-year data from ZUMA-1 in NHL (DLBCL, TFL, PMBCL), results from the ZUMA-1 safety expansion study, and interim data from ZUMA-6 in combination with a PD-L1 inhibitor in December, potentially at the American Society of Hematology (ASH) meeting.
Second-generation CD19-targeting CAR-T therapy	The NCI is studying this candidate in a Phase I study in hematological malignancies.	
KTE-585; CAR-T therapy targeting BCMA	An investigational new drug (IND) application recently was filed with the FDA.	Initiation of a Phase I study in multiple myeloma is expected in the second half of 2017.
TCR targeting MAGE A3/6	The NCI is conducting a Phase I study in solid tumors.	
KTE-718; TCR targeting MAGE A3/6	Kite is conducting a Phase I study in solid tumors, including non-small cell lung cancer, bladder cancer and head and neck cancer.	
TCR targeting MAGE A3	The NCI is conducting a Phase I study in solid tumors.	
TCR targeting HPV-16 E6 and E7	The NCI is conducting a Phase I study in cervical and head-and-neck cancer.	

Sources: Kite quarterly earnings reports and investor presentations; Jefferies.

were filed, especially as data unfolded during the course of this year, not only from Kite, but from other groups working on CAR-T … It became clear that it was going to work and it was going to work in more than one kind of tumor. It became clear that the side effects were becoming more and more manageable, and then, importantly, that the manufacturing on an industrial scale could work. All these things lined up over the course of the summer to convince us that now is the right time to get involved in this kind of therapy and that Kite was the right partner."

Gilead is optimistic about the forthcoming FDA decision on axi-cel, based on data from the Phase II ZUMA-1 clinical trial supporting Kite's BLA. *(Also see "ASH Ends With Consistent Kite CAR-T Data, Some Hope For Juno" Scrip, 7 Dec, 2016.)* Gilead also is comfortable with the safety of CAR-T therapies, which have resulted in severe initial side effects and a few deaths from cytokine release syndrome and neurotoxicity. The company is comfortable that Kite has appropriate treatment guidelines in place to handle CRS and neurological adverse events. *(Also see "Too Sick For CAR-T? Kite Reports Cerebral Edema Death" Scrip, 8 May, 2017.)*

Beyond relapsed third-line NHL – including DLBCL, TFL and PMBCL – axi-cel is being developed for a second-line indication for NHL patients who haven't yet failed an autologous stem cell transplant. Future Kite-developed CAR-T and TCR therapies are in development for B cell malignancies, multiple myeloma and solid tumors (see table on page 6).

Gilead's enthusiasm for Kite's pipeline shows in the 29% premium the company is paying relative to Kite's pre-acquisition value, especially on top of a stock price that's more than tripled so far this year.

However, Mizuho Securities polled its clients to gauge investors' views of the acquisition and found that 59% believe Gilead overpaid for Kite while 39% think the company paid fair value. Only 40% of Mizuho's surveyed investors said they liked the deal, 32% said they don't like it and 28% were neutral.

AXI-CEL ADDS REVENUE RIGHT AWAY

But with axi-cel on track for FDA approval around the same time the Kite acquisition closes in the fourth quarter of this year, Gilead's high-value transaction will begin generating revenue right away, though it will take some time to make up for both the purchase price and the necessary research and development to keep the cell therapy pipeline going.

Kite's operating expenses totaled $295.4m in 2016, including $197.9m in R&D expenses, and in 2017 the company had $781.1m in cash as of June 30 with plans to burn through $325m to $340m in 2017 as R&D expenses rise and axi-cel nears a commercial launch, assuming FDA approval in November. Evercore ISI's Raffat said in his note about the CAR-T deal that "the true inflection points in the Kite story are yet to come. 2018 will now become a very important year [for Gilead, because the] Street will be very focused on validating this purchase (both from a launch perspective and, perhaps more importantly, new clinical data in earlier lines of therapy plus other indications like multiple myeloma and early activity in solid tumors)."

Gilead hopes to expand on Kite's value by testing its CAR-T therapies in combination with immuno-oncology and other cancer drugs. The company also will pursue deals that make the technology more effective, safer or less costly to produce on top of transactions that Kite already has pursued to strengthen its portfolio. Axi-cel itself originally was developed by the National Institutes of Health's National Cancer Institute.

"Now that Gilead has executed on a sizeable transaction, we expect the investor focus to shift from 'what' are they going to do, to 'was this the right deal,'" Deutsche Bank analyst Andrew Peters wrote in an Aug. 28 note. "Key to the Kite deal is that management hopes to build upon this emerging capability, likely with a mix of internal assets, new pipeline from Kite, and importantly, new products/programs/technologies through additional potential strategic investment."

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What's Next On Gilead's Shopping List

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Despite a cash stockpile of roughly $36bn on hand at the end of the second quarter, **Gilead Sciences Inc.**'s announced plan to acquire **Kite Pharma Inc.** on Aug. 28 for $11.9bn – structured as a mix of cash, senior unsecured notes and bank financing – likely forestalls it from undertaking any further large-scale M&A in the near term.

But, as Ian Somaiya of BMO Capital Markets put it in an Aug. 28 research note, the Kite acquisition is "a strategic fit, not a revenue fix." It certainly plants a flag for the Foster City, Calif.-based specialty firm in immuno-oncology and follows through on laying groundwork for an oncology franchise, but it doesn't fill the revenue void Gilead faces as its hepatitis C business declines and it doesn't use up the company's cash reserves.

With an estimated $31bn or so of Gilead's cash held outside the US, that money is unlikely to be used in acquiring US assets because of the tax liabilities that could result – at minimum, Gilead will wait to see if US tax reform legislation takes shape that could enable US-based corporations to repatriate their off-shore cash more economically than they can now. *(Also see "Promise Of US Tax Reform Simmers, But On The Backburner" Scrip, 12 Apr, 2017.)*

It appears all but certain that Gilead will look to augment its new immuno-oncology and cell therapy holdings with smaller deals that may add other forms of cancer expertise or bring in on oncology assets that could be used in combination with Kite's CAR-T and T-cell receptor (TCR) candidates. *(Also see "What's Gilead Getting From Kite For Nearly $12bn?" Scrip, 29 Aug, 2017.)* As it awaits the Nov. 29 user fee date for potential US approval of lead candidate axicabtagene ciloleucel (KTE-C19) in relapsed or refractory aggressive non-Hodgkin lymphoma, Gilead has indicated it plans build

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a larger oncology business around Kite's cell therapy platform.

During a same-day conference call to outline the Kite transaction, President and CEO John Milligan explained that Gilead will begin a review of its own oncology portfolio to determine what it has that may complement Kite's pipeline and explore what other deals it might be able to make to further its goal to become a leader in the CAR-T/TCR area of immuno-oncology.

"We're quite interested in things that would augment cell therapy," the exec said. "We're going to take some time to look at our own portfolio and determine what, if any, other things we should do. … We are going to stay very active as a business development group. We have a number of other partnerships and opportunities for in-licensing of things that we will continue to pursue. So, we're not going quite after this [type of] deal, but we'll continue to use our team to look at many opportunities."

Milligan added that cell therapy will be "the cornerstone" of Gilead's therapeutic focus and strategy moving forward.

MIGHT GILEAD PURSUE NASH OR AUTOIMMUNE ASSETS?

Outside of cancer, the most likely areas in which Gilead might pursue M&A activity include non-alcoholic steatohepatitis (NASH), where it has the ASK-1 inhibitor selonsertib in Phase III as well as a pair of Phase II candidates – the FXR agonist GS-9674 and ACC inhibitor GS-0976. It also partnered with Belgium's **Galapagos NV** in autoimmune disease under a 2015 deal. The two companies are collaborating on development of the JAK1 inhibitor filgotinib in rheumatoid arthritis, psoriatic arthritis, Crohn's disease and ulcerative colitis.

While several market analysts opined that Gilead likely will focus business development efforts on smaller immuno-oncology-related plays, BMO Capital's Somaiya speculated that the company still has capacity for another late-stage acquisition. He pointed specifically to Galapagos, once a standstill agreement in their partnership expires (which he estimates will occur sometime in 2018), or **Intercept Pharmaceuticals Inc.**, one of the three companies that have reached Phase III in NASH, along with Gilead and **Genfit SA**. *(Also see "Genfit's Enrollment Delay In NASH May Aid Intercept's First-To-Market Goal" Scrip, 25 Apr, 2017.)*

However, Gilead seems to have little to gain right now in trying to buy out Intercept until it sees further data on the NASH compounds. Further, a Biomedtracker survey earlier this year indicated that physicians may be more positively inclined toward Gilead's NASH candidates than the late-stage competition. *(Also see "Intercept's NASH Phase III Enrolling Slowly; Gilead Could Gain Ground" Scrip, 13 Jan, 2017.)*

A wide array of analysts expect Gilead will make additional cancer-related deals, with BMO's Somaiya noting that Kite is a strategic fit but could necessitate additional deals to strengthen an immuno-oncology focus.

> 'We have a number of other partnerships and opportunities for in-licensing of things that we will continue to pursue'

HOW BIG CAN GILEAD GO?

Somaiya isn't alone in thinking Gilead has more work to do. Leerink Partners analyst Geoffrey Porges offered a similar view, stating on Aug. 29 that while investors will be relieved that Gilead finally has deployed some of its substantial capital, "this transaction makes relatively little impact on Gilead's overall growth outlook."

At present, Gilead's business drivers remain hepatitis C, which is contracting due to price pressures and decreasing volume as patients are cured, and HIV, which faces market share challenges from other players, notably **ViiV Healthcare**, the analyst pointed out. And, even if axicabtagene ciloleucel is approved later this year, it is only projected to bring in about $400m in sales in 2019 and close to $800m in 2020, he said.

Kite has been jockeying with **Novartis AG** to bring the first CAR-T therapeutic to market. (see article on page 10). Porges previously estimated that Gilead potentially could spend between $50bn and $60bn on M&A transactions – supplementing its cash with financing – but noted that it has expressed little interest in deals of that scale.

"This announcement makes such deals seem unlikely," he wrote on Aug. 29. "At the margin, hypothetical targets such as **Vertex Pharmaceuticals Inc.** or **Alexion Pharmaceuticals Inc.** become less likely, or even remote. Gilead seems to have committed to the 'string of deals' approach and we expect more transactions to follow this announcement. Such transactions now seem likely to be in the sub-$20bn range and probably still more likely to come from oncology than any other therapeutic area."

