J.P. Morgan

Roundup of highlights from the 2017 J.P. Morgan Healthcare conference in San Francisco **(p8)**

Expert View

Big pharma is poised to dominate dealmaking this year while the firepower of specialty pharma to do deals has waned **(p20)**

Valeant Attempts To Divert Attention

A well-orchestrated build-up to J.P. Morgan and rush of fundraisings was helped by the acquisition of Ariad by Takeda – but the good times were derailed **(p21)**

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Trump Throws Pharma A Curve Ball

JESSICA MERRILL, MANDY JACKSON, EMILY HAYES

Pharmaceutical manufacturers have been waiting for Trump's axe to fall – and it finally did, on the final full day of the J.P. Morgan Healthcare Conference.

Pharmaceutical executives have been waiting under a building cloud of anxiety for US President-elect Donald Trump to turn his Twitter account on the industry with a 140-character hit aimed at the high price of drugs. Instead, Trump criticized the industry Jan. 11 from behind a podium during his first press conference since being elected president.

The press conference fell on the third day of the J.P. Morgan Healthcare Conference when top executives from the drug industry were gathered in San Francisco, and news of the comments spread quickly in hotel hallways and outside on the sidewalks around Union Square as pharma and biotech stocks started to dip.

The Nasdaq Biotechnology Index fell about 3% Jan. 11. Big pharma stocks dipped: Pfizer Inc. (-1.82%), Bristol-Myers Squibb Co. (-5.30%), Johnson & Johnson (-1.23%), and Novartis AG (-1.88%).

Attendees at J.P. Morgan were concerned, but not surprised. The pharma industry was generally upbeat when Trump beat Democratic presidential candidate Hillary Clinton in November, because of her criticism of high drug prices and the potential for tax reform under a Republican administration, but they also were unsure how the issue of drug pricing would play out under populist Trump. He also criticized drug prices on the campaign trail and pharma was well aware that his Twitter comments have had negative consequences for companies in other sectors since the election.

The biggest reaction in San Francisco was a sense of uncertainty and new questions were raised. What exactly did Trump mean when he said the country needs "new bidding procedures" for the drug industry? Was he talking about new sweeping drug pricing negotiations under Medicare or something less consequential?

There also was some dismay over Trump's comments that the industry is "getting away with murder," given that most people in the industry prefer to think of their work as saving lives.

Even before Trump's press conference, drug pricing had been the single biggest theme of the 2017 J.P. Morgan meeting, with executives scrambling to find solutions to address mounting criticism over high prices. While most pharma leaders readily acknowledge there are issues with the country's drug pricing model and some "bad actors" in the space that have raised public alarm, few publicly acknowledge their company's own culpability.

Nonetheless, the industry is concerned about managing the issue before the US government reacts with broad controls on drug prices. The industry unilaterally agrees that government price controls in the US would disrupt investment in the high-risk area of business.

Allergan PLC CEO Brent Saunders has become a big proponent of biopharma

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from the editor

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It's been another week of industry soul-searching and anxiety over the great drug pricing debate. There are so many facets to this issue that Joe Jimenez's confident assertion (see p6) that industry can diffuse public criticism by being more transparent about how drugs are priced and "how we get to the value" looks a little disingenuous.

Defining value in a resource-constrained world is not exactly an exercise for which there is clear consensus on methodology. Around the world, companies, governments, payers, patients and doctors have been grappling with the value conundrum, generating plenty of conflict and discontent without any apparent diffusion of public criticism. Trying to do it at a time of heightened political upheaval as pricing scandal after pricing scandal hits the headlines is quite a challenge.

Finally, a correction. In last week's issue I mentioned that Bernie Saunders had tweeted "Trump is right" on drug pricing. Although there is a Saunders – Allergan's Brent Saunders – who believes that "we want what Trump wants" (see cover story), I didn't mean to bring a retired Canadian ice hockey player into the debate. I should have said Bernie Sanders.

exclusive online content

Pharma Executives To Watch In China In 2017
From general managers of multinationals to new CEOs of domestic innovative startups, a string of recently minted executives will help shape the future of the pharma industry in China.
http://bit.ly/2j0pSdf

Pharma ExtrapolaTable: The 2016 Top 20
The pharma top 20 will not be definitively known until May when Takeda and Astellas publish their 2016 annual results, the last Big Pharma companies to do so. But for those who cannot wait until then, *Scrip*'s ExtrapolaTable gives an early glance at the shape of pharma as another year rolls on.
http://bit.ly/2j0utMT

Game Changer: Merck's Stealth Keytruda-Chemo Filing Stirs NSCLC Market Dynamics

Merck & Co. has stealthily filed its highly anticipated Keytruda plus chemotherapy combination for first-line treatment of non-small cell lung cancer on the back of Phase II data, months earlier than expected and before the completion of a Phase III study.

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The countdown to May 10 – the much earlier than expected FDA assessment date for Merck's *Keytruda* (pembrolizumab) plus chemotherapy treatment for first-line use in lung cancer – has begun, and the anticipated regulatory nod in this patient population has analysts editing their forecasts for the entire non-small cell lung cancer market.

On Jan. 10, the US FDA accepted Merck & Co. Inc.'s supplemental biologics license application for Keytruda in combination with chemotherapy for first-line treatment of metastatic non-squamous non-small cell lung cancer – pushing the company's product way ahead of other PD-1/PD-L1 competitors chasing this patient population. The sBLA will be reviewed under the FDA's Accelerated Approval program.

Keytuda's May 10 PDUFA date could potentially put Keytruda on the market in a combination therapy before any of the other combination Phase III trials for PD-1/PD-L1 products expected this year have had a chance to read out, noted Evercore ISI analyst John Scotti.

Merck's oncology business was already on a high after the FDA approved Keytruda for first-line use in NSCLC at the end of October last year – an action heralded as the start of a new treatment paradigm for lung cancer. The success was even sweeter for the US pharma giant, as its closest competitor Bristol-Myers Squibb Co. faced a setback for its PD-1 product, *Opdivo* (nivolumab), in the first-line lung cancer setting last year. The Phase III miss for Opdivo was a big surprise but the full data presentation from the CheckMate-026 study during the Presidential Symposium at the European Society for Medical Oncology (ESMO) meeting in Oct. 2016 showed that the study was not just a near miss but a "total disaster."

If approved for use in combination with chemotherapy for first-line NSCLC, Keytruda could address around 70% of patients, analysts at Leerink highlight in a Jan. 11 research note. "While Keytruda's current first-line indication is in patients with PD-L1 expression of 50% or higher (approx. 25-30% of all patients), this indication would cover all non-squamous patients (excluding those with EGFR and ALK mutations) regardless of PD-L1 status," they point out.

ALL-SEEING, ALL-KNOWING?

The earlier than expected filing, which had been slated for the fourth quarter of this year, is based on the results of cohort G in the Phase II KEYNOTE-021 trial. Expectations for this filing action from Merck had been lowered last year when data from the KEYNOTE-021 study failed to make it into compendia guidelines (an important metric defining standards of care in oncology).

Importantly though, the KEYNOTE-021 trial was conducted in "all-comers", regardless of PD-L1 expression, meaning a potential label would likely be for the same population.

Analysts also suspect the FDA may have more intelligence from the ongoing Phase III KEYNOTE-189 study of the combination. KEYNOTE-021G randomized 123 non-squamous NSCLC patients to either Keytruda plus carboplatin and pemetrexed (as maintenance) or carboplatin plus pemetrexed alone. Data presented at ESMO in 2016 and published in *The Lancet* showed an improvement in overall response rate (ORR; 55% vs. 29%) and median progression-free survival (PFS; 13.0 vs. 8.9 months; hazard ratio: 0.53; p=0.0102) in favor of the Keytruda-containing arm. Analysts at Leerink note that the KEYNOTE-189 trial is enrolling similar patients (anticipated to reach a total of 570 patients) and is expected to read out by September.

"Given that the FDA has accepted an sBLA filing based on a relatively small (albeit randomized) cohort of a Phase I/II trial, we would not be surprised if the agency may have had access to early Phase III data (we believe this has been a pattern with other accelerated filings within the oncology division)," Leerink analysts say.

However, Jefferies analysts were cautious in their assessment of the surprise label extension filing, calling the action a risky move. "Whilst we think KEYNOTE-021(G) data were positive, the approval is high risk, due to several weaknesses in the study, as well as its prior failure to gain a compendia listing," they say.

IO+IO VERSUS IO+CHEMO

While this filing acceptance is a win for Merck – with FDA approval largely expected in May this year without issue (although not guaranteed) – some analysts are still expecting combination studies testing two immuno-oncology assets together to yield better results than IO plus chemotherapy options. Still, an early approval for Keytruda plus chemo will upset the market dynamics in first-line NSCLC as CTLA4 plus PD-1/PD-L1 combination therapies were previously expected to reach the market before chemotherapy combinations.

Two big pharma studies are projected to read out soon for NSCLC first-line combination treatments combining IO agents: data from AstraZeneca PLC's MYSTIC trial, combining durvalumab (anti-PD-L1) plus tremelimumab (anti-CTLA-4), are expected in the first half of 2017; and results of Bristol-Myers' CheckMate-227 study of Opdivo (anti-PD-1) plus *Yervoy* (ipilimumab; anti-CTLA-4) are anticipated before the end of the first half of 2018 at the latest. BMS has also discussed accelerating a filing for this combination.

BMS's CheckMate-277 study also includes an IO plus chemo arm in PD-L1-negative patients; and data from Roche's IMpower 150 trial of *Tecentriq* (atezolizumab; anti-PD-L1) plus the targeted therapy *Avastin* (bevacizumab; anti-VEGF) plus chemo are also expected in the third quarter of this year.

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Takeda Acquires Ariad In $5.2bn Deal – US Infrastructure A Key Component?

LUCIE ELLIS, IAN HAYDOCK

Takeda will pay $5.2bn to buy Ariad Pharmaceuticals, the developer of one marketed cancer therapy, Iclusig – but the latter firm's US location and operations could be other important draws for the Japanese big pharma, which has previously announced plans to overhaul its own R&D activities.

Takeda Pharmaceutical Co. Ltd. is acquiring Cambridge, Massachusetts-based Ariad Pharmaceuticals Inc. for $5.2bn, adding marketed leukemia drug *Iclusig* (ponatinib) and a handful of other oncology candidates to its expanding cancer portfolio – but the high price tag will also buy the Japanese firm a desirable business unit in the US.

Takeda announced the deal on Jan. 9 – the first day of the 2017 JP Morgan Healthcare Conference – highlighting that the inclusion of Ariad's oncology portfolio will see Takeda expand into solid tumors and bulk up its presence in hematology, in line with the Japanese firm's targeting of oncology as a core strategic growth area.

Ariad's lead product Iclusig, an oral multi-tyrosine kinase inhibitor primarily targeting native/isoform BCR-ABL, is currently approved for use in chronic myelogenous leukemia (CML) and Philadelphia-positive acute lymphocytic leukemia (ALL) patients. It is the only approved therapy Ariad has in its pipeline for which it is the lead company (see table), and the guidance for calendar year 2016 sales is $170-180m.

However, the company recently filed a NDA in the US for pipeline therapy brigatinib as an ALK inhibiting treatment for non-small cell lung cancer (NSCLC), and approval after a priority review may be forthcoming in the first half of this year. Global filings are planned thereafter, including in the EU early this year.

However, Datamonitor Healthcare analyst Hardik Patel told *Scrip* that neither of these products "jump out as integral pieces for growing a pipeline," worthy of a $5.2bn price tag. Iclusig, especially, has seen its use limited due to safety concerns – the product is mostly prescribed in cases where competing tyrosine kinase inhibitors can no longer be used.

Meanwhile, brigatinib – if successful with regulators – would be the fourth drug approved for ALK+ NSCLC, which only makes up a small proportion of the total patient population (about 5%).

Ariad completed a rolling NDA submission for brigatinib in the second-line setting in the US in August 2016; its prescription drug user fee act (PDUFA) assessment date is set for April 29, 2017. The company is targeting a narrow *Xalkori* (crizotinib) resistant label in ALK+ NSCLC based on pivotal Phase II data where brigatinib yielded substantial responses and prolonged progression-free survival (PFS), with an acceptable safety profile.