GILEAD'S BIGGEST CATALYST SINCE PHARMASSET?

The Kite acquisition is Gilead's largest business development transaction since its attention-grabbing $11.2bn payout in 2011 for **Pharmasset Inc.**, solely on the strength of that firm's HCV candidate sofosbuvir. With roughly $111bn in lifetime franchise sales, that was certainly a canny investment.

It served as catalyst of Gilead's dominant HCV franchise, first as solo therapy *Sovaldi* and then as the backbone in combination products *Harvoni*, *Epclusa* and *Vosevi*.

Since that November 2011 acquisition, Gilead has completed another 21 business development transactions, according to Strategic Transactions, including the 2015 Galapagos partnership, the acquisition of two NASH programs, an HIV in-licensing deal and at least four platform technologies.

The list also includes six transactions that either are cancer-focused or that involve undisclosed targets that likely include oncology discovery and research work.

Kite's axicabtagene ciloleucel will be its first foray into immuno-oncology, however, and with the seeming potential of CAR-T therapy, Gilead could be recapturing the transformative value as when it scooped up Pharmasset's late-stage nucleoside polymerase inhibitor.

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View Gilead's deals over the past few years: **http://bit.ly/2vEstnV**

CONTINUED FROM COVER

ing inflammation to stabilize plaque and thereby prevent cardiovascular events and showing an intriguing benefit on lung cancer.

TAPPING AUTOMATION

CEO-designate Narasimhan is on record as saying the industry really hasn't fully taken advantage of the available automation and standardization technology to drive down the cost per asset developed.

One of the biggest opportunities that Narasimhan sees is to upgrade the technology used in Novartis' approaches to data, in all of its activities. There's a lot of opportunity to use automation to drive down costs, he believes.

> 'The world is becoming more data-driven. It is about maximizing output'

He has voiced hopes that such technology can also help Novartis get to better clinical endpoints, enabling the design of leaner clinical trials, driving down the cost of running each trial. Novartis is investing to transform their approach. A complete overhaul of the technology at Novartis development should be finished by 2018, allowing the group to "better drive productivity" in clinical trials.

ARTIFICIAL INTELLIGENCE

Novartis has also reported some positive early results from its use of AI, across early discovery, screening, molecular docking, pathology and patient selection.

The company is ramping up its efforts, even though it's unclear whether AI-based tools are leading to reduced attrition and faster lead time.

"You have to do it [AI] to really know" how and whether it's helping accelerate drug discovery, Narasimhan told *Scrip*'s sister publication *In Vivo* in a recent interview. "Exploiting of data is "something we just have to do," Narasimhan continued. "The world is becoming more data-driven. It is about maximizing output for minimum input. That's happening across all innovation sectors."

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Samsung Bioepis Builds Its Biosimilars Name In Europe

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Samsung Bioepis Co. Ltd. has received marketing authorization of Imraldi, its biosimilar version of AbbVie Inc.'s blockbuster *Humira* (adalimumab), from the European Commission, becoming the only company to receive EU approvals of three biosimilar anti-tumor necrosis factor (TNF) products.

Samsung Bioepis, which is a joint venture of **Samsung BioLogics** and **Biogen Inc.**, is selling *Benepali*, its biosimilar version of *Enbrel* (etanercept) and *Flixabi*, its biosimilar version of *Remicade* (infliximab) in Europe, through its partner Biogen. Samsung's biosimilar to Herceptin is also under regulatory approval review by the EMA.

Given that Samsung Bioepis' Benepali and Flixabi have been available in the EU for some time now, *Imraldi* (formerly SB5) could have a strong start given that rheumatologists might have become more familiar with Samsung Bioepis as a developer of anti-TNF biosimilars, Hristina Ivanova, an analyst at Datamonitor Healthcare said.

Amgen Inc. gained the first biosimilar adalimumab approval – as *Amgevita* in Europe in March and as *Amjetiva* in the US in September 2016. Currently, the other two adalimumab biosimilar medicines awaiting CHMP opinion are **Boehringer Ingelheim GMBH**'s BI 695501 and **Sandoz Inc.**'s GP2017. There are several Humira biosimilar products under development.

Meanwhile, the US FDA granted approval to Boehringer's adalimumab biosimilar *Cyltezo* (adalimumab-adbm), on Aug. 25. Cyltezo is the second biosimilar of Humira to receive the FDA's approval.

"It is unlikely any of the adalimumab developers would consider a launch at risk in Europe, so the launch dates would be dependent on the outcome of the ongoing patent litigation," Datamonitor's Ivanova said.

Without elaborating on the specific timing, Samsung Bioepis said it plans to launch Imraldi in Europe through Biogen, taking into consideration various factors, including patents in Europe. Humira's substance patent in Europe is slated to expire in October 2018. Although there could be worries that the three anti TNF biosimilar products may eat into one another's markets, Samsung noted that the original products steadily increased sales without doing this, so the biosimilars are expected to perform in a similar way.

CHANGING MARKETS

Samsung believes that mutual erosion of markets will be limited as doctors' preference for original drugs and switching patterns have stabilized. When looking at the changes in markets after launching biosimilars, the biosimilar products have mostly replaced their referencing drugs, so it is expected that any switching outside their own reference drugs is likely to be quite limited.

The impact of biosimilars on the TNF inhibitor class has been slow, but Remicade-maker Johnson & Johnson acknowledged that the competitive pressure has started to grow.

Samsung's Imraldi was cleared for the treatment of rheumatoid arthritis, juvenile idiopathic arthritis, axial spondyloarthritis, psoriatic arthritis, psoriasis, pediatric plaque psoriasis, hidradenitis suppurativa, Crohn's disease, pediatric Crohn's disease, ulcerative colitis and uveitis.

The EC approval comes two months after the CHMP's green light and 13 months after the Imraldi submission was accepted by the EMA.

Anti-TNF therapies represent some of the EU's largest drug expenditures, costing an estimated $9bn each year from 2011 to 2014. Introducing biosimilars of the top three anti-TNF therapies in Europe could lead to estimated potential savings of up to $11.44bn between the patent expiry date of each reference product and 2020, Biogen said.

Humira is the best-selling drug in the world, with net revenue of $16.07bn in 2016.

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From the editors of PharmAsia News

Novartis Beats CAR-T Competitors To The Pricing Punch With Kymriah Approval

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Novartis AG was the first company to submit a chimeric antigen receptor T cell (CAR-T) therapy for US FDA consideration and now with *Kymriah* (tisagenlecleucel) it is the first to win approval for the game-changing treatment modality, and thus set the pricing bar for competing CAR-T products.

The FDA approved Kymriah on Aug. 30 – about a month earlier than the Oct. 3 user fee date – for the treatment of pediatric and young adult patients (up to age 25) with B-cell precursor acute lymphoblastic leukemia (ALL) that is refractory or has relapsed after at least two prior lines of therapy. Novartis set a cost for the one-time treatment of $475,000, despite its own determination that a cost-effective price would be in the range of $600,000 to $750,000, and the company said it is negotiating "innovative" reimbursement agreements with public and private payers.

"We believe [the $475,000 price] will support sustainability of the health care system and patient access while allowing a return on our investment," Novartis global head of drug development and chief medical officer Vas Narasimhan said during a same-day conference call with reporters.

Pricing has been one of the biggest unknowns for the CAR-T field and speculation pegged the potential list prices for these therapies at several hundred thousand dollars. *(Also see "Trial And Trial: Bracing For Commercialization Of Cell & Gene Therapies" Scrip, 25 Aug, 2017.)* But by bringing the first CAR-T therapy to market, Novartis has established a benchmark for its competitors, including **Kite Pharma Inc.**, which has a Nov. 29 action date for axicabtagene ciloleucel (KTE-C19) in the treatment of non-Hodgkin lymphoma (NHL) – although considering Kymriah's earlier-than-expected approval, the FDA also could approve Kite's drug at any time.

Novartis closed down 1.1% at $82.74 per share on Aug. 30 following Kymriah's approval, but the company regained ground in after-hours trading with a 1.3% boost to $84. Kite essentially closed flat at $177.90, but **Gilead Sciences Inc.** – which announced on Aug. 28 that it is going to buy Kite for $11.9bn – jumped 7.3% to close at $81.23. *(Also see "Gilead Makes Cell Therapy The Base Of Its Oncology Platform With Kite Buy" Scrip, 29 Aug, 2017.)*

Manufacturing capacity and efficiency also has been a big challenge for autologous CAR-T therapies, like the Novartis and Kite products, which require the physicians to harvest T-cells from patients and send them to the manufacturer to reengineer the cells to target cancer cells expressing a specific antigen (CD19 for both Kymriah and axicabtagene ciloleucel) before sending them back to the patient's hospital or other treatment center.

Novartis expects to have 20 treatment centers certified to administer Kymriah within the next 30 days and 32 centers by the end of the year, but some clinicians will be ready to harvest T-cells from patients within three to five days of the approval. The company said it has gotten the multi-step process down to about 22 days on average.

Gilead executives noted earlier this week, when it announced the acquisition, that it was particularly impressed with the efficiency of Kite's manufacturing process, which results in a 16- to 18-day turnaround (see article on page 6).

Gilead also was pleased with Kite's pricing and reimbursement strategy to date, but did not indicate what kind of price would be charged for axicabtagene ciloleucel in the US once it is approved for relapsed or refractory NHL patients who are ineligible for autologous stem cell transplant (ASCT), including patients with diffuse large B-cell lymphoma (DLBCL), transformed follicular lymphoma (TFL) and primary mediastinal B-cell lymphoma (PMBCL).

MORE KYMRIAH INDICATIONS COMING SOON

Novartis plans to submit a supplemental biologic license application (sBLA) to the FDA in the fourth quarter for Kymriah in the treatment of DLBCL – a much larger market than the approximately 600-patient pediatric and young adult ALL indication approved under the original BLA. The company also plans to submit a marketing authorization application (MAA) to the European Medicines Agency (EMA) in the fourth quarter for DLBCL and pediatric ALL.

Kite already has an MAA for axicabtagene ciloleucel as a treatment for DLBCL on file in the EU, and was included in the EMA's Priority Medicines (PRIME) regulatory initiative aimed at getting therapies addressing unmet needs to patients faster. *(Also see "Kite First Off The Blocks For EU CAR-T Filing" Scrip, 1 Aug, 2017.)* Novartis won't know about its inclusion in PRIME until the company submits its MAA. In the US, the FDA granted breakthrough therapy designations for Kymriah as a treatment for pediatric ALL and for axicabtagene ciloleucel in the treatment of DLBCL, TFL and PMBCL.

Novartis notes that DLBCL is the most common form of lymphoma – about 30% of all NHL cases – and 10% to 15% of DLBCL patients don't respond to initial therapy or relapse within three months of treatment, with another 20% to 25% relapsing after initial response to therapy.

BMO Capitals Markets analyst Ian Somaiya noted in an Aug. 28 report assessing Gilead's Kite purchase that 20,000 patients are diagnosed with DLBCL each year in the US and they're typically treated with R-CHOP chemotherapy. However, 2,500 of those patients are refractory to treatment each year and 7,000 relapse, meaning the 9,500-patient DLBCL indication that Novartis will pursue next is nearly 16 times Kymriah's initial 600-patient pediatric ALL indication.

INDICATION- AND OUTCOMES-BASED PRICING

Novartis will supply an array of patient assistance programs to make sure those who are eligible for treatment can get access to Kymriah, including help getting payers to cover the therapy and financial assistance for uninsured or underinsured patients, including money to pay for travel to a treatment center – ground and air travel, hotel accommodations and meals. The company also is collaborating with the Centers for Medicare

and Medicaid Services (CMS) on value-based contracts for reimbursement, and planning on indication-based pricing that could be higher or lower depending on the patient population's size and medical needs.

That means treatments within the larger DLBCL indication for Kymriah could be reimbursed at a lower cost. In pediatric and young adult ALL, Novartis has agreed to provide the CAR-T therapy at no cost if patients do not respond within the first month, but such terms may vary for different indications based on responses seen in clinical trials.

"It has been expected that Novartis would bear financial risk in an arrangement like this," Bernstein analyst Tim Anderson said in an Aug. 30 report on Kymriah's approval. "While these terms are specific to CMS, discussions are ongoing with commercial payers, and we expect similar terms."

Novartis said it is also negotiating value- and indication-based agreements with private payers.

CMS administrator Seema Verma said in a statement from the agency that the negotiation of reimbursement agreements like the terms that are being discussed with Novartis for Kymriah "is a critical step towards fulfilling President Trump's promise to lower the cost of drugs."

US President Donald Trump called out the pharma industry for high drug prices in January before his inauguration, saying that his administration would negotiate better reimbursement contracts with companies that are now "getting away with murder." *(Also see "Trump Throws Pharma A Curve Ball On The Third Day Of J.P. Morgan" Scrip, 12 Jan, 2017.)* However, there have been no policy moves since he took office to address the cost of medicines.

PATIENTS, DOCTORS READY TO ACCESS CAR-T

With limited commentary on the CAR-T therapy's price, Kymriah's approval was heralded by doctors and patient groups, given the medical need of patients covered by the drug's initial indication. Novartis noted that these are children and young adults who have run out of treatments options – usually chemotherapy in the first line and allogenic stem cell transplant as a last resort – and who usually die within three to nine months. The company noted that at least one of the patients treated with Kymriah in a clinical trial is alive and remains in remission five years later.

"The approval of CAR T-cell therapy for pediatric leukemia marks an important shift in the blood cancer treatment paradigm," American Society of Hematology President Kenneth Anderson of the Dana-Farber Cancer Institute said in an Aug. 30 statement. "We now have proof that it is possible to eradicate cancer by harnessing the power of a patient's own immune system. This is a potentially curative therapy in patients whose leukemia is unresponsive to other treatments and represents the latest milestone in the shift away from chemotherapy toward precision medicine."

Patients For Affordable Drugs also hailed the FDA's approval of Kymriah as offering "hope for hundreds of children and their families," but Founder and President David Mitchell criticized the CAR-T therapy's price as "excessive."

Leukemia & Lymphoma Society (LLS) chief medical officer Gwen Nichols said in an interview with *Scrip* that the organization views Novartis's Kymriah pricing and reimbursement strategy from two perspectives – the cumulative cost of care for these patients as well as the value-based initiatives that the company intends to pursue. (The LLS has funded and continues to fund research involving CAR-T treatments, including Kite's axicabtagene ciloleucel.)

"We're looking at the whole spectrum of the cost of care, not just the pricing of individual therapies. We have to compare this cost to what these young people would be getting otherwise," Nichols said, referring to multi-agent chemotherapy and stem cell or bone marrow transplants, which can include lengthy hospital stays. "You have to look at it in the context of what we're doing for these kids, which is not effective."

"At least in this case – and LLS is in favor of this – there is a value proposition," she continued. "It looks like Novartis will not be charging the same value for people that are not having a benefit."

TREATMENT-CHANGING EFFICACY

Kymriah was approved based on results from the Phase II ELIANA clinical trial, in which 68 patients were infused and 63 patients were evaluable for efficacy. In ELIANA, 83% of patients (52 of 63) treated with the CAR-T therapy achieved complete remission (CR) or CR with incomplete blood count recovery (CRi) within three months of infusion – an improvement over the 82% reported in December based on the evaluation of 50 patients. *(Also see "Novartis, Kite Neck-And-Neck In CAR-T Race; Deaths Keep Juno In Third Place" Scrip, 4 Dec, 2016.)*

The trade-off for that efficacy is a long list of side effects that occurred in 20% or more of patients: cytokine release syndrome (CRS), hypogammaglobulinemia, infections-pathogen unspecified, pyrexia, decreased appetite, headache, encephalopathy, hypotension, bleeding episodes, tachycardia, nausea, diarrhea, vomiting, viral infectious disorders, hypoxia, fatigue, acute kidney injury and delirium.

Concurrent with the Kymriah approval, the FDA approved **Roche**'s interleukin-6 (IL-6) receptor inhibitor *Actemra* (tocilizumab) for the treatment of CAR-T therapy-induced CRS. Novartis, Kite and other CAR-T developers have used the biologic off-label to treat the condition, which has been frequent and severe among patients treated with the therapies. Novartis noted that 49% of patients in ELIANA experienced Grade 3 or 4 CRS.

Another safety concern has been severe neurotoxicity and in ELIANA 18% of patients experienced Grade 3 or 4 neurologic events, but there were no cases of cerebral edema, which killed patients in studies conducted by Kite and **Juno Therapeutics Inc.** *(Also see "Too Sick For CAR-T? Kite Reports Cerebral Edema Death" Scrip, 8 May, 2017.)* The most common neurologic events in ELIANA were encephalopathy (34%), headache (37%), delirium (21%), anxiety (13%) and tremor (9%).

The Kymriah label carries a black box warning about CRS and neurological events and the therapy was approved with a Risk Evaluation and Mitigation Strategy (REMS) that requires the hospitals and clinics dispensing the treatment to be specially certified after training to recognize and treat CRS and neurotoxicity. Kymriah must not be administered without assurance that Actemra is available to treat CRS as needed. Patients also must be informed about the signs and symptoms of CRS.

Novartis must also complete a post-marketing study to assess Kymriah's long-term safety.

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When Science Is Not Enough: Pharma Needs Organizational Change

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Will Dunlop, head of market access, Mundipharma International

Mundipharma International

There's a host of reasons why progress has been slow in optimizing the focus on customers in pharmaceutical companies, and two researchers working in the UK, **Mundipharma International**'s head of market access, Will Dunlop, and Nektarios Oraiopoulos of Cambridge University's Judge Business School, have come up with a series of suggestions to address the shortfall.

Dunlop and Oraiopoulos argue that three types of change – economic, behavioral and organizational – are needed to put customers, and in particular payers, at the core of the drug development process in pharma companies. Traditionally, pharmaceutical companies have focused on patients and physicians as customers, but the needs and priorities of payers equally need to be understood, and acted upon, the UK researchers say, in a report published in *Advances in Therapy* ((2017), Vol 34, pp 1,572-1,583).

"It sounds like a truism, any business should be customer focused, but when you are dealing with large complex organizations, it's easier said than done," Dunlop told *Scrip* in a recent interview. Moreover, "you can't afford to get the health system perspective wrong on what the health system is willing to pay," Dunlop added.

The drug development process in pharmaceutical companies has several characteristics that make it unique among industrial sectors: the process takes a long time, it is hugely expensive, and the failure rate is high. Coupled with those difficulties is that to do great science in this area, researchers often have strong beliefs in their science and can lose perspective on what society will pay for. And there's also the "huge number of people involved in development of a single drug, including researchers, medics, regulatory affairs, and marketers, that can number in their hundreds if not the thousands."

The report suggests companies should implement a framework that includes focusing employee incentives on the end goal of commercial success, rather than on promising interim analyses. Incentives should also become more tolerant of product failure by rewarding the decision-making process rather than the outcome.

Decision-makers should realize the limitations of relying solely on their own judgment, and should seek to validate it through objective feedback from other units in the business or from outside the organization, recommend Dunlop and Oraiopoulos. Advisory boards should be encouraged to ask challenging questions, regulators and health technology assessment bodies should be asked for advice, and senior managers should insist on objective and data-driven estimates about a project's potential profitability.

PEER EVALUATION NEEDED

For addressing organizational barriers to collaboration, there should be peer evaluation, even of the most senior management, the researchers believe. Collaboration should be measured and evaluated, and management should be "T-shaped" – able to excel in its own area but also able to collaborate effectively across an organization.

Although the increasing importance of payers in reaching commercial goals is well known within companies, and close collaboration between the R&D function and commercial teams is considered critical to addressing payers' requirements, there are still instances where such collaboration is just not happening, the researchers point out. Research teams are susceptible to progression-driven behavior, pushing drugs inappropriately to the next stage to meet yearly goals; business units come up with optimistic forecasts to justify their budgets, and continue to invest in failing projects; and the long-term and fragmented nature of much research leads to no-one taking overall control of a project.

But it's under the heading of "organizational" where major barriers to collaboration between different functions in a pharmaceutical company still exist, according to Dunlop and Oraiopoulos. The multitude of experts in their own fields involved in drug development means that transferring knowledge within a company is not a trivial task. And individuals still tend to work closely with, and learn only from, their own group, and when they reach out to others, they go mainly to people they know, rather than those with the greatest expertise.

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AstraZeneca Signs AI Deal To Pursue Novel Parkinson's Drugs

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AstraZeneca PLC is teaming up with artificial intelligence biopharma business BERG to identify and evaluate novel targets and therapeutics to treat neurological disorders such as Parkinson's disease – making it the latest of a string of big pharmas to sign discovery and development deals with AI technology firms.

Under this research arrangement, AstraZeneca will initially provide BERG with its curated library of central nervous system (CNS) optimized fragments.