OTHER MERGER VALUE?

"Perhaps this acquisition fits into a long-term plan Takeda has," Patel noted, adding that the benefit of the deal could be broader in value, such as improving Takeda's geographical reach. Biomedtracker analyst Armando Uribe added his thoughts to this wider value point. Uribe noted that in 2016 Takeda announced a strategic roadmap where it placed the oncology, gastroenterology and central nervous system franchises as its top R&D priorities moving forward. "The acquisition of Ariad Pharmaceuticals reinforces Takeda's commitment to its oncology portfolio," Uribe said.

He added that the deal also adds weight to Takeda's previously announced plans to focus its R&D operations in Japan and the US. "This acquisition is a step forward in the company's restructuring goal to optimize R&D operations," Uribe noted.

Rumors of a potential sale have surrounded Ariad since autumn last year, steadily pushing up the company's stock price, and in 2015 it was suggested that (then newly formed) Baxalta Inc. had been interested in buying out the company.

Ariad had revenues of $118.8m and logged a net loss of $231.1m in calendar 2015.

DEAL DETAILS

The acquisition is being structured as an all cash tender offer by a subsidiary of Takeda for all outstanding shares of Ariad

Ariad's Full Portfolio Of Wholly Owned Drugs

DRUG NAME	DISEASE GROUP	INDICATION NAME	LEAD INDICATION	CURRENT PHASE
Iclusig	Oncology	Chronic Myelogenous Leukemia (CML)	Y	Approved
Iclusig	Oncology	Acute Lymphocytic Leukemia (ALL)	N	Approved
AP32788	Oncology	Non-Small Cell Lung Cancer (NSCLC)	Y	I/II
BPX-501	Oncology	Bone Marrow Transplant and Stem Cell Transplant	N	I/II
Iclusig	Oncology	Acute Myelogenous Leukemia (AML)	N	II
Iclusig	Oncology	Gastrointestinal Stromal Tumor (GIST)	N	II
Iclusig	Oncology	Non-Small Cell Lung Cancer (NSCLC)	N	Investigator Initiated
Iclusig	Oncology	Thyroid Cancer	N	Investigator Initiated
Brigatinib	Oncology	Non-Small Cell Lung Cancer (NSCLC)	Y	NDA
Iclusig	Oncology	Solid Tumors	Y	Preclinical
Iclusig	Oncology	Diffuse Large B-Cell Lymphoma (DLBCL) – NHL	N	Preclinical

common stock, at a price of $24.00 cash per share, commencing within 10 business days of the merger agreement. Ariad will become an indirect wholly owned subsidiary of Takeda. The Japanese big pharma noted that the deal will be funded by up to $4bn of new debt and the remainder from existing cash.

It is expected that the acquisition of Ariad will be accretive to Takeda's underlying core earnings by FY2018 and broadly neutral in FY2017. The company expects strong revenue growth and synergy savings to offset increased sales and marketing costs for the brigatinib launch, with a minimal impact on underlying revenue and core earnings this fiscal year (ending March 31).

The transaction has been approved unanimously by the boards of directors of both companies, and is expected to close by the end of February 2017. JP Morgan Securities, Goldman Sachs & Co. and Lazard acted as financial advisors to Ariad; Evercore Partners were the advisory party to Takeda.

STRATEGIC RATIONALE

Takeda president and CEO Christophe Weber told a conference call that the move to strengthen the company's oncology portfolio fitted closely with Takeda's strategic decision to focus investment in this core therapeutic area, along with its other chosen fields of gastrointestinal and CNS.

"We see it [the Ariad deal] as not a tactical but a strategic move. I would stress that we are not obsessed with acquisitions, and we look at the whole field and try to find a deal that makes sense. We will only do it if it's a good fit with our broad strategy and we believe the medicines bring true benefits.

"These opportunities do not come along very often," particularly in oncology, Weber said.

The company pointed to the 50 or so other R&D collaborations that it had signed over the past year or so as evidence that it was taking a multi-pronged approach to building up its R&D.

Chief financial officer James Kehoe commented that financially, the main goal for Takeda is to retain its investment grade regardless of any M&A activity. Despite the size of the Ariad deal, Takeda's 2017 net debt/EBITDA is estimated at around 2.6 times, and he said there would be no impact on existing dividend policy, "to which we remain completely committed."

"This deal does not mean we have become more acquisitive, and we are not targeting another big deal in the short term," Kehoe stressed. "But we will still have enough [financial] flexibility to pursue smaller and mid-sized deals, and it does not mean that we have to stay out of M&A for an extended time."

CLINICAL/COMMERCIAL ATTRACTIONS

Despite the safety issues for Iclusig and the specific patient populations for both this product and brigatinib, Takeda executives said they expect significant long-term revenue potential from both drugs, highlighting for instance the potential to expand Iclusig – which is active against the T315I mutation associated with tyrosine kinase inhibitor resistance – into earlier lines of treatment.

The Japanese firm's chief medical and scientific officer, Andy Plump, did not shy away from Iclusig's known cardiovascular risks, telling the briefing that the drug's existing label and black box warning in the US won't change. "But the safety profile will become better understood and physician guidance improved" through ongoing and planned studies, he said.

> Takeda still has financial flexibility to pursue mid-sized deals

It was evident during the call that brigatinib is viewed as the key value driver behind the deal given Takeda's estimated potential for peak annual sales of more than $1bn, if approved. "There are many upsides we expect to see pan out" from acquiring Ariad, Weber commented.

Plump conceded that there are currently only limited data for the molecule, but that these show promising PFS, that it is "clearly highly active against brain metastases and resistance mutations", and has the potential to become the best in the ALK class.

PFS data from post-crizotinib studies presented at the World Conference on Lung Cancer 2016 and highlighted by Takeda show a median PFS of 9.2 months for 90mg once daily and 15.6 months for 90mg rising to 180mg/day for brigatinib, higher than similar figures reported from studies with ceritinib (Novartis AG's *Zykadia*) and alectinib (Genentech Inc.'s *Alecensa*).

The molecule already has US breakthrough designation and orphan status for its lead NSCLC indication, and a Phase III program in first-line use in this disease is ongoing. "We also see opportunities for further studies and possible label expansion into other genetically defined NSCLC subgroups," based on early studies showing a pan-inhibitory profile against ALK resistance mutants, Plump told the meeting.

Takeda already has a number of other early-stage assets for solid tumors, including the PI3K alpha isoform inhibitor TAK-117 for NSCLC, and TAK-228, an MTORC ½ inhibitor for breast, endometrial, and renal cell cancer (both Phase II).

POST-MERGER CONSOLIDATION

Weber told the briefing that Takeda's R&D spending is expected to remain flat for the next several years despite the addition of Ariad, whose research costs will be mostly absorbed into existing group spending. He pointed to the "very little attrition" in Ariad's pipeline and the benefits of adding an already successful R&D engine that brings platform technology for computational and structure-based drug design.

In response to analysts' questions, Plump reiterated that the Takeda "remains absolutely committed to our R&D base in Japan", which will be one of the main global hubs with a particular and unique emphasis on CNS and regenerative medicines under the major reorganization and outsourcing restructuring announced last year.

Given that Ariad has already built up some commercial capabilities and infrastructure, particularly in the US, for Iclusig and brigatinib, Weber admitted that these would be valuable given Takeda's currently limited capabilities in hematology and solid tumors. "We will leverage and extend existing Ariad capabilities," he said, without elaborating.

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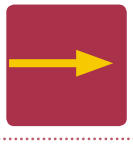

View Ariad's stock price between Jan 2016 – 2017: **http://bit.ly/2jAZxDo**

Pharma Strategizes On Drug Pricing

Drug pricing was a big theme at the industry's biggest business meeting of the year even before president-elect Donald Trump weighed in on the matter. While drug makers acknowledged there was an issue, they mostly defended their pricing strategies.

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Drug pricing was a recurring theme on the opening day of the J.P. Morgan Healthcare conference in San Francisco Jan. 9., with pharmaceutical investors increasingly concerned about the sustainability of high drug pricing in the US. With payer push-back on drug prices intensifying and many consumers and regulators outraged over high drug prices, the issue was expected to be a dominant one in 2017 that could clip sector growth.

The question of drug pricing and pricing power came up in almost every big biopharma presentation, and while executives openly acknowledged it as a festering issue that needs to be addressed, many also defended their own companies' pricing strategies.

> 'We need to be focused on the true cost river, and it really is the cost of these diseases'

"I don't think we have to change our perspective. Our perspective has always been principled," Celgene Corp. CEO Mark Alles said when asked about pricing during the company's breakout session. "Our products fit into an ecosystem of bringing down costs by managing and helping people with a disease. If we are ever in a position where that is not the case then we have a different business mode."

Innovative biopharmas like Celgene developing drugs in areas of high unmet need appear to be distancing themselves from peers that have come under fire for taking regular price increases on mature medicines.

Regeneron Pharmaceuticals Inc. CEO Leonard Schleifer, for example, used the Westin St. Francis' Grand Ballroom stage to plead with peers to adopt responsible pricing practices, while defending his own company's pricing strategy.

"We are despised because we don't do things right," he said. "We talk about doing them right and we pretend frequently as an industry that we do things right, but I'm going to tell you that I don't think we do."

He pointed the finger at drug makers that take regular price increases on marketed drugs. "You hear a lot of people saying they have priced on value," he added. "If that's true, how come six months later they raise the price, one year later, they raise the price."

"The value hasn't changed, and we aren't fooling anybody," Schleifer said. Regeneron has never raised the price on any drugs, he said.

Others agreed that the practice of regular price increases is part of the problem, even though many manufacturers in competitive areas like diabetes or respiratory disease claim that most of the increase is returned to payers and others in the system in form of rebates and fees.

In an interview David Meeker, the CEO of Sanofi's Genzyme unit, agreed the initial price is not usually the problem. "I don't think it's so much of an issue of the starting point. It's really how they manage their year-on-year pricing discussions." He predicted in two years industry pricing practices will look different, however, with more emphasis on demonstrating value.

Allergan PLC CEO Brent Saunders has been a big advocate of limiting price increases and being more transparent about pricing. Last year, the company announced a social contract with consumers, vowing that it would not raise prices by more than 10%. Indeed, when the company raised prices on many of its drugs in January, the price hikes were under 10%, though just barely.

"Making promises that we're not going to raise prices more than 10% and then raising them by 9.9% is not the answer," he said.

During a panel session on pricing, PhRMA CEO Steven Ubl said that some of the companies that have made headlines for egregious pricing tactics like Valeant Pharmaceuticals International Inc., Mylan NV and Turing Pharmaceuticals AG are not members of the trade organization.

Ubl said drug manufacturers need to work more aggressively to change the message on drug prices and healthcare costs.

"The biggest cost driver in healthcare is chronic disease," he said. "We need to be focused on the true cost river, and it really is the cost of these diseases."

Novartis AG CEO Joseph Jimenez, who also participated in the panel said industry needs to move increasingly toward outcomes-based pricing approaches.

"How can we get that waste out of the system? We believe at Novartis that we must start to shift away from a transactional approach to pricing towards an outcomes-based approach to pricing, where we will pay based on what our drug delivers." Novartis has developed outcomes-based contracts with some payers for its heart failure medicine Entresto, which faced issues gaining market access after it launched in 2014.

A broad shift to outcomes-based payment won't be "soon," he predicted, because of the complexities and roadblocks involved in the schemes. But, he said, "You are going to have pressure points where health systems are going to need to do this."

In the meantime, companies need to work harder to quantify the value of their drug and then communicate that to patients in a more transparent manner.

"I think we can diffuse quite a lot of criticism," he said. "Part of it is people don't understand how we price and how we get to the value."

Amgen Inc.'s Robert Bradway said his company is open to more value-based reimbursement contracts.

"You should expect that we will be very focused on value-based pricing opportunities," Bradway said. "We will be looking to enter into contracts that give us the opportunity to put our money where our mouth is with regard to our products." Amgen has also signed outcomes-based reimbursement contracts with the cholesterol lowering medicine Praluent.