Boston-based BERG's Interrogative Biology platform identifies therapies and biomarkers by applying algorithm- and probability-based artificial intelligence to analyze large numbers of patients' genotypic, phenotypic and other characteristics. The system integrates many data characteristics regarding patients' lifestyles, demographics and biology.

"AstraZeneca is committed to advancing therapies in neuroscience. Through this research collaboration, we can approach drug discovery in an innovative new way using BERG's artificial intelligence platform," Iain Chessell, head of neuroscience at AstraZeneca, said in a statement.

AstraZeneca signed another agreement focused on Parkinson's this week, worth up to $400m. The UK group is teaming up with **Takeda Pharmaceutical Co. Ltd.** for the development of MEDI1341, an antibody treatment due to enter Phase I clinical trials later this year. As part of this arrangement, AstraZeneca will lead Phase I testing of MEDI1341 in Parkinson's disease while Takeda will lead future clinical development. With BERG, AstraZeneca will initially target new drugs for Parkinson's disease. However, the partners expect to explore therapeutic targets for additional neurological diseases under the agreement. Financial terms of the deal were not disclosed.

BERG, which has a business model that combines biology, technology and AI analytics, believes its platform can provide a better understanding of disease profiles and consequently lead to the identification of molecular signatures to guide and accelerate therapeutic candidate selection and development.

BERG's current clinical pipeline consists of therapeutics as well as companion and disease diagnostics that support clinical development in the areas of oncology, neurology and endocrinology.

ON TREND

AstraZeneca is not the only big pharma to join forces with an AI biopharma company. In June this year, Takeda signed a multi-year agreement with **Numerate Inc.**, a computational drug design company based in California, to identify multiple clinical candidates in the areas of oncology, gastroenterology, and central nervous system disorders. Financial terms of this deal were not revealed but Numerate said the pact includes a combination of milestone payments and royalties.

Last month, UK drug major **GlaxoSmithKline PLC** signed a preclinical collaboration with Scottish AI business **Exscientia Ltd.** Together the two firms expect to discover novel and selective small molecules for up to 10 disease-related targets, nominated by GSK across multiple therapeutic areas. Exscientia is eligible to receive near-term lead and preclinical candidate milestones if all objectives are achieved. The total amount payable by GSK is £33m ($43m), if all 10 projects are advanced. No further financial details were disclosed. GSK hopes Exscientia's technology will reduce the number of compounds required for synthesis and assay in order to achieve lead and candidate compound goals.

Exscientia has been busy lining up pharma partners, having signed a drug discovery deal, potentially worth €250m, with **Sanofi** in May 2017; the group also has agreements in place with **Evotec AG** (in immuno-oncology), and **Sumitomo Dainippon Pharma Co. Ltd.** and **Sunovion Pharmaceuticals Inc.** (in CNS).

Ahead of the curve, in late 2016, **Johnson & Johnson** licensed several pipeline candidates to UK-based AI company **BenevolentAI**. The deal, which targets "hard to treat" diseases, granted BenevolentAI the sole rights to develop, manufacture and commercialize these novel drug candidates in all indications and in all territories.

BenevolentAI recently hired ex-GSK executive Ian Churcher as vice president of drug discovery and preclinical development for its BenevolentBio subsidiary. Previously, Churcher led a range of groups at GSK in the areas of medicinal chemistry, new technology and drug discovery, and held a visiting professorial appointment at the University of Oxford.

Meanwhile, several companies across pharma, healthcare and other industries are working with computing giant IBM Watson. The group has deals with the American Cancer Society, Cleveland Clinic and GSK, among others.

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Trial And Trial: Bracing For Commercialization Of Cell & Gene Therapies

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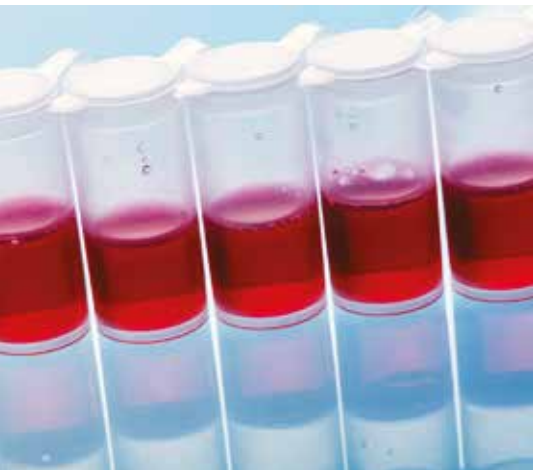
The first of a potential new wave of cell and gene therapies is expected to reach the US market shortly, but drug manufacturers and payers still aren't sure how expensive new medicines that may represent long-lasting treatments – or even cures – will be paid for.



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Nonetheless, more conversations between drug manufacturers and payers are happening, according to **AmerisourceBergen Corp.** Senior VP-strategy & commercialization Amy Grogg.

"There are a number of discussions going on," Grogg said. AmerisourceBergen issued a white paper outlining successful go-to-market strategies for commercializing cell and gene therapies in July. The drug distributor has business units that work across the distribution and commercialization process and has the ambition of being a partner of choice for drug manufacturers working in the complex field.

"This is the new frontier for treating disease, as we move forward into the next decade," Grogg said. **Novartis AG**'s tisagenlecleucel (CTL019) is posed to be the first cell therapy to reach the US market, following a positive review by the FDA's Oncologic Drugs Advisory Committee in July. The chimeric antigen receptor T cell (CAR-T) therapy has an Oct. 3 PDUFA date for the treatment of children and young adults with acute lymphoblastic leukemia (ALL).

The drug demonstrated impressive efficacy in some patients, but it's not without toxicities and serious side effects. Novartis hasn't provided much detail yet about how much the treatment will cost, but the company has talked about the opportunity for premium pricing. But six-digit prices make payers nervous, especially given the number of cell and gene therapies in the drug industry's pipeline.

"Novartis will be an interesting one to watch," said Grogg, who confirmed that AmerisourceBergen is working with the big pharma on the commercialization of CTL019 in some areas, including logistics and pharmaco-economic evidence generation.

Reimbursement structures for the first cell therapies to reach the market will be complex, she predicted. "There will be what I call, not trial and error, but trial and trial. You'll have people trying a couple of different reimbursement structures and then we will see what happens," she said. "We will see what manifests and we can manage those."

Longer-term, as more cell and gene therapies reach the market, including potentially some that address larger patient populations, she predicted that the reimbursement strategies will evolve to include reimbursement structures that amortize payments over an extended period of time.

Q-CODES: IMPORTANT TECHNICAL DETAILS

Some of the reimbursement issues that need to be sorted out are technical, such as those around the reimbursement coding used by government and private insurers in the US to receive payment. Q-Codes, as they are called, can impact when drug manufacturers receive payment for their product, which could be important in instances where administration of a therapy involves several procedures, such as extracting cells, manipulating them and re-administering them, which is the case with CAR-T. If there is no separate code to account for cell processing by the manufacturer, there is no separate payment for that service, so the product won't be reimbursed until it is administered to the patient. The risks could be high for drug manufacturers if, for example, a patient's cells were extracted and manipulated but couldn't be administered to the patient in the required timeframe due to illness or another reason, AmerisourceBergen points out in the white paper.

"In some pipeline cell and gene therapies, production of the full treatment course (several doses) will occur from a single extraction of patient-specific material," the white paper says. "A therapy owner may be required to absorb the cost of an entire treatment if therapy is discontinued." It can also affect the way providers are reimbursed.

Therefore, it's important to decide if the existing coding is sufficient or if drug manufacturers should apply for new payment codes, the white paper points out. The case of **Dendreon Corp.**'s *Provenge* (sipuleucel-T), the first cancer vaccine approved in the US, points to the challenges. Provenge, approved in 2010, was granted just one Q-code, including leukapheresis and other preparatory procedures, despite requests to the Centers for Medicare & Medicaid Services to review novel payment methodologies.

A coding strategy should be carried out two to three years prior to launch, while a product is in Phase II or Phase III development, AmerisourceBergen recommends.

As Grogg explained it, "manufacturers and payers do have a shared commitment to making the coding clear and responsible. It doesn't serve a manufacturer to have a process where the coding only serves them, because that is going to make it difficult for patients to get on therapy and for patients to afford therapy, and payers by the same token.

"They do have shared goals to try to find the right process," she said.

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GSK Bets On Online-To-Offline Push To Expand Reach

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Just days after closing its neurosciences research unit in Shanghai, **GlaxoSmithKline PLC** announced a collaboration with China's e-commerce giant Alibaba leveraging Alibaba's online-to-offline (O2O) platform to promote GSK vaccines for adults.

GSK's goal is to reach out to millions of healthy Chinese adults who browse online regularly but haven't thought about getting shots to protect themselves from illness.

While children get regular vaccination under China's National Immunization Program (NIP), and parents routinely pay added costs to get additional shots that are not covered by the NIP, adults seldom get preventative shots unless required for work or travel.

Now, GSK has created an innovative service platform to cater to the "large unmet need", said the company in a statement.

The platform will use Alibaba's online commerce site Taobao, featuring information on GSK vaccines, starting from the HPV vaccine *Cervarix* and providing links to China's vast number of community health clinics for vaccination consultation and appointment - all done through the convenience of a smartphone or access via the website.

Cervarix, the first HPV vaccine that received approval in China, was officially launched in July. Previously, young girls had to travel to Hong Kong, Taiwan or overseas markets to get the three required shots to protect themselves from the cervical-cancer virus, and these costs add up to over $500.

Meanwhile, another competing HPV vaccine, **Merck & Co. Inc.**'s *Gardasil* is pending approval with the China FDA.

Armed with the lead, GSK hopes to quickly capture a large market share via the tie-up with AliHealth - 1,500 clinics in 100 cities around China will be covered by the end of the year across all major commercial hubs including Beijing, Shanghai, Hangzhou, Shenzhou, Nanjing, Guangzhou and Wuhan.

Eventually, the two companies plan to extend the partnership to include GSK's pediatric and adult vaccines.

MORE PHARMAS GO O2O?

The GSK deal marks the second such alliance inked between multinational drug makers in China and Chinese e-commerce giant Alibaba. French drug maker **Sanofi** last year signed on the Beijing-based Alihealth to promote drug traceability system amid a national vaccines scandal.

Meanwhile, hoping to beat competition coming from two other Chinese internet giants, Baidu and Tecent, Alibaba is actively looking to tap into big data and become a personalized healthcare player, emerging as the Chinese version of **PatientsLikeMe Inc.** and IBM's Watson.