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CONTINUED FROM COVER

companies self-policing their drug pricing practices and previously warned his peers that Trump was a populist president-elect who could easily insert himself and his administration into the pricing issue, so when he spoke with *Scrip* about Trump's press conference comments, Saunders said: "Unfortunately, it does not surprise me."

"We know that President-Elect Trump is pro-growth and innovation, but he is a populist," Saunders said. "The way he phrased it – that we were 'getting away with murder' – is a poor characterization, but it is a reminder for the industry that we need to be mindful of prices."

The Allergan CEO said he viewed Trump's claim that his administration would negotiate better drug prices as more of a warning than a threat. In fact, Saunders said, Allergan already negotiates with Medicare Part D plans and the company finds those to be very competitive negotiations.

Saunders asserted that "we want the same as Trump wants" – regulatory and tax systems that are supportive of bringing new medicines to patients at affordable prices that generate a reasonable return, so that companies can employ smart people with good-paying jobs in the US and continue to innovate.

"I've been saying since he's been elected that this industry needs to be on notice," Saunders said. "His administration will be supportive of the issues we're concerned about – providing innovation to meet unmet need – but there will be a focus on affordability and access."

James Sabry, senior vice president of partnering at Genentech Inc., said in an interview that despite Trump's press conference comments, it's not clear what his administration will do about drug pricing.

"Like his tweets, we don't really know what it will mean," Sabry said. "Our approach is to continue to be dedicated to what we've always been dedicated to – providing access to medicine in a way that's fair to society and allows us to build a business."

"I believe, in the end, that stock prices may fall because of this, but companies creating innovative medicines with value to patients will survive," he added. "Wall Street will be reactive. This company will continue to play the long game."

From the investor perspective, venture capitalist Jay Lichter of Avalon Ventures said in an interview, "If there were some blanket policy on drug pricing I think you'll see the end of the industry." However, he noted, "I think that Congress is smart enough to understand that."

Another longtime investor, Lindsay Rosenwald, now the CEO of Fortress Biotech Inc., which has developed a portfolio of early-stage subsidiary companies, wasn't overly concerned about the long-term implications of Trump's comments.

"Read his book. He's a dealmaker. He says, 'I take the extreme positon and then settle.' He's doing the same thing with the drug industry," Rosenwald said.

Purdue Pharma LP CEO Mark Timney joked, "I guess it's a good thing for us we're private." But, the chief executive, who sits on the board of directors of PhRMA, acknowledged the issue is one the industry needs to acknowledge and tackle.

"The industry has to work with the government to work this out," he said. "I don't think we can afford to sit on the sidelines. I don't think we can afford to ignore the issue. We have to take a leaderships role. We've got good ideas. I think those ideas have to be brought forward. I think we have to work with the administration."

Agenus Inc. president of research and development Robert Stein pointed to the high cost of cancer, in particular, without life-saving or life-extending medicines. "From the standpoint of the patients and society at large, it is expensive to die from cancer," he said. "I think that the pricing issue will be relatively manageable relative to the benefit that can be conveyed."

Stein noted that supportive care is expensive for dying cancer patients and can include frequent hospital stays, which may cost as much as $15,000 to $20,000 per day in the intensive care unit.

"Immuno-oncology interventions are still going to be worth the cost. This is not one where I feel like patients or society are going to be gouged," Stein said.

Ultimately, more information is needed before the industry and investors can begin to understand what a Trump administration might have in store.

Published online 12 January 2017

View stock movements for Top Pharmas on Jan. 11 here: **http://bit.ly/2jg8KRG**

Ipsen Pays $575m For Struggling Onivyde

Ipsen's new CEO David Meek has conducted the French company's biggest ever deal by acquiring Onivyde for pancreatic cancer from Merrimack Pharmaceuticals, and believes Ipsen will turn Onivyde's fortunes around.

Onivyde (irinotecan liposome injection) is approved and marketed for the treatment of patients with metastatic adenocarcinoma of the pancreas after disease progression following gemcitabine-based therapy, in combination with fluorouracil and leucovorin.

The product has had disappointing US sales since its launch at the end of last year. However, according to Meek, Ipsen will have "three times the number of people selling it than Merrimack did."

US sales for the first nine months of 2016 were around $60m but Ipsen is targeting peak annual sales in excess of $300m in the US. However, Meek told *Scrip* he would wait for the deal to close, slated for March this year, before providing a timeline for that forecast.

Under the agreement with Merrimack Pharmaceuticals Inc., Ipsen gains exclusive commercialization rights for the current and potential future Onivyde indications in the US, as well as the current licensing agreements with Shire PLC for commercialization rights ex-US and PharmaEngine Inc. for Taiwan. The transaction also includes Merrimack's commercial and manufacturing infrastructure, and generic doxorubicin HCl liposome injection.

Around 100 Merrimack staff will be transferred to Ipsen, mainly in the manufacturing space.

Merrimack will receive $575m upfront and up to $450m in regulatory milestones from Ipsen.

sukaina.virji@informa.com, 9 Jan 2017

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Read full story at:
http://bit.ly/2jjGJsM

J.P. Morgan Healthcare Conference: The Highlights From Company Presentations

Here we bring you a round up of company highlights from the 2017 J.P. Morgan Healthcare conference in San Francisco held between January 10th – January 12th.

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AMGEN, REGENERON FACE OFF OVER PCSK9 INJUNCTION

The legal battle between Amgen Inc. and Sanofi/Regeneron Pharmaceuticals Inc. is intensifying over rival PCSK9 blockers for high cholesterol – and words were exchanged in separate investor presentations at the meeting.

Amgen recently won an injunction blocking sales of Sanofi/Regeneron's *Praluent* (alirocumab), which was found to infringe patents for Amgen's *Repatha* (evolocumab). Billions of dollars could be on the line if Sanofi/Regeneron have to take their drug off the market. The two firms plan to appeal the decision and have been granted 45 days to request an appeal and expedited review before having to pull Praluent.

Regeneron CEO Leonard Schleifer expressed disdain for Amgen's decision to pursue the injunction.

"We said, how about just holding things off for the benefit of patients so we can just get this appeal heard," Schleifer said. "Now, if you were a company that really cared about patients first, wouldn't you say, 'That sounds reasonable, I can get it fixed later, I can get monetary damages, I'm not going to rip this product from 30,000 people or more who are getting it?'"

"To say that you can't wait, is that putting patients first? Is that what this business is about?" Schleifer asked. "It's no small wonder that our industry isn't beloved." Meanwhile, earlier in the day Amgen CEO Robert Bradway also addressed the win from Amgen's point of view.

"We are pleased that the courts agreed with us that our patents are valid and our competitor chose to launch at risk knowing that they had infringed those patents," Bradway said. "That's the nature of the business that we operate in. We have a very successful innovative biopharmaceutical industry in this country, which is based around our ability to invest in risky assets that we believe can be appropriately protected." – **Jessica Merrill**

TEVA'S VIGODMAN ON DISMAL 2017 FINANCIAL UPDATE

"That's something that should not happen and we'll do everything in our power in order to make sure that something like that does not happen again," Teva Pharmaceutical Industries Ltd. CEO Erez Vigodman told investors, referring to the lower than expected 2017 financial guidance Teva released Jan. 6.

The company underestimated the revenue coming from new products in 2016. "It had an impact on 2016. It created a new run rate for 2017. We reduced the expectations also for 2017," Vigodman said. Teva has been struggling to jumpstart growth in its stagnating generic drug business. It's one reason the company spent $40.5bn to buy Allergan PLC's generic drug business last year.

The deal is expected to drive substantial growth for the company, but the integration has already run into one surprise. In December, Teva said Sigurdur Olafsson, one of the architects behind the deal and the person charged with leading the integration, would leave the company. He was succeeded by Dipankar Bhattacharjee. There was no mention of the sudden leadership change during Teva's presentation or break-out.

Investors haven't been pleased with the slowing growth. The stock is down 36% since the Allergan deal closed July 27. It closed Jan. 9 at $35.06.

Teva said it now expects net revenue in 2017 to be $23.8bn to $24.5bn and earnings per share to be $4.90 to $5.30. – **Jessica Merrill**

MERCK MUST 'CONTINUE TO WIN' WITH KEYTRUDA

The PD-1 inhibitor *Keytruda* (pembrolizumab) has become a cornerstone of Merck & Co. Inc.'s portfolio and a key catalyst for revenue growth, so it was no surprise during the question-and-answer session after the company's J.P. Morgan presentation that its executives faced multiple queries about the development and commercialization of the immuno-oncology agent as a monotherapy and in combination with other therapies.

"We have got to continue to win in the first line," Merck executive vice president and president of global human health Adam Schechter said in regard to clinical trials, approvals and payer reimbursement for Keytruda in lung cancer.

In particular, Schechter said Merck is making progress in Europe with regulators and with payers in various EU countries. In fact, he noted, European health agencies are more accepting of testing to assess PD-L1 expression prior to administration of Keytruda – a concept that makes sense among price-conscious payers that want to make sure patients most likely to benefit from the drug get access. Uptake of PD-L1 testing could happen faster in Europe than in the US, the executive noted.

Schechter also pointed out that European payers are more receptive to combination therapy with Keytruda plus chemotherapy than Keytruda plus another immunotherapy, given the potentially high cost of two novel drugs dosed concurrently.

Even so, Merck is studying several combination regimens with Keytruda, including lower cost generic chemotherapies and investigational immuno-oncology agents, such as Incyte Corp.'s oral IDO1 inhibitor epacadostat. The partners announced in the morning before Merck's Jan. 9 afternoon J.P. Morgan presentation that they will initiate Phase III pivotal studies of Keytruda and epacadostat in four additional tumor types: non-small cell lung cancer, renal cell carcinoma, bladder cancer and squamous cell carcinoma of the head and neck.

"Data from across the ECHO development program for epacadostat continues to be accrued, including from the ECHO-202 Phase II cohorts in combination with Keytruda, which support the decision to move forward into pivotal studies beyond melanoma," Incyte chief medical officer Steven Stein said in the company's joint statement with Merck.

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The ongoing Phase I and II ECHO studies will enroll more than 900 patients in multiple solid tumor types and hematological malignancies. The Phase III ECHO-301 placebo-controlled study testing the two drugs in first-line advanced or metastatic melanoma began in June and initial data are expected in 2018.

Merck executive vice president and president of Merck Research Laboratories Roger Perlmutter acknowledged that it is risky to move Keytruda combinations with earlier-stage immunotherapies into later-stage clinical trials based on evidence from small studies, but he said the company feels confident about certain pivotal programs – like the Incyte studies – based on consistent efficacy across multiple tumor types in those smaller trials. – **Mandy Jackson**

LILLY GETTING EXCITED ABOUT CDK4/6 INHIBITOR

Eli Lilly & Co. will have its first Phase III data in 2017 for its cyclin dependent kinase 4/6 (CDK4/6) inhibitor abemaciclib in breast cancer, which could show a competitive profile compared with Pfizer Inc.'s *Ibrance* (palbociclib) – the only approved CDK4/6 inhibitor. Both drugs also may have competition this year from Novartis AG's LEE011, a CDK4/6 inhibitor that was granted priority review in November.

Lilly senior vice president of clinical and product development Daniel Skovronsky told *Scrip* during an interview in San Francisco that the Phase III MONARCH-2 and MONARCH-3 trials could support regulatory submissions seeking approval of abemaciclib this year. "I think abemaciclib could be even more important [than Ibrance] for women with breast cancer," Skovronsky said, noting that Lilly's drug is more specific for CDK4 than Pfizer's drug and dials down CDK6 – a mechanistic combination that could improve safety and tolerability. Specifically, Ibrance can cause severe neutropenia, requiring dosing for only limited periods of time, whereas abemaciclib could be dosed continuously. Nonetheless, Pfizer's drug has secured an entrenched first-to-market position.

The Lilly executive said abemaciclib, if the Phase III studies live up to expectations, could be a good example of providing "value" to patients and payers given the potentially improved safety and efficacy. He noted that drug pricing concerns and the need to demonstrate value to patients is bleeding into the research and development segment of the company.