GSK said that Alibaba's ability to attract 500m users from online to offline (O2O) gives it access to China's grassroots health clinics.

"'Healthy China 2030 stipulates that developing Internet-based health services has become a part of national healthcare strategy," commented Thomas Wellimsen, general manager, GSK China Pharmaceuticals and Vaccines in a statement. The partnership will allow "innovative and convenient disease prevention knowledge and services to China's grassroots disease prevention system and the people of China," he added.

The UK drug maker recently has undergone a large R&D reorganization, closing its neuroscience center in Shanghai, and re-emphasizing its focus on infections and other conditions.

> 'Healthy China 2030 stipulates that developing Internet-based health services has become a part of national healthcare strategy'

"Our research in China will focus on projects that generate real impact to the patients, promoting public health in China, through our Infectious Disease and Public Health Institute in Beijing, and innovative clinical research and investment in China's grassroots medical infrastructure," said a GSK China spokesperson in an earlier response to *Scrip*.

In August, GSK announced that its antiretroviral (ARV) single tablet regimen *Truimeq* (abacavir, dolutegravir, and lamivudine) has received approval in China; it follows the launch of another ARV *Tivicay* (dolutegravir) in the country last year.

In China, smartphone users are one of the most active users in the region, aided by growing popularity of social media *Wechat*, as well as meal ordering and delivery and mobile pay.

As multinationals including GSK, Sanofi, **AstraZeneca PLC**, **Eli Lilly & Co.** increasingly bet on China's grassroots clinics, and the large smartphone users in urban areas, marriages between pharmaceutical companies and Internet giants are expected to increase further, experts say.

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From the editors of PharmAsia News

AZ Chief Scientist Wants Britain To Be Like Boston

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The pharmaceutical industry has responded positively to the publication of the UK government's wide-ranging Life Sciences Industrial Strategy report, which sets out concrete proposals to boost a sector that consists of 5,000 companies, 235,000 employees and produced turnover of £64bn last year.

The report was unveiled at the University of Birmingham by Sir John Bell, Regius chair of medicine at the University of Oxford, with the ambitious goal of "putting the UK in a world-leading position to take advantage of the health technology trends of the next 20 years." He said that "we have created a strategy which capitalizes on our strong science base to further build the industry into a globally-unique and internationally competitive life sciences eco-system, supported by collaboration across industry, government, the NHS, academia, and research funders to deliver health and wealth."

Sir John's report brings together input and recommendations from a broad range of stakeholders, including pharmaceutical majors, such as **Johnson & Johnson**, **Merck Sharp & Dohme Ltd.**, **GlaxoSmithKline PLC** and **AstraZeneca PLC**. In an interview with *Scrip*, Mene Pangalos, the latter's head of innovative medicines and early development biotech unit and global business development, said AstraZeneca has been very involved, with chief executive Pascal Soriot on the board and Pangalos having several meetings with Sir John "to flesh it out."

He added that "it is nice to see a coherent plan that brings all of the components of the life sciences together to create a visionary and exciting strategy that will drive growth and prosperity in the UK in the future."

One of the elements of particular interest in the report is a recommendation for the establishment of the Healthcare Advanced Research Program (HARP), through which industries, charities and the NHS can collaborate on ambitious and long-term UK-based projects. This would involve a coalition of funders "to undertake large research infrastructure projects and high-risk 'moonshot programs', that will help create entirely new industries in healthcare," the report states.

Some of them "should be large-scale infrastructure projects that have historically put the UK in globally leading positions in areas such as precision medicine and genomics," the report says, referencing UK Biobank and Genomics England (GeL) as two existing examples of such programs. However, "there is a need to consider other such possibilities," such as creating a platform for developing effective diagnostics for early, asymptomatic chronic disease, using digitization and artificial intelligence to transform pathology and imaging and projects looking at healthy ageing.

HARP COULD BE UK'S DARPA

Pangalos told *Scrip* that HARP could be the DARPA of health in the UK," referring to the US Department of Defense's Defense Advanced Research Projects Agency which is responsible for the development of emerging technologies for use by the military. He noted that DARPA has been very successful in taking innovation and applying it, and to tackle moonshots in healthcare, it is vital to bring together stakeholders - pharma, biotech, academia and the NHS.

It would be a "separate stream of work funded with a vision that will hopefully deliver new technologies and new companies that will be made in Britain and stay in Britain," he said. In addition to having a system where existing pharma and biotech groups can thrive, "we need to create fledging companies that grow into companies that can be worth tens of millions, hundreds of millions and ultimately billions of dollars that stay in the UK and don't move to the US."

This new ecosystem will need "an NHS that is fully entwined in innovation, and adoption of innovation from translational science and medicine," Pangalos said. This requires "significant investment on all fronts," he added, noting that though the £160m initial cash boost that the government announced at the launch of the report is very encouraging, "to execute and implement the life sciences strategy will need a lot more than that."

Pangalos said he is looking forward to seeing new companies "growing into the new AstraZenecas and GSKs" but warned that conditions need to change in order for the most promising start-ups to stay in the UK and not head off across the Atlantic and list on the Nasdaq. "We haven't got the same 'patient capital' as in the US - in Boston, it has the financial, scientific, pharma and biotech environment - you need all of those things and we have to build that here."

'PUNCHING ABOVE OUR WEIGHT'

He went on to say that "we do have some of those things, we have a great science base, we punch above our weight, we have some of the top universities in the world and a unique thing we do have is the NHS. However, we have to capitalize on that strong academic base and translate that into the application of innovation."

There was also enthusiasm for the report from other big pharma players. Phil Thomson, president of global affairs at GSK, said "the UK is a powerhouse for life sciences" and the company welcomes the vision set out by Sir John for the sector's future. He added that at the core of this new industrial strategy "is a stronger and deeper level of collaboration between industry, government, the NHS, academia and funders. Working together, we can make the UK internationally competitive in life sciences for the long-term, capitalizing on the country's world-class science base and realizing innovation to drive economic growth and improve patient care."

Equally enthusiastic was Mike Thompson, chief executive of the Association of the British Pharmaceutical Industry. He said the Life Sciences Industrial Strategy "is an impressive document which captures the importance of our sector to a successful post-Brexit Britain," adding that Sir John "is to be congratulated in pulling together a complex and diverse sector and showing the benefits to the UK of getting us all to align."

Thomson stated that "the NHS is rightly at the heart of the strategy - if it can build on its unique capability to use health data in research and development and address the UK's long-standing challenge of adopting new treatments, it will create a virtuous circle for all and deliver massive health and economic benefits to the UK."

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Lilly/Incyte's JAK Inhibitor Baricitinib Poised For FDA Approval After All

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Analysts expect that the resubmission of **Eli Lilly & Co./Incyte Corp.**'s JAK1/2 inhibitor baricitinib in rheumatoid arthritis will be successful and that the drug will be received warmly in the market by specialists, despite concerns by the US FDA about thromboembolic safety.

Lilly and Incyte announced Aug. 30 that they will be resubmitting the NDA for the once-daily JAK inhibitor in moderate-to-severe rheumatoid arthritis (RA) in the US by the end of January 2018. Since February, the drug has been approved in Europe, where it is marketed as *Olumiant*. Olumiant also obtained approval in Japan in July.

In the US, however, a filing for baricitinib received a complete response letter from the US FDA this April.

The agency cited concerns about dosing – in particular, whether the dose should be 2mg or 4mg – and about the risk for thromboembolic events. The sponsors said previously that a new clinical study would be needed, which posed the possibility of a big delay for the filing.

However, the companies now say that following discussions in late August with the FDA, a new study will not be needed. Lilly explained to *Scrip* that the original filing included data up to early 2016, when it was submitted, and that the company will be providing safety and efficacy data from studies that became available since then as part of the resubmission.

BMO Capital Markets analyst Alex Arfaei said in an Aug. 30 note that it's unclear whether the new data would be "sufficient to address the FDA's concerns about the thromboembolic events imbalance seen with [baricitinib]," but it's possible that this risk could be managed through a note in labeling, as is the case in Japan and Europe.

News of the resubmission means the drug could reach the market in the fourth quarter of 2018, 18 months earlier than expected, he added. The sponsors expect a Class II resubmission and a six-month review.

APPROVAL GENERALLY ANTICIPATED

Hilliard Lyons analyst Kurt Kemper said in an Aug. 30 note that the news is no guarantee, but that approval is highly likely. "We doubt Lilly's experienced regulatory team would take this risk without solid positive feedback from the FDA," he wrote.

Similarly, Datamonitor Healthcare analysts also believe that baricitinib will ultimately win the FDA's approval.

Feedback from specialists attending the European Congress of Rheumatology meeting in June indicated that the complete response letter was a surprise, based on the safety data and impressive efficacy in the pivotal program, Datamonitor Healthcare analyst Christina Vasiliou told *Scrip*. Four Phase III studies were conducted of the drug in different settings.

"Notably, the JAK inhibitor demonstrated superiority to **AbbVie Inc.**'s TNF inhibitor *Humira* (adalimumab) in the RA-BEAM study. Eli Lilly designed a strong and comprehensive clinical trial program for baricitinib in RA, assessing its efficacy and safety in patients who were naïve to disease-modifying anti-rheumatic drugs (DMARDs), inadequate responders to methotrexate, inadequate responders to conventional DMARDs, or inadequate responders to biologic DMARDs," Vasiliou said.

However, Vasiliou expects that uptake will depend largely on cost because anti-TNF biosimilars are increasingly available. Payers are likely to enforce step-therapy requiring treatment with an anti-TNF before baricitinib can be used, which could prevent the drug from penetrating the early-line treatment setting, Vasiliou said.

In Europe, the drug has been priced competitively; for example the list price in Germany is $1,560 per month, which is about 15% lower than the discounted rates for TNF inhibitors.

BMO Capital Markets forecasts global sales for baricitinib of $1.5bn, which could be increased by $200m-$300m in light of the news on Aug. 30.

"Perhaps the greatest uncertainty in our [baricitinib] forecast is that in the 2020s we expect significant growth in the TNF biosimilar market, which we believe could lead to at least 50%-60% price erosion by 2025. [Baricitinib] would likely have to compete with TNF biosimilars for new patients, and we believe it would be difficult for it to maintain a disproportionate price premium. Therefore, there could be some downside risk to our forecast as well," Arfaei said.