"We have to align our investments with value to patients," Skovronsky said, hence investments in R&D programs like abemaciclib, the potential psoriasis blockbuster *Taltz* (ixekizumab), and *Jardiance* (empagliflozin) for diabetes, which had its label updated in December to reflect the drug's cardiovascular benefits.

Lilly wants to invest in drugs that change expectations, he said, so that patients will say in five years that they can't imagine life anymore without certain new medicines. – **Mandy Jackson**

BMS CAFORIO ACKNOWLEDGES CHALLENGES

Bristol-Myers Squibb Co. CEO Giovanni Caforio took the stage at the Jan. 10 meeting humbled by a clinical trial disappointment and increased competition for the company's PD-1 inhibitor *Opdivo* (nivolumab), but he was hopeful about building and maintaining a strong market share across Bristol's immuno-oncology platform. The surprising failure of the Checkmate-026 clinical trial testing Opdivo versus chemotherapy in first-line lung cancer opened a huge opportunity for Merck & Co. Inc.'s *Keytruda* (pembrolizumab) to take the lead in the frontline setting, which is already taking place following the US FDA's approval of Keytruda monotherapy in first-line lung cancer in October.

Making matters worse for Bristol, Merck revealed a few hours after Caforio's J.P. Morgan presentation that the agency has accepted the company's sBLA for Keytruda plus chemotherapy for the treatment of metastatic non-squamous non-small cell lung cancer (NSCLC) in the frontline setting.

"Obviously, we do expect to see more competition in 2017, particularly in lung cancer," Caforio said, noting later that the market would soon transition to a combination therapy market, which would benefit the combination of Opdivo with Bristol's CTLA4 inhibitor *Yervoy* (ipilimumab) – the same kind of transition that was seen in the melanoma market. However, it looks like Merck may have the advantage in combination immunotherapy too with its highly effective and less costly Keytruda plus chemotherapy combination.

"We need to move with speed and agility to remain competitive," Caforio said, revealing that Bristol will keep its operating expenses flat from year to year through 2020 while still investing a lot of money in its immuno-oncology and other product pipelines.

The BMS CEO said during the question and answer session following the company's formal presentation that it will pursue both external and internal programs to build a market-leading immuno-oncology portfolio. Bristol believes that its IDO inhibitor F001287, which it bought in the acquisition of Flexus Biosciences Inc. for up to $1.25bn in 2015, has the potential to be a best-in-class drug.

However, that's another area where Merck has an advantage as well – it recently ex-

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panded a partnership with Incyte Corp. for clinical trials combining Keytruda and the IDO inhibitor epacadostat, adding plans to conduct multiple Phase III trials.

BMS is also looking forward to presenting data this year for other assets in its immuno-oncology pipeline, which includes therapeutic candidates targeting LAG3, GITR and CSF1R. Bristol's executive vice president and chief scientific officer Francis Cuss said potential Phase I best-in-class IDO data, for instance, will be presented later this year. – **Mandy Jackson**

SANOFI MANUFACTURING ON TRACK FOR CLEARANCE

A critical Sanofi manufacturing facility that will be used to produce two potential new biologics has been deemed "acceptable" by FDA after corrective actions were made, CEO Olivier Brandicourt announced during a presentation Jan. 10. The deficiencies, identified in a routine inspection, have already hung up one of the company's BLAs, for the IL-6 inhibitor sarilumab for rheumatoid arthritis.

Investors at both Sanofi and partner Regeneron Pharmaceuticals Inc. are especially anxious to see that the deficiencies at the Le Trait, France fill-and-finish facility don't block another upcoming approval considered to be a significant commercial opportunity, *Dupixent* (dupilumab), pending at FDA for the treatment of atopic dermatitis. The application has a March 29 user fee date.

FDA still needs to inspect the facility, but that is anticipated in the first quarter and ahead of the PDUFA date for Dupixent, Brandicourt said. David Meeker, head of Sanofi's Genzyme unit responsible for overseeing the launches, said in an interview that the fact that Dupixent has been granted breakthrough therapy designation by FDA has helped expedite the resolution. "The FDA has been highly collaborative in terms of working with us to resolve this," he said. "It has been a good indication of breakthrough therapy, the level of engagement."

After the facility is inspected by FDA, Sanofi will also refile the sarilumab BLA, which will then be reviewed in two or six months, Meeker said. "We are all hoping for a six-month review," he said. – **Jessica Merrill**

SPINRAZA DRUG MAKERS DEFEND PRICE

Biogen Inc. has drawn some negative media attention for the high price of its new rare disease drug *Spinraza* (nusinersen) for spinal muscular atrophy because of the $750,000 price tag for the first year of treatment. The price drops to $375,000 in subsequent years due to the lower dosing schedule. But Biogen and its development partner Ionis Pharmaceuticals Inc. said in separate interviews that the price is justified because of the value it delivers to patients who have the rare debilitating disease, which leads to early death in infants and children. The drug was approved by FDA Dec. 23.

Biogen executive vice president of R&D Michael Ehlers said such a high price is justified for rare disease medicines like Spinraza because of their transformative nature. "The data and the impact speaks for itself," Ehlers said. "Honestly, I've not had to defend that."

Ionis, which discovered and developed Spinraza, granted a worldwide license to Biogen last year. Ionis CEO Stanley Crooke said, "The value of this drug, I think, is inestimable almost." Ionis wasn't involved in the pricing decision and Crooke said the company, like some analysts, had projected a lower price, but he said he supports the final decision.

"It's not just a life. It's a life that can be productive," Crooke said. "The annual costs [of the disease] are staggering, and that's how I think payers will look at it." – **Jessica Merrill**

SHIRE'S XIIDRA RAPIDLY ADDING PATIENTS

Shire PLC's head of US commercial Perry Sternberg described to *Scrip* on Jan. 10 how pleased he is with the launch of *Xiidra* (lifitegrast) for dry eye disease, which competes head-to-head with Allergan PLC's established blockbuster product *Restasis* (cyclosporine). Actual 2016 sales figures weren't revealed during the company's J.P. Morgan presentation, but Shire reported $14m in the third quarter – just weeks into the product's launch. Xiidra has grabbed a 20% share of the dry eye market in just a few months as a commercial product with more than 200,000 prescriptions written to date. The product's not just stealing share from Restasis, however, because the dry eye market has grown 45% since Xiidra's launch.

The Shire product has captured 51% of new prescriptions for a branded dry eye drug, reflecting the company's strategy for the product. Xiidra marketing, including direct-to-consumer television and print advertising, focused on educating patients about dry eye disease in general as well as making them aware of Xiidra as a treatment option.

"Our objective when we looked at the market was that we can fight for the small number of patients on treatment or look at getting consumers who aren't diagnosed on treatment," Sternberg said, noting that only a fraction of patients actually are on treatment.

Sternberg said private payers have embraced Xiidra too with all of the major US payers adding the ophthalmology drug to their formularies. Shire did not focus initially on reimbursement from Medicare Part D, but will pursue coverage there also.

A submission seeking approval for Xiidra in the EU is expected in the third quarter of 2017. – **Mandy Jackson**

WHERE IS NOVARTIS ONCOLOGY HEADING?

Novartis AG has made big changes to its oncology research organization in recent months, as the company looks to recapture lost ground in the immuno-oncology field, and chief medical officer Vasant Narasimhan said in an interview the changes are all part of a "rejuvenation."

There have been some high-profile R&D departures too, most notably the head of global oncology development Alessandro Riva, who was recruited by Gilead Sciences Inc. The head of Novartis' cell and gene therapy unit Oz Azam also left last year after the company disbanded the unit.

"We have looked at the talent, where can we refresh the talent," he said. "In oncology, we had a great set of leaders, but many of those leaders were in place for a long time. It's a natural thing to turn over leadership and bring in new fresh ideas, and that's just part of the rejuvenation of a company of our size."

Narasimhan said Novartis intends to finalize a new head of oncology development in the first quarter, and is evaluating internal and external candidates.

The R&D chief also reinforced Novartis' commitment to its CAR-T program, which some investors wondered about after Novartis folded the separate unit into its broader oncology group.

"I was really struck by the media coverage," he said. "This was a logical progression. In a big company like ours we take an innovative idea, we incubate it in an independent group and then at the right moment, when it starts to become more mature, we bring it into our broader organization."

Narashimhan said the change will help the company prepare for the development and commercialization of its first potential CAR-T therapy CTL019, which it is on track to file with FDA for relapsed/refractory pediatric acute lymphoblastic leukemia (ALL) in early 2017. "We didn't lose anything on the timeline," Narashimhan said. "Our pipeline behind [CTL019] with UPenn continues on pace. – **Jessica Merrill**

ABBVIE TAKE PRICE PLEDGE

AbbVie Inc. CEO Richard Gonzalez managed to get in the company's pledge to limit price increases to single digits at the very start of the firm's Jan. 11 presentation at J.P. Morgan, right before US President-elect Donald Trump voiced his intent to take on drug pricing.

Several firms have followed Allergan PLC CEO Brent Saunders' lead of a "social contract" to control price escalations, a voluntary step that just might get ahead of actual government controls. AbbVie announced it will take "one price increase per calendar year for all brands," Gonzalez said, "and no increases will exceed single digits for any product in our portfolio." The CEO stressed AbbVie's commitment to innovation, the continuing strength of its market-leading TNF inhibitor *Humira* (adalimumab), and its efforts to diversify – especially in core areas like oncology, neuroscience and virology, where its emphasis is on the remaining unmet need in the HCV market. In oncology AbbVie is "on the way to building a leadership position in hematology," Gonzalez asserted, on the backs of *Imbruvica* (ibrutinib) and *Venclexta* (venetoclax).

But the company's core remains immunology, where it is focused on maintaining Humira as standard of care through the end of its patent life in Q4 2018, and then "redefining that standard of care" out of its pipeline. Gonzalez pointed to the IL23 inhibitor risankizumab from Boehringer Ingelheim GMBH and the JAK inhibitor ABT494 as having best-in-class potential. The dermatology and psoriasis markets have grown and will continue to grow as new drugs come to market, the CEO noted, because there needs to be a range of drugs to treat the spectrum of patients. "It's a market that needs a portfolio of agents to best manage," Gonzalez noted. "In many of the immune-mediated diseases, you need a portfolio." – **Mary Jo Laffler**

GENENTECH'S SABRY SEES PARTNERING OPPORTUNITIES

Investment capital continues to drive early-stage biopharma development, but investors have eased their feet off the gas just enough to have some impact on the deal making environment.

James Sabry, senior vice president of partnering at Genentech Inc., said there were plenty of innovative ideas for the Roche subsidiary to consider in 2016, but even companies with compelling technology – not me-too proposals – needed a large partner to share their financial and development risk.

"We did more early clinical-stage deals – the most in a long time or maybe ever," Sabry said. Genentech negotiated four such early-stage transactions in 2016.

"Biotech is strong, capital is flowing in, and I think that will continue in 2017," he said. "But, there is a strong emphasis on innovation, not me-too [products]." Immuno-oncology plays by its own rules, however. For instance, even with dozens of PD-1 inhibitors in development, biopharma firms developing them are able to raise capital and find buyers for those assets, because other companies think they have to have a PD-1 inhibitor to anchor immunotherapy combinations. Also, cancer drug developers that were struggling before the immuno-oncology boom have repackaged themselves as immuno-oncology companies, with some success.

Such strategies will eventually run out of gas, however, because most major immuno-oncology players like Genentech/Roche are very careful about the external immunotherapy programs they bring in-house.

"The signal-to-noise ratio has gone down," Sabry said.

But Genentech is looking beyond hot targets to the biology involved in immuno-oncology to find solutions to unanswered questions, such as why some tumors have a lot of T-cells and others are immune deserts. Genentech wants to partner with companies that have answers to those kinds of questions and technology that uses that information to develop novel therapies.

The company's also looking beyond therapies that bring T-cells to the tumor, searching for technology that could make sure those T-cells do what they're supposed to do when they get to the tumor. For instance, Sabry said, Genentech may invest in cancer vaccines that are designed to boost T-cell activity.

Outside of cancer and immuno-oncology, Genentech continues to invest in neuroscience internally and externally in areas such as Alzheimer's disease, Parkinson's disease and amyotrophic lateral sclerosis (ALS). The company's interest in multiple sclerosis also has increased based on positive data for ocrelizumab in MS. Antibacterials also are of interest as are assets in immunology – particularly asthma, rheumatoid arthritis and lupus therapies. – **Mandy Jackson**

Further coverage of the 2017 J.P. Morgan Healthcare Conference here
Day 1: **http://bit.ly/2ifDNy9**
Day 2: **http://bit.ly/2ixWDNY**
Day 3: **http://bit.ly/2jWs0Hh**

Kite Flies CAR-T Into Asia With Daiichi Sankyo, Fosun Deals

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Now that Kite Pharma Inc.'s first chimeric antigen receptor T cell (CAR-T) therapy axicabtagene ciloleucel (KTE-C19) is being submitted for US FDA approval, chair, president and CEO Arie Belldegrun said it is the right time to think about ways to make the company's technology available in additional markets, like Japan and China where Kite entered into partnership agreements with Daiichi Sankyo Co. Ltd. and Shanghai Fosun Pharmaceutical Group Co. Ltd., respectively.

Belldegrun told *Scrip* in a Jan. 9 interview during the J.P. Morgan Healthcare Conference in San Francisco that Kite will hold on to US and European rights to axicabtagene ciloleucel and other CAR-T therapies, but explore partnerships in other territories. The company will receive $50m up front from Daiichi Sankyo and up to $200m in development and commercial milestone fees plus low to mid double-digit royalties, while Fosun will make an initial payment of $20m for clinical development and manufacturing activities plus a $40m upfront fee, $35m in regulatory and commercial fees, and mid-single-digit royalties. Kite and Fosun also will share profits on a 40/60 basis.

"As we are completing the work for the BLA submission, it was the right time to take axicabtagene ciloleucel to patients outside the US," Belldegrun said. "Europe will stay part of our own responsibilities."

Kite expects to report additional clinical trial results for axicabtagene ciloleucel in diffuse large B cell lymphoma (DLBCL) during the first quarter of this year and complete a rolling BLA submission to the FDA shortly thereafter. A marketing authorization application for axicabtagene ciloleucel will be submitted to the European Medicines Agency in 2017.

Belldegrun said the company's decision to retain US and EU rights and commercialize in those markets without a partner was based on two factors.

First, the company hired Shawn Tomasello as its Chief Commercial Officer a year ago and is confident in her abilities to oversee both US and European sales, given her experience in the same role at Pharmacyclics Inc. and other senior commercial executive positions at Celgene Corp. and Genentech Inc.

Second, the US market for axicabtagene ciloleucel in DLBCL is about 7,900 patients, about 90% of whom are treated at 72 specialized stem cell transplant facilities, and the EU market is similar with about 90% of 7,500 DLBCL patients receiving treatment at 70 specialty stem cell transplant facilities. Kite already is familiar with a lot of the US stem cell transplant centers and vice versa, because patients enrolled in the company's clinical trials have been treated at about 40 of those sites.

CHINA, JAPAN ARE 'DIFFERENT ANIMALS'

"China and Japan are different animals," Belldegrun said. "It's much more efficient if you do it with a partner."

The joint venture with Fosun initially is focused on axicabtagene ciloleucel, but the deal gives Fosun an option to license additional product candidates. Opt-in and milestone payments for the first two products could total $140m plus profit sharing and mid-single digit sales royalties.

Similarly, Daiichi Sankyo may license additional Kite product candidates for Japan. Upfront and milestone payments for each additional product candidate could total as much as $200m plus low to mid-double-digit royalties.

"On both deals, we opened up the opportunity for both of these companies to give them our next product," Belldergrun said. He noted that Fosun and Daiichi felt more comfortable about their deals with Kite knowing that they may be able to prevent competing engineered T cell therapies from entering their respective markets.

"We are very enthusiastic about this partnership with Kite, which has the most advanced technology platform in this area, and the potential for cell-based therapy to change the way in which we treat cancer in Japan," said Koichi Akahane, Daiichi Sankyo's Japan head of oncology R&D.

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Novartis Resurrects Failed Muscle Wasting Drug In New Obesity Trial

Bimagrumab failed in a pivotal late stage clinical trial last year for an orphan muscle wasting disorder. Novartis now wants to assess its potential in obesity, an area not exactly renowned for its pharmaceutical successes.

Novartis AG plans to conduct a Phase II trial of the antibody drug candidate bimagrumab in obese patients with type 2 diabetes. The activin receptor type II antagonist was developed by the Novartis Institutes for Biomedical Research in collaboration with MorphoSys AG, whose HuCAL library was used to identify the antibody.

Novartis reported in April last year that bimagrumab failed to meet its primary endpoint in a pivotal Phase IIb/III trial for the treatment of sporadic inclusion body myositis (sIMB). The company said it was "evaluating the complete dataset to inform decisions regarding ongoing development of bimagrumab." At the time, the drug was also in being tested in Phase II for the treatment of sarcopenia and hip fracture.

"Development in sIMB was halted [last year]. However, bimagrumab is in clinical development for hip fracture recovery and sarcopenia, a disease characterized by age-related low muscle mass and functional impairment," a Novartis spokesperson told *Scrip*.

According to the spokesperson, Novartis has one other clinical program in obesity: LIK-066, an oral SGLT1/2 inhibitor, which is in Phase II.

The new bimagrumab trial is a Phase II double-blind, randomized, placebo-controlled trial with change in fat body mass at 24 and 48 weeks as a primary endpoint, according to information published on clinicaltrials.gov.

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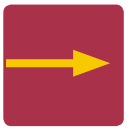

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Sarepta Snaps Up Gene Therapy Approaches to DMD

Sarepta Therapeutics Inc. has licensed rights to two gene therapy research programs underway at the Nationwide Children's Hospital, Columbus, Ohio, adding new projects to its growing Duchenne muscular dystrophy pipeline to complement its recently launched lead DMD product *Exondys 51* (eteplirsen). Marketing a range of therapies for a specific disease or condition is a well-established strategy for pharmaceutical companies, particularly in a disease like DMD that is mediated by a number of different genetic mutations. "Given the complexities of Duchenne muscular dystrophy, we know that it is going to require multiple treatment approaches," said Sarepta's CEO Ed Kaye. Of course, it's even better to develop a new therapy that has the potential to be used in most patients with the condition, and that's the promise of the two new gene therapy approaches to DMD that are the subject of the agreements between Sarepta and the Nationwide Children's Hospital in Columbus, Ohio. In the first collaboration, hospital researcher Dr Paul Martin has developed a "surrogate gene" therapy approach aimed at upregulating the production of the muscle protein urotrophin, that can deputize for, or replace, the abnormal muscle protein dystrophin in DMD patients. The approach uses the Galgt2 gene that encodes GalNAc transferase, an enzyme usually only found in neuromuscular junctions that upregulates urotrophin. Making it available throughout muscle fibers using a gene therapy approach could be beneficial in DMD patients. Sarepta expects this approach to enter the clinic this year. In its second deal with the Hospital, the Cambridge, Mass.-based biotech has entered into a research agreement involving the micro-dystrophin gene therapy program being developed at Nationwide by investigators Jerry Mendell and Louise Rodino-Klapac. Sarepta has taken an exclusive option to license the program. The research is being supported by the Parent Project Muscular Dystrophy (PPMD) that is providing $2.2m in funding, and other foundations and charities, and a Phase I/IIa trial is expected to start in late 2017.

john.davis@informa.com, 12 Jan 2017

Intercept's NASH Phase III Enrolling Slowly; Gilead Could Gain Ground

Gilead Sciences Inc.'s announcement at the J.P. Morgan Healthcare Conference that it will take its lead candidate for non-alcoholic steatohepatitis, the apoptosis signal-regulating kinase-1 (ASK1) inhibitor selonsertib, into Phase III soon is shaking up the NASH race. It's premature to predict anything approaching a tectonic shift, but Gilead's announcement opens up the possibility that the virology powerhouse may be catching up to the presumed clinical development leader, Intercept Pharmaceuticals Inc., in this heavily competitive space. To date, Intercept and France's Genfit SA, which did not present at JP Morgan, have the only candidates in Phase III for NASH, a major unmet medical need with blockbuster earnings potential. Gilead reported that it will start Phase III for selonsertib (GS-4997) – with a focus on sicker patients with F3 and F4 fibrosis scores – during the first quarter of 2017. Beyond that, the firm hopes to get positive Phase II data from its two other clinical-stage NASH candidates – the acetyl CoA carboxylase (ACC) inhibitor GS-0976 and farnesoid X receptor (FXR) agonist GS-9674 – as monotherapy and then begin combination studies with all three agents.

joseph.haas@informa.com, 13 Jan 2017

New OA Cell Therapy On Horizon

South Korea's Nature Cell Co. Ltd. is stepping closer to the commercialization of JointStem, its autologous adipose-derived stem cell therapy for degenerative osteoarthritis (OA), following the successful completion of a Phase IIb clinical trial, and is aiming to gain regulatory approval and launch the product in its home market this year. The therapy involves the intra-articular injection of stem cells separated from subcutaneous fat collected from the patient's own body, and the company says it is the first such cell or stem cell treatment for OA to be administered by a simple injection instead of a surgical procedure. The company has also begun a Phase II study of JointStem in the US. A number of cellular and stem cell therapies have been launched in South Korea for OA, but most of them, except for Medipost's Cartistem, have not been successful commercially. In the fourth quarter of 2016, domestic sales of Cartistem, which uses mesenchymal stem cells derived from allogeneic umbilical cord blood, surged 43% from a year earlier. "We are targeting a different patient group, advanced-stage osteoarthritis patients with worn-out cartilage, while Cartistem targets treatment of earlier-stage patients with cartilage defects," explained an official at Nature Cell. Kolon Life Science Inc.'s Invossa, a genetically modified allogeneic cell therapy for OA, is also awaiting regulatory approval in South Korea and is set to debut in the country in the second half of this year. The therapy is drawing attention as it is administered via intra-articular injection and could become the world's first disease-modifying OA therapy.

jungwon.shin@informa.com, 10 Jan 2017

AstraZeneca, Eli Lilly and Cancer Dominate 2016 EU New Drug Approvals

2016 saw 30 new active substances approved in the EU, in a total of 29 different products, of which 10 were for cancer indications. Two companies shared the honors for productivity: AstraZeneca and Lilly each saw three new active substances approved by the European Commission during the year.

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Cancer drugs increased their share of EU initial marketing authorizations in 2016, accounting for a third of the 30 new active substances approved by the European Commission.

Although the total number of new active substances (NASs) in 2016 was significantly down on the high of 46 seen in the previous year, it was pretty much in line with the 34 NASs approved in 2014. Among the approvals were a number of combination treatments, including one containing two new active substances – Merck Sharp & Dohme Ltd.'s hepatitis C treatment *Zepatier* (elbasvir plus grazoprevir).

COMPANIES

Eli Lilly & Co. and AstraZeneca PLC topped the list with three NAS approvals apiece, and no other company managed to win more than one NAS approval last year. But big pharma still dominated, gaining approvals for 17 of the 29 products on the list. One notable debut was from Intercept Pharmaceuticals Inc., with its first product, and only the second treatment for primary biliary cholangitis, the orphan drug *Ocaliva* (obeticholic acid). Other companies receiving their first approvals were MolMed SPA, Birken AG (now part of Amryt Pharma PLC) and Amicus Therapeutics Inc.

ONCOLOGY

The oncology area saw 10 new active substance approvals in 2016, including two of Lilly's three NASs and one of AstraZeneca's.

Fellow big pharma Pfizer Inc.'s *Ibrance* (palbociclib) for HR-positive, HER2-negative locally advanced or metastatic breast cancer became the first cyclin-dependent kinase 4/6 inhibitor to be given the green light in Europe. The HR+/HER2- breast cancer market is valued at around $3.4bn in the US, Japan and the five major EU markets, a figure that Datamonitor Healthcare forecasts could rise to $10.7bn by 2022, largely due to the uptake of Ibrance and the approval of other late-phase pipeline candidates.