Competition for Lilly's diabetes drug *Trulicity* (dulaglutide), a once-weekly GLP-1 agonist, is putting more pressure on baricitinib and other new products. **Novo Nordisk AS** recently announced that its investigational once-weekly GLP-1 agonist semaglutide outperformed Trulicity in a head-to-head study, with no increase in diabetic retinopathy, a risk that some analysts had been wary of.

"The safety profile was a surprise, as earlier trials displayed an uptick in diabetic retinopathy. Thus, while we had previously expected increased competition, we were far less concerned. However, the safety surprise leads us to lower our estimates for Trulicity," Kemper said.

COMPETITIVE OUTLOOK

Currently, the only JAK inhibitor approved for rheumatoid arthritis is **Pfizer Inc./Takeda Pharmaceutical Co. Ltd.**'s *Xeljanz* (tofacitinib), which targets JAK1 and JAK3. Xeljanz was first approved by the FDA as a twice-daily formulation in 2012 but had a challenging time getting established in the market. A once-daily formulation – *Xeljanz XR* – was approved by the agency in early 2016.

Datamonitor sees baricitinib at the 4mg dose as having a competitive profile relative to Xeljanz, based on cross-trial comparisons, though no head-to-head data are available.

It took longer than expected for Xeljanz to get approved in Europe – the drug was finally cleared for rheumatoid arthritis in March in that region. Xeljanz is also now being reviewed by the

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FDA for new indications: ulcerative colitis and psoriatic arthritis.

Thromboembolic events may theoretically be a class effect – there have been post-marketing reports of thromboembolic events associated with Xeljanz. However, sponsors of JAK inhibitors have noted that rheumatoid arthritis patients have increased risk for deep vein thrombosis and pulmonary embolism and these events have been seen in trials of drugs with other mechanisms of action.

Michael Dolsten, president of worldwide research and development, said during Pfizer's Aug. 1 earnings call that the company is very pleased with the safety profile of Xeljanz. Trial data for 21,000 patients and post-marketing experience for 90,000 patients "shows there is no causal relationship between Xeljanz and venous thromboembolism," he said.

"We have not seen any signals for thrombosis. This suggests that not all JAKs are the same," the exec maintained.

Elevated platelets and thrombocytosis have been reported for baricitinib and can be associated with increased risk for thrombosis, he added.

"We have not seen that either with our Xeljanz inhibitor, and we are very pleased with its balanced and well-performing profile," Dolsten said.

Pfizer has been reporting improved performance for Xeljanz. The drug yielded sales of $336m in the second quarter, up 55% based on improved access and volume increases. Xeljanz XR also is playing a significant role right now, the company reported. In 2016, Xeljanz brought in $927m in sales, up 77%.

AbbVie Inc. is expected to file its JAK1 inhibitor upadacitinib (ABT-494) in rheumatoid arthritis in 2018. *(Also see "Safety Issues Not Dampening AbbVie Optimism For Humira Successors" Scrip, 2 Aug, 2017.)*

Galapagos NV/Gilead Sciences Inc. started a Phase III program for their JAK1 inhibitor filgotinib in August 2016.

"Unless filgotinib demonstrates superior efficacy or safety in its Phase III trials, and/or offers a significant price advantage, its anticipated late launch will restrict its patient share in RA," Datamonitor analysts said in a March report about the rheumatoid arthritis pipeline.

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CANTOS: Modest CV And Intriguing Lung Cancer Benefit

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Reducing inflammation with **Novartis AG**'s canakinumab (ACZ885) can lower the risk of lung cancer as well as cardiovascular disease, the full data from the CANTOS study show. Its researchers say the findings are a validation of the inflammation hypothesis in atherosclerosis, ushering in a "third era" in cardiovascular disease prevention, and at the same time open up new possibilities in cancer treatment.

In June, observers expressed surprise when the top-line data from the 10,000-patient CANTOS study proved positive, showing the anti-IL1β monoclonal anti-inflammatory agent had hit the primary endpoint of reducing major adverse cardiac events (MACE) in patients with previous myocardial infarction when used on top of standard of care – the trial had been considered a bit of a gamble, not being backed up by a solid Phase II dataset and based on a largely unproven scientific hypothesis.

But now the full data released at the European Society of Cardiology meeting in Barcelona on Aug. 27 have brought another surprise: a pre-planned oncology safety analysis showed a 77% reduction in lung cancer mortality and 67% reduction in lung cancer cases in patients receiving the highest dose tested (300 mg), results considered too robust to be dismissed as a fluke.

"These data provide proof that inflammation inhibition, in the absence of lipid lowering, can improve atherothrombotic outcomes and potentially alter the progression of some fatal cancers," said the lead researcher Paul Ridker of the Brigham and Women's Hospital, Boston. Other experts, however, want to see more evidence of both efficacy and safety before the drug is routinely used in cardiovascular disease patients.

Together the two findings leave Novartis with the interesting situation of deciding where to go next. A spokesperson said the company would discuss both datasets with the FDA in October. While the way forward in atherosclerosis is relatively straightforward and filings for the cardiovascular indication are planned by the end of the year, in lung cancer the path ahead is not so clear.

SUBGROUPS KEY

The roughly 15% relative risk reduction for the MACE primary endpoint is at the low end of what analysts had hoped to see, but Novartis said subgroup data would be key to its success. Patients were included in CANTOS based on their levels of the inflammatory marker C-reactive protein (CRP) and it seems this can be used to gauge their initial response to the drug. The results suggest that those patients whose CRP levels dropped quickly had better outcomes than those whose did not, and more analyses on this are pending.

In lung cancer, Novartis has scheduled additional Phase III trials for the first quarter of 2018, but further details of how the study population will be defined are yet to be determined; more should be known in late autumn, the spokesperson told *Scrip*.

Then there is the question of pricing. Canakinumab is already marketed as *Ilaris* for rare inherited conditions associated with overproduction of IL-1β, such as cryopirin-associated periodic syndromes (CAPS) and juvenile arthritis, at a price of $16,000 per 150 mg vial, but a move into more common indications would profoundly change the market dynamics. Even dosed just once every three months for the CV indication, this would place the drug well above the price of the PCSK9 inhibitors which have struggled to gain market traction. Novartis said it was too early to comment yet but that the pricing would need to reflect the value to patients at a high risk for recurrence.

The market looks substantial: about 580,000 people every year in the five largest EU countries and 750,000 people in the US have a heart attack each year, and about 40% of prior myocardial infarction patients have a high inflammation burden based on hsCRP levels. With such numbers even subgroups

of patients could mean a market worth billions, swallowing the $283m sales Ilaris brought in for its orphan indications in 2016.

INFLAMMATORY THEORY

CANTOS was designed to test directly the inflammatory hypothesis of atherothrombosis. Around half of heart attacks and strokes occur in patients who have low cholesterol levels or are otherwise considered a low risk for cardiovascular disease and it was speculated that underlying inflammation could be one cause.

As a central part of the interleukin-6 pathway, the pro-inflammatory cytokine interleukin-1β plays multiple roles in the development of atherothrombotic plaque, including the induction of pro-coagulant activity, the promotion of monocyte and leukocyte adhesion to vascular endothelial cells, and the growth of vascular smooth-muscle cells.

By blocking the action of IL-1β for sustained periods, canakinumab inhibits the inflammation caused by its over-production. With CANTOS, the Novartis product has become the first and only investigational treatment to show that selectively targeting inflammation significantly reduces cardiovascular risk.

STUDY DETAILS

CANTOS enrolled 10,061 patients from 39 countries with previous myocardial infarction and a high-sensitivity C-reactive protein (hsCRP) level of ≥2 mg/L. The data were simultaneously published in the *New England Journal of Medicine*.

The trial compared three doses of canakinumab (50 mg, 150 mg, and 300 mg, administered subcutaneously every three months) with placebo. All patients received aggressive standard care, which included high doses of cholesterol-lowering statins, but still had a residual inflammatory risk as shown by the inflammatory marker hsCRP levels.

Treatment with canakinumab had no effect on levels of HDL or LDL cholesterol compared with baseline, but did reduce levels of hsCRP, at 48 months.

For the primary MACE endpoint of nonfatal myocardial infarction, nonfatal stroke, or cardiovascular death, the two highest canakinumab doses of 150 or 300 mg produced significant relative risk reductions of 15% and 14%, respectively.

Hazard ratios (HRs) for the primary endpoint in the 50, 150, and 300 mg groups were 0.93 (95% confidence interval [CI], 0.80–1.07; p=0.30), 0.85 (95% CI, 0.74–0.98; p=0.021), and 0.86 (95% CI, 0.75–0.99; p=0.031), respectively.

The secondary endpoint – the first occurrence of any of the above, or of hospitalization for unstable angina requiring urgent revascularization – was reduced by 17% in the 150 or 300 mg canakinumab arms. The corresponding HRs in the 50, 150, and 300 mg groups were 0.90 (95% CI, 0.78–1.03; p=0.12), 0.83 (95% CI, 0.73–0.95; p=0.005), and 0.83 (95% CI, 0.72–0.94; p=0.004).

> 'CANTOS has helped move the inflammatory hypothesis of coronary artery disease forward scientifically'

Due to multiplicity testing, only the 150 mg dose formally met statistical significance for both the primary and secondary endpoints. One interesting finding was that those patients who had a swift response to the anti-inflammatory therapy, showing a reduction in hsCRP at three months greater than the median, fared better than those whose reduction in CRP was less than the median, suggesting that it may be possible to personalize therapy.

This was picked up on by the study discussant, Malke Kelm of the University of Dusseldorf, Germany, who said that "for the first time this offers the prospect of tailored treatment in secondary prevention of coronary artery disease".

Ridker said the data overall point to the beginning of a third era in preventative cardiology. "First we recognised the importance of diet, exercise and smoking cessation. Then we saw the tremendous value of lipid-lowering drugs such as statins. Now we're cracking the door open on the third era. This is very exciting," he said.

Adverse event data were reassuring, but approximately one in every 1,000 patients had a potentially fatal infection, suggesting that physicians would have to be as careful with infections as those used to treating traditional inflammatory conditions. On the flip side, there were significant reductions in adverse events like rheumatoid arthritis, osteoarthritis and gout, which makes sense considering the drug target, Ridker said. Overall, there was no significant difference in all-cause mortality (hazard ratio for all canakinumab doses vs. placebo, 0.94; 95% CI, 0.83 to 1.06; p=0.31).