Lilly's drugs figured among the four new cancer products drugs that were given a conditional marketing authorization – where approval is granted on condition that more data are produced to support a switch to a full marketing authorization – and also had orphan status:

Key EU NAS Approval Data For 2016

30 new active substances, in a total of 29 different products
10 new oncology treatments
AstraZeneca and Lilly lead approvals list
Top NAS categories: oncology, alimentary/metabolic, neurology

Lilly's *Lartruvo* (olaratumab), for soft tissue sarcoma in adults non-responsive to radiotherapy or surgery. Lartruvo also benefited from an accelerated assessment by the European Medicines Agency's scientific committee, the CHMP. This was Lilly's first conditional approval in the EU: it has been asked to produce post-authorization data from the ongoing Phase III ANNOUNCE study, which is expected to complete in 2019.

AbbVie Inc./Roche's *Venclyxto* (venetoclax) for adults with chronic lymphocytic leukemia. This is a first-in-class BCL2-specific oral inhibitor, and, according to the companies, the first medicine approved that is designed to trigger a natural process that helps cells self-destruct in CLL patients who have received previous treatment or who have a high-risk form of the disease.

Takeda Pharmaceutical Co. Ltd.'s *Ninlaro* (ixazomib) for multiple myeloma in patients who have taken at least one prior therapy. This was approved only after the CHMP reversed an initial negative opinion on the product and on condition that the company provide more confirmatory data on its effectiveness.

MolMed's Zalmoxis, consisting of genetically modified allogeneic T cells, for adjunctive treatment in haploidentical hematopoietic cell transplantation in adults with high-risk hematological malignancies.

Two new drugs were approved for multiple myeloma. Janssen Pharmaceuticals Inc.'s orphan drug *Darzalex* (daratumumab), a first-in-class anti-CD38 antibody intended for relapsed and refractory multiple myeloma, received a CMA.

The approval of Darzalex came hot on the heels of that of Bristol-Myers Squibb Co.'s *Empliciti* (elotuzumab), which underwent accelerated assessment for use in combination with lenalidomide (Celgene Corp.'s *Revlimid*) and dexamethasone in adult multiple myeloma patients who have received at least one prior therapy. Empliciti will be entering an increasingly crowded market, but its approval for second-line or higher use should help it stand out from the crowd. It is expected to have the edge over Darzalex, as it is approved for use earlier in the treatment paradigm, although Darzalex is expected to move to earlier-stage use in due course.

One other new oncology drug was given a conditional approval: AstraZeneca's *Tagrisso* (osimertinib) for locally advanced or metastatic EGFR T790M mutation-positive non-small-cell lung cancer (following accelerated assessment). As a condition of the approval, the company must provide data from the Phase III AURA3 study comparing osimertinib with platinum-based chemotherapy, which is expected to be available in June 2017.

Two other cancer products received EU approval. Servier SA's *Lonsurf* (trifluridine/tipiracil) was OKd for metastatic colorectal

cancer (tipiracil is the new active substance in the combination). Although it is authorized only for third- and fourth-line settings, these are still areas with high unmet needs.

Lilly's *Portrazza* (necitumumab) was OKd for locally advanced or metastatic EGFR-expressing squamous non-small-cell lung cancer in chemotherapy-naïve patients.

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ALIMENTARY/METABOLIC

Four new products were approved in the alimentary/metabolic disease area, including Grünenthal GmbH's *Zurampic* (lesinurad) for hyperuricemia in gout patients. The drug was developed by AstraZeneca, which licensed the European and Latin American rights to the German company earlier this year. It is also one of the first products for which the EMA has published clinical reports under its proactive clinical data publication policy.

Amgen Inc.'s *Parsabiv* (etelcalcetide) was authorized for secondary hyperparathyroidism (SHPT) in adult patients with chronic kidney disease (CKD) on haemodialysis therapy. While the drug, a follow-on from *Mimpara* (cinacalcet), seems to have passed through the CHMP process without much ado, it has been held up in the US, where FDA issued a complete response letter in August.

Representing only the second treatment for primary biliary cholangitis was Intercept Pharmaceuticals Inc.'s orphan drug *Ocaliva* (obeticholic acid), which is indicated for use with the only other available treatment for the condition, ursodeoxycholic acid (UDCA). The product, a farnesoid X receptor agonist, was given a conditional marketing authorization; Intercept will need to provide further data from the COBALT outcomes trial and a short-term study in patients with hepatic impairment.

The fourth approval in this area was Amicus Therapeutics' orphan drug *Galafold* (migalastat) for Fabry disease.

NEUROLOGY

Three new products were authorized in the neurology area in 2016. Bioprojet's *Wakix* (pitolisant HCl) is a first-in-class orphan drug that acts on histamine H3 receptors in the brain and is intended to treat narcolepsy with or without cataplexy, while Bial's *Ongentys* (opicapone) is for adjunctive therapy in adults with Parkinson's disease and end-of-dose motor fluctuations who cannot be stabilized on levodopa/DOPA decarboxylase inhibitors (DDCIs). The third drug approved was UCB Pharma SA's epilepsy treatment *Briviact* (brivaracetam).

INFECTIOUS DISEASES

In the infectious diseases category, two new combination drugs were approved for hepatitis C. One was MS&D's Zepatier, a fixed-dose combination of two NAS, elbasvir and grazoprevir. Approved in July, it was due to launch across Europe starting in late November. The other was *Epclusa* (sofosbuvir/velpatasvir) from Gilead Sciences Inc. (velpatasvir is the NAS).

Epclusa will probably be the more successful of the two combinations "because it is the first pan-genotypic regimen to be approved and will be positioned as a one-size-fits-all once daily cure," according to Michael Haydock, lead analyst at Datamonitor Healthcare.

Illustrating the dearth of research in the antibacterial area, only one new NAS-containing product, AstraZeneca's *Zavicefta* (a combination of ceftazidime and the new beta-lactamase inhibitor avibactam), was approved in 2016. It is indicated for adults with multi-drug resistant bacteria and other severe bacterial infections, including carbapenem-resistant Enterobacteriaceae.

One new vaccine was approved in 2016: MedImmune LLC (AstraZeneca)'s pandemic H5N1 flu vaccine, for prophylactic use in an officially declared pandemic situation in people aged 12 months to 18 years. This was a conditional approval.

OTHER NEW SUBSTANCES

Two hemophilia B products were approved, both of them with orphan designation: CSL Behring's *Idelvion* (albutrepenonacog alfa) and Swedish Orphan Biovitrum AB's *Alprolix* (eftrenonacog alfa). A European Commission decision transferring the marketing authorization for Alprolix to Swedish Orphan from Biogen Inc. was published in September.

GlaxoSmithKline PLC saw its orphan drug *Strimvelis* (autologous CD34+ enriched cell fraction) approved for severe combined immunodeficiency due to adenosine deaminase (ADA) deficiency. The company has completed significant studies contained in the pediatric investigation plan (PIP) for the product, and so its market exclusivity has been extended from 10 to 12 years, in accordance with the legislation.

The CHMP said that the benefits of Actelion Pharmaceuticals Ltd.'s *Uptravi* (selexipag) for pulmonary arterial hypertension included dilation of the pulmonary arteries as well as antiprofilerative and antifibrotic effects, which decrease pulmonary arterial pressure and delay disease progression.

Lilly's *Taltz* (ixekizumab) is a new treatment for moderate to severe plaque psoriasis in adults that binds with high affinity and specificity to both forms of interleukin 17A. The CHMP described Taltz's benefits as being its significant and clinically relevant effects compared with placebo or etanercept.

Teva Pharmaceutical Industries Ltd.'s *Cinqaero* (reslizumab) is an add-on therapy in severe eosinophilic asthma in adults whose condition is inadequately controlled despite high-dose inhaled corticosteroids plus another medicinal product for maintenance treatment.

In a new departure in the wound healing department, Birken AG saw its birch bark extract, Episalvan, authorized for the treatment of partial thickness wounds in adults – this is the first treatment to receive EU centralized approval for this condition. Earlier this year, Birken was acquired by the UK specialty company Amryt Pharma PLC, which said it plans to develop Episalvan for epidermolysis bullosa in Europe and the US.

Allergan PLC Pharmaceuticals received approval for *Truberzi* (eluxadoline) for irritable bowel syndrome with diarrhea. The marketing authorization was granted in September 2016 to Aptalis Pharmatech Inc. but was transferred to Allergan in December.

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View New Active Substances Approved In The EU In 2016 here: **http://bit.ly/2ithRla**

WuXi Biologics Readies For Hong Kong IPO

Following the completion of its privatization at the end of 2015 after delisting from the New York Stock Exchange, WuXi has officially kicked off a new round of capital-raising. On Jan. 4, Hong Kong Exchange and Clearing published an application proof, post-hearing information pack and related materials from WuXi Biologics, a subsidiary of WuXi AppTec Inc., for an initial public offering in Hong Kong. The joint sponsors of the IPO include BofA Merrill Lynch, Morgan Stanley and China Merchants Securities, and the offering value was not disclosed. Speculation about WuXi PharmaTech Inc.'s possible re-listing have been mounting for some time. Back in April 2015, the company listed wholly-owned Shanghai Syn-The-All Pharmaceutical (STA), a contract research and manufacturing unit for small molecules, on the New Third Board, the over-the-counter stock exchange in China. The move appears to have been a success. According to STA's annual report in 2015, it generated revenues of CNY1.269bn ($183m) with net profit of CNY330m, with year-on-year growth increasing 18% and 38%, respectively. The current market cap of the operation is CNY15.6bn.

ying.huang@informa.com, 10 Jan 2017

Debt-laden Valeant Sells Its Assets

Valeant Pharmaceuticals International Inc., the embattled Canadian drugmaker under investigation for price gouging, has agreed to sell about $2.1bn in assets to get cash to streamline its businesses and begin easing its $30bn debt burden – and observers believe more sell-offs are on the way. The first of the two-step move announced Jan. 10 will see Paris-based L'Oreal SA paying Valeant $1.3bn in cash for three skincare brands: CeraVe, AcneFree and AMBI, which have annualized sales of some $168m. Valeant is also selling its Dendreon Corp. unit to closely held Chinese conglomerate Sanpower Group Co. for about $820 million. The sale of the three skincare brands, expected to close in the first quarter, comes in contrast to comments made just two months ago by CEO Joseph Papa who confirmed the Canadian company was discussing sale of its gastrointestinal business, but stressed at the time that Valeant did not need to divest assets to maintain liquidity. Papa had signaled that GI, eye care, dermatology and consumer products were core businesses when he unveiled his turnaround plan for the company in August 2016 after taking over the CEO role from former CEO Michael Pearson in May.

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Aurobindo Takes Pole Position In Portugal

India's Aurobindo Pharma has catapulted to the top spot in the Portuguese generic market with the buyout of Generis Farmacêutica SA and hopes to cash in on its extensive portfolio and brand loyalty to drive growth. Aurobindo Pharma Ltd. has begun 2017 with an acquisition, snapping up Generis Farmacêutica SA in Portugal for €135m from Magnum Capital Partners. The deal, valued at about two times Generis' net sales in 2016, has been routed through Aurobindo's wholly owned step-down subsidiary, Agile Pharma BV Netherlands, and includes the Portuguese firm's manufacturing facility in Amadora. The transaction comes after Aurobindo lost out to Intas Pharmaceuticals Ltd. in the race for Teva Pharmaceutical Industries Ltd.'s assets in Europe and takes Aurobindo to top position in the Portuguese generics market. The Generis group is currently ranked number two by value in the Portuguese generic market.

anju.ghangurde@informa.com, 9 Jan 2017

Daiichi Closed Indian Site

Daiichi Sankyo Co. Ltd. has taken another step in its ongoing global restructuring process, this time closing an R&D subsidiary in India that employs around 170 people. The plans to shut its Daiichi Sankyo India Pharma Private Limited facility in Gurgaon - probably the last remnant of the major Japanese firm's direct local presence in the country - have elicited mixed responses locally, with some experts suggesting that an erosion in trust following the Ranbaxy Laboratories Ltd. foray may have been among the factors that forced the Japanese firm to act in abundant caution. The research arm is involved mainly in basic low molecular weight drug discovery research in the areas of infectious diseases and inflammation. Its remit also includes some themes in tropical diseases such as dengue and tuberculosis, selected under Daiichi's partnership with Japan's Global Health Innovative Technology (GHIT) Fund. These projects will all be transferred back to the parent company's R&D division, in a step the company said is designed to "increase R&D productivity".

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Anju Ghangurde & Ian Haydock
11 Jan 2017

Insights Into Gut-Brain Signaling Raise Hopes For Treating Neurological Disorders

MARK RATNER

New research offers mechanistic proof of signaling between gut and brain in Parkinson's disease, showing that introducing an altered microbiome from PD patients into a mouse model can recreate the motor symptoms of the disease.

Disruptive innovations sometimes come directly from the development of a novel enabling technology. In other cases, however, they result from focusing on a known problem using a different lens. Such creativity underlies new research suggesting the potential for harnessing the microbiome to treat neurological disorders.

A Dec. 1 paper in Cell offers mechanistic proof of signaling between gut and brain in Parkinson's disease (PD). It shows that introducing an altered microbiome from PD patients into a mouse model can recreate the motor symptoms of PD. The work, from the laboratory of Sarkis Mazmanian at the California Institute of Technology, is the foundation for a newly funded start-up aimed at developing microbiome-based therapeutics for PD and, based on other work from the Caltech lab using a similar discovery approach, autism disorders.

The notion of a gut-brain signaling connection has been around for decades. But only recently, in part due to an explosion in animal research, have biologists identified pathways linking the gut to the brain, Mazmanian says. And only in the last couple of years has the microbiome been implicated in that crosstalk and some experimental validation emerged. "Only a handful of rigorous experimental lines of evidence link the microbiome to neurological activity in the brain," he says.

The bulk of this line of research has centered on anxiety-related behaviors and autism disorders, including studies that have identified changes that occur in the microbiome of children with autism and, more recently, in individuals with anxiety. Several publications have identified specific organisms and pathways linking the gut to the brain and shown that the microbiome may be mediating outcomes in both anxiety and autism disorders. However, Mazmanian notes his group's work is the first to mechanistically link the microbiome to a neurodegenerative disease.

The researchers devised a preclinical model using mice that overexpress α-synuclein, a protein that in aggregate form causes motor dysfunction. α-synuclein overexpressing (ASO) mice display progressive deficits in motor function as well as defects in gut motility. They also bred ASO animals to be germ-free. A series of experiments comparing the motor and GI functions of germ-free ASO mice and germ-free wild-type mice, and also comparing specific-pathogen-free (SPF) ASO mice to SPF-wild-type animals, showed that the presence of gut microbiota promote the hallmark motor and intestinal dysfunction of PD.

With a germ-free mouse model, it may be hard to dismiss the possibility that an observed phenotype is due to abnormal development of the animal – because it did not get normal signals from its microbiome. But the researchers went further. They observed differing effects when comparing human microbiota transplanted into the animals from a healthy microbiome versus microbiota from a PD patient. They also gave adult animals antibiotics to deplete their microbiota, which alleviated or highly reduced the motor symptoms, and fed adult germ-free animals short-chain fatty acids (SCFA), which promote α-synuclein-mediated neuroinflammation, and observed the results. "All three lines of evidence suggest that for this model, active signaling is occurring," Mazmanian says. "It is not a developmental issue."

Both Parkinson's disease and autism disorders have a very profound gastro-intestinal connection. Somewhere on the order of 70% and maybe up to 90% of children with autism have GI complications that can be severe: constipation, abdominal cramps, bloating, and alternating constipation and diarrhea. In PD, constipation can precede motor deficits by years if not decades. Indeed, Heiko Braak proposed in 2003 that PD could begin with an accumulation of α-synuclein in the GI tract, which propagates via the vagus nerve to the brain.

"When there is such a strong GI component, it leaves the door open for a role for the microbiome," says Mazmanian. The same may be true of anxiety disorders. "It's often believed that the physical symptoms of anxiety are a result of changes in neurochemistry," he says. But whereas in PD and autism disorders the GI symptoms may drive the neurological symptoms, in anxiety it is believed to go the other way, he says, where something happens in the brain and subsequently results in a physical impact in the gut.

Generally, these conditions should not only be thought of as neurological conditions but as whole-body disorders, Mazmanian says. "Part of why our work appears to be moving the needle is because we are making connections that have been known but just not followed up on," he says: neurologists know these peripheral or non-CNS comorbidities are associated with these diseases, but those symptoms have never been thought to be part of the disease process, he says. His research and that of others is showing that GI symptoms are not just a consequence of something happening in the brain but may be contributing to, promoting or even causing those abnormalities in the nervous system. "It's a conceptual shift," he says.

The work could lead to development of single organisms or consortia as therapeutics for PD. Developing prebiotics, supplements or OTC probiotics are also viable approaches, Mazmanian says. "I am very enthusiastic about dietary approaches," he adds. "There is no reason one is going to work better than the other."

Start-up Axial Biotherapeutics Inc., launched in late November with a $19.5m Series A round led by Longwood Fund and Domain Associates, has licensed worldwide rights to IP out of Mazmanian's lab, including the PD assets and assets around treating autism disorders. In a related 2013 Cell publication, the Mazmanian group showed that a single microbe, Bacteroides fragilis, was able to ameliorate almost all symptoms in several mouse models of autism. Axial is developing that organism as a drug candidate, and also has other interventions for autism disorders not yet disclosed.

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Ascletis Eyes Launch Of China's First Oral HCV Drug, Possible IPO

Ascletis Inc., a Chinese biotech specializing in liver disease treatments with a focus on hepatitis C, has completed a major $100m Series B financing, following a first round $55m fundraising in the second half of 2015. The second round was led by C-Bridge Capital, joined by a number of new investors including

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QianHai Equity Investment FOF, FOCUS Media Jiangnanchun Foundation and WTT Investment, together with Series A participants Goldman Sachs and Tasly Pharmaceutical Co. Ltd. Back to 2011 in Hangzhou after the company's groundbreaking, Ascletis's CEO and co-founder Jinzi Wu told *Scrip* in an exclusive interview that one of the differentiators of the company is its sound investor base, banking on a $100m private commitment, and a focus on long-term growth. "We have a private investor who is very supportive, so it is easy for us to manage the company and focus on the pipeline and building value creation," Wu explained. Ascletis entered into a new era in 2015 by taking in venture capital, with other financial support from both global and domestic investors to help expand its pipeline and increase international recognition. "We are evaluating possible initial public offering [IPO] options but have no further details to share at the current stage," Jianjiong Wang, associate director, general affairs at Ascletis, told *Scrip*. "Ascletis is a young company, we don't have a sales team yet. The proceeds [from the new financing] will be used to establish a professional sales and marketing system, as well as to promote new drugs after launch," Wang said. According to local media, Wu said the Series B took only four months to complete as Ascletis piqued investors' interest because of its relatively advanced pipeline, particularly as a new drug application for danoprevir (ASC08) was recently accepted by the China Food and Drug Administration (CFDA), which could mean the drug will become China's first oral antiviral for treating HCV. According to China's latest "Hepatitis C Prevention Guide," the country has the world's largest population of hepatitis C patients at 8.56 million, among which genotype 1b accounts for about 57%. Currently, China's standard of care for the viral disease is an injectable regimen of peginterferon with ribavirin, which only shows 70-80% efficacy and has a long treatment cycle and side effects that can prompt patients to seek newer direct-acting antiviral agents (DAAs) from overseas. With two novel DAAs in development, danoprevir and ravidasvir (ASC16), Ascletis is looking to provide two regimens for chronic hepatitis C: a triple therapy and an all-oral interferon-free therapy.

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US Price Fixing Probe Piles Pressure On Indian Generics Sector

A number of Indian-owned generic pharmaceutical companies have been caught up in a sweeping US anti-trust investigation into price-fixing, bid-rigging and other anticompetitive behavior, amid mounting public anger over soaring drug bills. The probe has further increased the pressure on the Indian industry, which is already feeling the strain from US regulatory compliance issues and intensifying market competition. Last month, 20 US states filed a civil lawsuit against six firms, including two that are Indian-owned -- Aurobindo Pharma USA Inc. belonging to Hyderabad-based Aurobindo Pharma Ltd., and Heritage Pharmaceuticals Inc., an arm of Pune-headquartered Emcure Pharmaceuticals Ltd. All were accused of conspiring to inflate prices for the commonly used antibiotic doxycycline hyclate and an older diabetes drug, glyburide. Two top former Heritage executives have now pleaded guilty to separate criminal charges laid by the Department of Justice of conspiring to fix prices of the drugs, according to media reports. Jeffrey Glazer, the ex-CEO of Heritage, and Jason Malek, a former company president, entered the pleas on Jan. 9 and are now believed to be cooperating with investigators in the DoJ probe into allegations of widespread collusion among drug manufacturers. The anti-trust lawsuit and the widening US federal investigation could "have serious implications" for Indian generic manufacturers and curb their pricing power in the crucial US market, said leading Indian credit rating agency ICRA Ltd. "Such increased generic pricing-related scrutiny is a concern for Indian pharmaceutical companies," Kinjal Shah, ICRA's assistant vice president and associate head of corporate ratings, told *Scrip*. "Given the heightened focus on controlling drug prices in the US, implementation of certain legislative proposals could have significant implications for pharmaceutical pricing." These proposals include linking generic drug price increases with the wholesale price index and a ban on "pay for delay" deals between branded and generic companies that critics say postpone the launch of cheaper generics. The developments could have "significant impact" on revenue growth as well as on profit margins of the companies, Shah predicted. "Further, the penalties associated with the charges would also be substantial...and such events have a cascading effect on lowering of prices and holding back companies' pricing abilities," she commented.

Penelope MacRae, 10 Jan 2017

Vertex Sells Legacy Oncology Portfolio To German Merck

Vertex Pharmaceuticals has sold off its oncology portfolio, comprised of six molecules across four early stage programs, to Merck of Germany for $230m and future royalties on sales – a low price tag in the immune-oncology deal spree arena.

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German Merck has filled out its early stage oncology pipeline via a $230m licensing deal with Vertex Pharmaceuticals Inc. covering four drug development programs, with a focus on solid tumors and DNA repair technology.

Vertex told *Scrip* it was not an oncology company and that it had been looking for a buyer for early stage oncology programs left over from its "legacy business." Vertex shifted its focus in the last five or so years to building up a specialty and rare disease portfolio – an action which has seen the company produce two successful cystic fibrosis treatments so far, with others in the pipeline. However, Vertex's oncology portfolio had been with the firm for more than a decade, made up of in-house, first-in-class drug candidates. Having advanced three of these assets into the clinic, Vertex said it was ready to pass them on to another company, better built for cancer drug development.

A spokesperson said that cancer drugs simply did not fit with Vertex's specialist strategy and the company was not suited to pursuing therapies of this sort that would in the future require grand clinical studies and a much larger sales force. Vertex is instead focused on rare or specialist disease areas and the $230m payment from Merck will mostly be filtered into the company's R&D budget, the spokesperson said.

Merck's head of R&D Luciano Rossetti told *Scrip* that the deal was a strong strategic move for the German pharma, which is looking to build up its early-stage development portfolio across three specific areas: immunology, oncology and immune-oncology.

Rossetti said, "I have been with the company two and half years now and to me the most important part of our early development strategy is that we focus our efforts. With this deal, we are acquiring new assets that fit very well within our focus areas of DNA repair and immune-oncology." Merck's R&D head added that the company previously had Vertex on its radar as its biggest competitor in the DNA-PK space. He also noted that in the oncology space this deal, for four drug programs with three compounds already in the clinic, is great value for money. "In oncology, this is an attractive deal," he said.

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Big Pharma Is Back In The M&A Driver's Seat For 2017

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Big pharma is poised to dominate deal-making this year while the firepower of specialty pharma to do deals has waned. 2017 could be a record year for M&A, EY predicts in its annual M&A Outlook and Fire Power Report.