CANCER UPSIDE

By contrast, cancer mortality was significantly lower among canakinumab patients than in the placebo group. The pre-planned analysis showed that canakinumab reduced the rate of lung cancer incidence and mortality among study participants in a dose-dependent manner. The highest dose 150 mg produced a relative risk reduction of 67% for lung cancer (HR 0.33 [95% CI: 0.18-0.59]) and 77% for lung cancer mortality (HR 0.23 [95% CI: 0.10-0.54]). These data were published simultaneously in *The Lancet*.

The cancer finding is consistent with experimental data relating interleukin-1β to the progression and invasiveness of certain tumors, particularly lung cancer, the researchers said.

"Our hypothesis-generating data suggest the possibility that anti-inflammatory therapy with canakinumab targeting the interleukin-1β innate immunity pathway could significantly reduce incident lung cancer and lung cancer mortality. Replication of these data in formal settings of cancer screening and treatment is required," the researchers concluded.

In an editorial accompanying the paper, Dr Robert Harrington from Stanford University, California, was more cautious. "Despite the scientific and clinical excitement associated with having a new mechanism of action to attack in the treatment of coronary artery disease, a better understanding of the risks and benefits of this form of therapy is needed."

He concluded: "CANTOS has helped move the inflammatory hypothesis of coronary artery disease forward scientifically. However, the modest absolute clinical benefit of canakinumab cannot justify its routine use in patients with previous myocardial infarction until we understand more about the efficacy and safety trade-offs and unless a price restructuring and formal cost-effectiveness evaluation supports it."

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Merck & Co Undecided On Anacetrapib's Future

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Merck & Co. Inc. is still deciding whether to file anacetrapib after the presentation of full data from the four-year, 30,000-patient REVEAL study at the European Society of Cardiology meeting in Barcelona on Aug. 29 showed it reduced the risk of major coronary events in high risk patients by a modest 9% compared with placebo, when used on top of intensive statin therapy.

The company's position remains unchanged from the one it gave in June when the positive top-line data for the investigational CETP inhibitor were announced: Merck still says it is reviewing the results with external experts and will "consider whether to file new drug applications" with the FDA and other regulatory agencies.

The lack of impetus speaks volumes, analysts say, and few expect the drug to be filed, despite it being the first inhibitor of cholesteryl ester transfer protein to show a benefit on hard cardiovascular endpoints.

It was initially hoped that the CETP inhibitors would build on the success of the LDL-lowering statins by raising levels of the protective HDL-cholesterol but events have proved the science to be rather more complicated, and many candidates have failed. The lead CETP inhibitor, **Pfizer Inc.**'s torcetrapib, was the first to fall back in 2006 after an increase in CV death despite an increase in the HDL-cholesterol was seen with the product. **Eli Lilly & Co.** ended the Phase III program for its evacetrapib in late 2015 after the 13,000-patient ACCELERATE CVOT study was stopped for futility and **Roche**'s dalcetrapib failed in the dal-OUTCOMES trial in 2012, although this product has since been acquired by **DalCor Pharmaceuticals**, which is testing it in a genetic subpopulation. Also still in development is **Amgen Inc.**'s AMG-899 at Phase II.

After this litany of failure, the positive top-line data for REVEAL were a surprise, but even then there were doubts over how clinically relevant the finding would be, particularly given safety concerns over the drug's propensity to accumulate in adipose tissue. The size of the study meant that significance could have been hit with a risk reduction of around 5%, and while the actual 9% reduction seen is better than that, it is still lower than the 15% the study was powered to detect. For comparison, Merck's major cardiovascular outcomes trial IMPROVE-IT study of its older combination hypolipemic *Vytorin* (simvastatin/ezetimibe) showed a more than 6% reduction and this failed to convince the FDA to add a CV risk reduction claim to its label.

STUDY DETAILS

In the REVEAL study, 30,449 adults with atherosclerotic vascular disease on study-mandated intensive atorvastatin therapy were randomized to receive either anacetrapib 100 mg once daily or placebo.

At baseline, patients' LDL-cholesterol was very well controlled: mean baseline LDL level was 61 mg/dL, non-HDL cholesterol was 92 mg/dL, and HDL-cholesterol was 40 mg/dL. The addition of anacetrapib further reduced the mean level of non-HDL cholesterol by 17 mg/dL (18%) and more than doubled the HDL cholesterol level (up by 43 mg/dL (104%)) at the study midpoint.

The primary assessment was a composite of major coronary events, defined as the first occurrence of coronary death, myocardial infarction, or coronary revascularization. During median follow-up of 4.1 years, a 9% relative reduction in the risk major coronary events was observed among those receiving anacetrapib compared to placebo (1,640 events [10.8%] vs. 1,803 events [11.8%]; rate ratio 0.91; 95% CI 0.85 to 0.97; p=0.004). The benefit was similar across multiple pre-specified subgroups.

There was no significant difference from placebo for the key secondary composite outcome of major atherosclerotic events (myocardial infarction, coronary death or presumed ischemic stroke) (rate ratio, 0.93; 95% CI, 0.86 to 1.00; p=0.052), which the researchers said was possibly due to a lack of observed benefit of anacetrapib on presumed ischemic stroke.

Other key findings were that it gave a small reduction in the risk of new-onset diabetes mellitus, and there was no excess of symptomatic side-effects with anacetrapib, even though the drug levels in adipose tissue rose with continued treatment.

Also there was no excess of mortality, cancer or other serious adverse events, but a small increase in blood pressure (systolic and a diastolic blood pressures of 0.7 mmHg and 0.3 mmHg, respectively) and small reduction in kidney function but no significant impact on the development of albuminuria or serious adverse events attributed to renal failure. The full data have been published simultaneously in the *New England Journal of Medicine*.

The trial's co-principal investigator Prof Martin Landray of University of Oxford said the REVEAL data were in marked contrast to the disappointing results from previous CETP inhibitors, but noted that the benefits seen with anacetrapib did not appear due to its effects on raising HDL-cholesterol. "The scale of reduction was similar to other LDL cholesterol lowering drugs, such as statins. The large increase in HDL cholesterol levels produced by anacetrapib did not appear to have much impact on risk," he said.

Even so, Landray believes the results seen in the study are clinically meaningful and noted that it took time for the drug's benefit to emerge. "One of the reasons why REVEAL worked is because it had twice the number of patients, twice the number of events and follow-up that was twice as long as other CETP inhibitors." These were stopped after about two years due to unexpected hazards or an apparent lack of efficacy, he said.

Overall, the study seems to have thrown up more questions than it has answered, particularly in terms of the biological effects of the drug and the value of raising HDL levels. "It's impossible to disaggregate the different contributions of the many different actions that we know about for this drug, let alone the actions that we don't know about," Landray told *Scrip*.

DEAD DUCK?

Overall, analysts are not convinced that the clinical benefit is enough to warrant filings. Tim Bernstein commented in a research note: "Even if Merck did file and regulatory agencies did approve the drug, it is not clear that prescribers would use it frequently, or that payers would readily pay for it. This is partly due to the fact that there are already other non-statin therapies available that lower LDL, both branded (e.g. the [PCSK9s]) and generic (like Merck's own Zetia/ezetimibe). The impact of raising HDL from CETP inhibition remains uncertain."

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COMPASS Sets Course For J&J/Bayer's Xarelto

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Janssen Pharmaceuticals Inc. and **Bayer AG** will make an assault on the largely uncaptured market of coronary artery and peripheral arterial disease patients after the 27,000-patient COMPASS study showed that their Factor Xa inhibitor *Xarelto* as an add-on to aspirin therapy reduced the risk of major adverse cardiovascular events compared to aspirin alone.

Full data for COMPASS (Cardiovascular Outcomes for People Using Anticoagulation Strategies) in coronary artery disease (CAD) and peripheral arterial disease (PAD) were revealed at the European Society of Cardiology meeting in Barcelona on Aug. 27 and published simultaneously in the *New England Journal of Medicine*.

In the study, the combination of a low 2.5 mg twice-daily dose of Xarelto with aspirin was superior to aspirin alone at 100 mg once daily for reducing major adverse cardiovascular events (MACE), while Xarelto monotherapy at a dose of 5 mg twice daily reduced the primary composite endpoint numerically only compared to aspirin alone.

Efficacy for the combination came at the expense of a significant increase in major bleeding, but the sponsors believe this is a price worth paying, as the problem was mostly confined to less serious bleeds and overall there was a non-significant reduction in mortality and a significant increase in net clinical benefit for the combination. The companies are expected to file for additional approval of the product in the US (Janssen) and outside the US (Bayer) by the end of the year.

Clear benefits for the combination were also seen on most secondary outcomes including stroke (42% risk reduction), cardiovascular death (22% reduction) and all-cause mortality (18% reduction), and a trend for a benefit in myocardial infarction. Some cardiologists now expect treatment guidelines to change, and analysts are forecasting blockbuster increases in product sales on the back of the data before the drug loses patent protection in 2024. In 2016, J&J reported US sales of $2.3bn while Bayer reported sales of €2.9bn ($3.45bn), including US royalties.

COMPASS co-principal investigator John Eikelboom of McMaster University in Canada said the results represented a true breakthrough in coronary artery disease and peripheral arterial disease: "The substantial benefits seen with rivaroxaban and aspirin support the approach of using low doses of the two treatments in combination."

COMPASS was stopped a year early for efficacy in February on the recommendation of the trial's independent data and monitoring committee; it had been due to run until March 2018. At the time, the study was seen as validation for the companies' broad EXPLORER development program for rivaroxaban, which was designed for differentiation from rivals in the competitive novel oral anticoagulant (NOAC) space.

Rivaroxaban is the only approved NOAC in large-scale development for CAD and PAD patients. The product is already approved for venous thromboembolism (VTE) prevention and for stroke prevention in atrial fibrillation patients.

POINT TOWARDS SALES

PAD and CAD indications represent the most substantial of the additional indications being pursued for Xarelto. Despite the use of effective secondary prevention strategies, 5-10% of patients with cardiovascular disease have recurrent events each year. Aspirin is the most widely used treatment but is only modestly effective, reducing MACE risk by 19% and the risk of cardiovascular death by 9% compared with placebo.

Previous attempts to reduce these rates further with vitamin K antagonists and platelet aggregation inhibitors like generic clopidogrel and **AstraZeneca PLC**'s next-generation *Brilinta* (ticagrelor), were found wanting, either from a lack of efficacy or an unacceptable increase in bleeding, including intracranial bleeding. Moreover, no benefit in PAD has been seen.

This has left a substantial underserved market – around 50 million patients worldwide and around 30 million diagnosed as high risk. Xarelto's largest current indication – stroke prevention in atrial fibrillation – is thought to be just half this size. Johnson & Johnson estimates that Xarelto is currently indicated for seven to eight million patients in the US and that the addition of the CAD and PAD indications could expand the US market by 10 to 12 million patients.

This could theoretically correspond to similar increases in sales. "We see a potential doubling of the rate of growth post-COMPASS: We estimate that COMPASS could double the near to mid-term rate of growth for Bayer's share of reported Xarelto revenue to at least c€6.0bn by 2021E ([consensus] c€5.3bn), with further growth beyond that," according to analysts at Jefferies.

Deutsche Bank analysts, however, were more cautious: "Although we view this as being a clinically meaningful benefit … real world use of Xarelto in this setting is likely to require careful selection of patients with high risk of CV events but low risk of bleeding."

They also expect "Xarelto's potential penetration of the CAD & PAD indications to take time given the need for support in clinical guidelines and need for careful patient selections."

MONOTHERAPY ARM MISSES

The COMPASS study enrolled 27,395 patients with stable CAD and/or PAD and randomized them to three treatment groups: 2.5 mg of Xarelto twice daily plus 100 mg of aspirin once daily, a higher monotherapy dose of 5 mg twice daily plus placebo, or 100 mg aspirin once daily. COMPASS also examined the safety and efficacy of the proton pump inhibitor pantoprazole compared with placebo in preventing upper GI complications in patients taking Xarelto, but this part of the study is still ongoing.

The primary endpoint was prevention of MACE, including cardiovascular death, myocardial infarction and stroke in patients with CAD or with PAD.

The study was stopped for superiority of the rivaroxaban-plus-aspirin group after a mean follow-up of 23 months. By this time, a primary outcome event had occurred in 4.1% (379) patients in the rivaroxaban plus aspirin arm compared with 5.4% (496) patients receiving aspirin alone, giving a 24% relative risk reduction for the combination (HR=0.76;

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

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Selected clinical trial developments for the week 25–31 August 2017

LEAD COMPANY/PARTNER	COMPOUND	INDICATION	COMMENTS
Phase III Suspended			
Otonomy Inc.	*Otividex* (dexamethasone) intratympanic inj.	Ménière's disease	AVERTS-1; missed primary endpoint of reducing vertigo days.
Phase III Results Published			
Novartis AG	canakinumab	cardiovascular event reduction in atherosclerosis	CANTOS; in the *NEJM* online, Aug. 27, 2017.
Novartis AG	canakinumab	lung cancer risk reduction in atherosclerosis	CANTOS; *The Lancet* online, Aug. 27, 2017.
Amgen Inc.	*Repatha* (evolocumab)	cardiovascular outcomes, new analysis	FOURIER; *The Lancet* online, Aug. 28, 2017.
Merck & Co. Inc.	anacetrapib	cardiovascular outcomes	REVEAL; the *NEJM* online, Aug. 29, 2017.
Johnson & Johnson/Bayer AG	*Xarelto* (rivaroxaban) with aspirin	cardiovascular event prevention in atherosclerosis	COMPASS; the *NEJM* online, Aug. 27, 2017.
Boehringer Ingelheim GMBH	*Pradaxa* (dabigatran) as part of dual or triple therapy	stroke prevention in atrial fibrillation undergoing stenting	RE-DUAL PCI; the *NEJM* online, Aug. 27, 2017.
Updated Phase III Results			
AstraZeneca PLC	*Brilinta* (ticegrelor)	acute coronary syndrome, post MI	PEGASUS-TIMI 54; reduced cardiovascular outcomes.
Johnson & Johnson/Bayer AG	*Xarelto* (rivaroxaban)	stroke prevention in atrial fibrillation	PIONEER AF-PCI; reduced bleeding versus warfarin.
Daiichi Sankyo Co. Ltd.	*Lixiana* (edoxaban)	stroke prevention in atrial fibrillation	ENGAGE AF-TIMI 48; benefits seen versus warfarin.
Phase III Interim/Top-line Results			
Daiichi Sankyo Co. Ltd.	mirogabalin	diabetic peripheral neuropathic pain	REDUCER; achieved primary endpoint of reduced pain.
Boehringer Ingelheim GMBH	*Pradaxa* (dabigatran)	stroke prevention in atrial fibrillation	RE-DUAL PCI; as part of dual or triple therapy in patients undergoing stenting.
Sanofi/Regeneron Pharmaceuticals Inc.	*Praluent* (alirocumab)	dyslipidemia	ODYSSEY APPRISE; well tolerated and effective.
Bristol-Myers Squibb Co./Pfizer Inc.	*Eliquis* (apixaban)	stroke, systemic embolism after cardioversion	EMANATE; A Phase IV study, safe and effective.
Phase III Initiated			
Regeneron Pharmaceuticals Inc.	fasinumab	knee or hip pain due to osteoarthritis	FACT OA1; a MAb.
Aslan Pharmaceuticals Pte. Ltd.	varlitinib	gastric cancer	As first line therapy.
SymBio Pharmaceuticals Ltd.	*Treakisym* (bendamustine)	diffuse large B-cell lymphoma	In relapsed or refractory disease.
Phase III Announced			
Portage Biotech Inc.	rimegepant	migraine	Long term safety study
Denovo Biopharma LLC	enzastaurin	diffuse B-cell lymphoma	With and without chemotherapy.

Source: Biomedtracker

CONTINUED FROM PAGE 21

95% CI, 0.66-0.86; p<0.001). This was set against a significantly higher number of major bleeding events in the rivaroxaban plus aspirin group of 3.1% (288) than in the aspirin alone group (1.9%, or 170 patients; hazard ratio, 1.70; 95% CI, 1.40 to 2.05; p<0.001). The most common site of bleeding was in the stomach or lower bowel and there was no significant difference in intracranial or fatal bleeding between the two arms.

There were fewer deaths in the in the rivaroxaban plus aspirin group: 313 deaths (3.4%) as compared with 378 (4.1%) in the aspirin-alone group, but this difference was not significant (hazard ratio, 0.82; 95% CI, 0.71 to 0.96; p=0.01; threshold p-value for significance 0.0025).

The rivaroxaban-alone arm did not meet significance for the primary endpoint compared with aspirin alone, though there was a numerical benefit: 4.9% vs 5.4% experienced a major CV event, respectively.

Peter DiBattiste, co-leader of Janssen's Cardiovascular & Metabolism Therapeutic Area at Janssen Research and Development, told *Scrip* that it was probably an advantage that the combination arm came out on top, as it meant that physicians would not need to be persuaded to replace an old therapy – aspirin – they are comfortable with.

Plus, he said that "thrombosis is both a platelet-mediated and coagulation cascade-mediated event so it makes sense to me that if you interfere with both you get a better outcome."

'I believe this should change the guidelines for the management of stable CAD'

PAD SUBGROUP

A separate subgroup analysis in patients with PAD, who comprised 27.3% of the COMPASS patients, found that the combination significantly reduced the combined risk of CV death, heart attack and stroke by 28% compared to aspirin alone (5.1% vs. 6.9%; HR=0.72; 95% CI, 0.57-0.90; p=0.005).

Moreover, PAD patients on the rivaroxaban/aspirin regimen had significantly fewer (46% reduction) major adverse limb events (1.2% vs. 2.2%; HR=0.54; 95% CI, 0.35-0.84; p=0.005), a 44% reduction in acute limb ischemia (0.8% vs. 1.4%; HR=0.56; 95% CI, 0.32-0.99; p=0.04) and a 70% reduction in major amputations (0.2% vs 0.7%; HR=0.30; 95% CI, 0.11-0.80; p=0.01) compared with those taking aspirin alone. These data are due to be published in *The Lancet* at a future date.

"People with PAD are generally at higher risk of CV events, including death, and have fewer medical options available than patients with CAD alone, making these results exceptionally meaningful," added Eikelboom.

BUILDING ON COMPASS

The COMPASS study discussant, Eugene Braunwald of Harvard Medical School, said the results represented a "step forward" in thrombocardiology. "I believe this should change the guidelines for the management of stable CAD," he told the meeting in Barcelona.

But Braunwald said that he wants further research to build on the COMPASS results, such as a head-to-head comparison between the addition to aspirin of a second antiplatelet drug versus a very low dose of a Factor Xa inhibitor.

There is also a possibility that substituting a platelet aggregation inhibitor or thrombin-receptor antagonist for aspirin, together with a very low dose of a Factor Xa inhibitor, might bring even greater efficacy, Braunwald said.

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View table showing Sales For Leading Novel Oral Anticoagulants here:
http://bit.ly/2vHGRM9

APPOINTMENTS

Jesper Ericsson will be succeeding ***Christer Wallin*** as **Symcel Sverige AB**'s CEO – effective immediately. Ericsson was previously director of marketing and sales at BioLamina AB and has experience commercializing research-based products through his work at the Unit for Bioentrepreneurship at the Karolinska Institute, Stockholm School of Entrepreneurship and as co-founder of the Stockholm BiotechBuilders Association.

Oxeia Biopharmaceuticals Inc. has appointed ***Michael Wyand*** CEO and to its board of directors. Most recently, Wyand was president and chief operating officer of Epirus Biopharmaceuticals and before this, he was head of R&D at Percivia and senior vice president of development at BioAssets Development.

Artios Pharma Ltd., a company focused on cancer, has named ***Graeme Smith*** chief scientific officer. With over 25 years of experience in oncology research, Smith joins Artios from AstraZeneca where he was senior director at bioscience within the oncology innovative medicines and early development division. Previously, he was research director at KuDOS Pharmaceuticals.

Bone Therapeutics has appointed ***Jean-Luc Vandebroek*** chief financial officer and will be succeeding ***Wim Goemaere***, who is leaving the company to assume a senior position in a not-for-profit organization. Goemaere will continue as a non-executive director for Bone Therapeutics. Vandebroek spent 15 years at the Belgian-US retailer, Delhaize Group (now Ahold Delhaize) where he held various senior financial positions, including corporate director finance Europe and US and vice president finance BeLux.

Eyevensys, a company focused on ophthalmic diseases, has named ***Ronald R. Buggage*** chief medical officer. Most recently, Buggage was division medical officer at Sanofi's Ophthalmology Unit and before this, he was chief scientific officer of Novagali Pharma.

Karl Hård has joined **Kiadis Pharma N.V.** as head of investor relations and communications, bringing nearly 20 years of experience from AstraZeneca Plc. to the company. Hård was head of investor relations at AstraZeneca and before this, he was global program director.

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