Biopharma M&A is poised to soar in 2017 because pharmaceutical companies are well funded to execute on deals and sorely in need of new growth-drivers to offset growing price pressure. The opportunity for corporate tax reform in the US under a new administration will further heighten the M&A frenzy in 2017, which could be a record year, according to EY's M&A Outlook and Fire Power Report.

The consulting firm released its annual M&A report Jan. 9. Notably, big pharma will dominate M&A this year, EY predicts, a change from recent years, when specialty pharmas were driving deals.

"Now in possession of nearly 70%, or $600bn, of the total industry firepower, big pharma is in the driver's seat for acquiring the most desirable M&A targets," EY said.

Specialty pharma – considered one of the biggest drivers of biopharma M&A just two years ago – experienced a 34% decline in valuations on average in 2016. Six of the 10 largest specialty pharma companies have exhausted their firepower for deals, and several are considering divestitures, EY said.

Specialty pharma, led by names like Allergan PLC, Valeant Pharmaceuticals International Inc. and Endo International PLC, dominated M&A headlines from 2013 to 2015, fueled by inversion deals. But the activity began to drop off in late 2015 as debt grew, some valuations fell and the ability of specialty pharma to conduct deals diminished.

Allergan is one specialty pharma name that still has the ability to pursue substantial M&A. It is flush with cash after divesting its generics business to Teva Pharmaceutical Industries Ltd. for $40.5bn last year. Valeant, meanwhile, with its buy-and-build business model, ran into an accounting and drug-pricing scandal that devalued its stock by more than 90% and resulted in top leadership changes. EY's Global Life Sciences Transaction Advisory Services Leader Jeffrey Green noted, "Even though overall firepower has declined, big pharma's share is large relative to what it has been in the last several years."

"When you combine that with increased pressure on prices that are dampening growth, it points to more deals, more inorganic investment in order to generate growth," Green added.

J&J/MERCK ARE WELL-POSITIONED FOR M&A

Mean firepower declined 17% from 2015 across the industry, but most big pharma companies still have large reserves to fund M&A. All things are not equal, however. Bristol-Myers Squibb Co.'s firepower fell in 2015 as its valuation dropped and AbbVie Inc. spent some of its reserves on M&A, EY pointed out. The consulting firm said AstraZeneca PLC and Novartis AG face the combined challenge of needing growth while facing declining firepower.

Other large pharmas like Johnson & Johnson and Merck & Co. Inc., as well as Allergan, are in the unique position of having increased their firepower in 2016, EY said. Indeed, J&J and biotech Actelion Pharmaceuticals Ltd. recently confirmed that they are in merger negotiations.

"We will continue to see deals in the $1bn to $10bn range," Green said. But he also believes there is opportunity for mega-deals.

"Our experience is that the senior management teams of the top 25 companies by and large are always evaluating the others as potential merger partners or acquisition targets," he said.

THE $200BN THRESHOLD HOLDS

An active year for M&A would be on trend with the recent past. The growth kicked into gear in 2014, when biopharma M&A surpassed $200bn, more than twice the average annual deal volume in the prior decade. It continued in 2015, leading EY to declare in its firepower report last year that $200bn was the "new normal."

In 2016, the $200bn threshold for biopharma M&A persisted, EY reported. The largest deals of the year included Teva/Allergan Generics, Bayer AG's acquisition of the chemical company Monsanto Co. for $66bn, Shire PLC's acquisition of Baxter International Inc.'s spinout Baxalta Inc. for $32bn, and Pfizer Inc.'s $14bn acquisition of oncology company Medivation Inc.

What is driving the activity? New drug launches have generally been slower out of the gate and payers are pushing back on drug pricing in blockbuster categories like diabetes, cardiovascular disease and respiratory disease. Analysts have downgraded growth expectations for the sector, EY noted. Sell-side analyst projections across leading investment banks show analysts have shaved about $25bn off their 2020 revenue projections, EY said.

Even in categories like oncology, where pharma manufacturers have had strong pricing power, growth is expected to become more challenging, both because of growing competition and payer pushback on pricing. The challenges are pushing pharma to supplement pipelines with assets and could move the industry into higher-risk opportunities, like Alzheimer's disease, according to the report, as companies compete for the best assets in therapeutic areas where drug sales represent a small portion of total health care spending. "We do expect continued consolidation within therapeutic areas on top of all the other forces," Green added, pointing to crowded therapeutic areas like oncology, autoimmune disease and diabetes.

EY said there are already signs of an uptick in deal-making activity. In a poll conducted by the consulting firm in mid-October, 42% of life sciences executives said they had five or more deals in the works as opposed to just 6% in mid-April.

Comprehensive tax reform could also level the playing field between companies that inverted to redomicile in a country with a lower tax rate versus those that did not, EY said, creating more competitive bidding situations.

It is all coming together to result in what could be one of the most interesting years for biopharma M&A.

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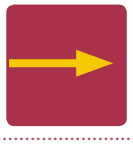

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Valeant Attempts To Divert Attention

A well-orchestrated build-up to the annual J.P. Morgan Healthcare Conference and subsequent rush of fundraisings was helped by the acquisition of Ariad by Takeda early last week. But the good times were derailed by a drug-pricing diversion, unleashed by the US president-elect.

ANDY SMITH

It was all going swimmingly. A build-up across the board in biotechnology stock prices that resisted the negative clinical and financial results of the week before the J.P. Morgan Healthcare Conference, and a smattering of M&A on the first day should have been enough to set up a small country's worth of fundraisings by a legion of investment bankers. That was right up until US president-elect Trump lashed out with a drug pricing diversion to the unverified dossier that threatened the legitimacy of his election and presidency. As a result, the NASDAQ Biotech Index (NBI) finished the week down over 1% compared to the S&P 500 index's flat week that ended within a whisker of its Jan. 9 all-time high. The NBI by contrast, finished the week about 40% below its July 2015 all-time high.

Supporting part of the president-elect's accusation that drug companies were "getting away with murder" was a plethora of drug price increases announced to the receptive San Francisco audience early last week. The analysts from Wells Fargo noted the 8.4% average price increase across 50 products of Valeant Pharmaceuticals International Inc. in the first week of January. Johnson & Johnson prepared the channel for its 2017 price increases next month after an average 9.9% increase for more half of its products in 2016. The analysts from Cowen reported the recent 9.5% price increase for Acorda Therapeutics Inc.'s *Ampyra* (dalfampridine extended release) for multiple sclerosis (MS) – which "was more or less in-line with Acorda's 2017 year-on-year revenue growth" – and Biogen Inc.'s 8% price increase for much of its MS franchise that "might allow Biogen to more easily achieve [its] 2017 revenue expectations." If investors were hoping for the drug pricing focus to remain on generic drugs merely because of their volume, it appears that ship has already sailed into the iceberg and similar treacherous waters are now ahead for branded and possibly orphan drugs.

Valeant did however attempt to redress some of the separate concerns about its $30bn debt burden ahead of its fourth-quarter financial results by announcing two product divestments. The sale of three skin care brands to L'Oreal SA for $1.3bn, or a 7.7 multiple of annual sales was a welcome divestment of low margin products. The divestment of the troubled Dendreon Corp. unit for about twice its $400m acquisition price was also a welcome realization multiple although with R&D at the business probably now long-gone the hefty premium paid is more likely to be indicative of a lack of sophistication of Asian acquirers of US pharmaceutical assets than a sign of Valeant's divestment prowess. More worrying is that typically in a forced sale of assets it is the easiest-to-sell assets that go first and also where most of the premiums are found. Investors' reaction to Valeant's divestments was initially positive with its share price rising by 20% before dissipating at the enormity of the job still to be done to finish the week up 2.3%.

As if to illustrate the difficulty in selling Valeant's other troubled assets the rumored acquisition of its dermatology unit Salix Pharmaceuticals Ltd. to Takeda Pharmaceutical Co. Ltd. appeared to be off the table last week – probably on the grounds of differing price expectations – as Takeda announced the $5.2bn acquisition of Ariad Pharmaceuticals Inc.. I have invested in Japanese pharmaceutical companies since their stock prices are rarely correlated with their US and European comparators however, it only took me seeing their management presenting at a conference to leave me nonplussed enough to divest the stocks.

The transactional record of Japanese pharmaceutical companies has also been mixed although I was once lucky enough to inherit the management of a portfolio that held Millennium Pharmaceuticals Ltd. just before Takeda's $8.8bn acquisition of Millennium for its lead marketed product *Velcade* (bortezomib) and its US commercial infrastructure. However, who could forget Takeda's $320m license of Cell Genesys Pharma Inc.'s GVAX cancer vaccine a few months before its early Phase III failure and Astellas Pharma Inc.'s mixed $4bn acquisition of OSI Pharmaceuticals Ltd. Takeda's acquisition of Ariad at nearly 30 times its 2016 sales was supposedly not just for the sales of Ariad's only approved product *Iclusig* (ponatinib) but for its pipeline potential and the duplication of its Millennium-like US commercial infrastructure. Tokyo is a long way from the US and its increasing drug pricing rhetoric so Takeda may have missed the 2016 political storm featuring Senator Sanders and Representative Cummings' accusations of Ariad's "repeated and staggering price increases" on Iclusig.

Overall, last week saw the US president-elect use the distraction of national drug price negotiation to deflect attention away from a dossier of unverified allegations. Valeant revealed two divestments to deflect attention away from the specter of a massive dilutive share issue which is probably the easiest way for it to avoid bankruptcy. There was a sort of symmetry to the acquisition of Ariad by Takeda since it appeared to be designed to deflect attention from a 2017 US generic Velcade launch – a product it gained from a previous acquisition – although the full price paid also came with a free front-row ticket to the US drug pricing debate.

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

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

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Selected clinical trial developments for the week 6–12 January 2017

LEAD COMPANY/PARTNER	COMPOUND	INDICATION	COMMENTS
Phase III Results Published			
Amgen Inc.	*Parsabiv* (etelcalcetide)	secondary hyperparathyroidism on dialysis	*JAMA*; Jan. 10, 2017 issue, three Phase III studies.
AB Science	masitinib	indolent systemic mastocytosis	*The Lancet*; Jan. 6 2017 online, Phase III study.
Advanced Accelerator Applications SA	*Lutathera* (177-lutetium labelled somatostatin analog)	neuroendocrine tumors	*NEJM*, Jan. 12, 2017; Phase III NETTER-1 study.
Keryx Biopharmaceuticals Inc.	*Auryxia* (ferric citrate)	iron deficiency anemia in chronic kidney disease	*Journal of the American Society of Nephrology*, Jan. 12, 2017, online.
Phase III Results			
Coherus BioSciences Inc.	adalimumab biosimilar (CHS-1420)	psoriasis	PsOsim; updated results confirmed similarity to *Humira*.
Phase III Interim/Top-line Results			
AbbVie Inc./Enanta Pharmaceuticals Inc.	glecaprevir plus pibrentasvir	hepatitis C	CERTAIN-1; 8 weeks of therapy shown to be safe and effective in Japanese patients.
Valeant Pharmaceuticals International Inc.	IDP-118 (halobetasol plus tazarotene)	psoriasis	302 Study; primary endpoint met in this second pivotal study.
Phase III Initiated			
Nektar Therapeutics	NKTR-181	chronic pain	SUMMIT-HAL; pivotal study.
Amgen Inc.	*Blincyto* (blinatumomab)	diffuse large B-cell lymphoma	Phase II/III studies, alone or with *Keytruda*.
Roche	*Tecentriq* (atezolizumab)	castration-resistant prostate cancer	IMbassador250; with enzalutamide versus enzalutamide alone.
Phase III Announced			
Eli Lilly & Co./Incyte Corp.	baricitinib	psoriatic arthritis	A JAK inhibitor already under review for rheumatoid arthritis.
Merck & Co. Inc./Incyte Corp.	epacadostat with pembrolizumab	non-small cell lung, renal, bladder, head and neck cancers	Combination Phase III studies expected to start in 2017.
Agios Pharmaceuticals Inc.	AG-348	pyruvate kinase (PK) deficiency	To start in 2018.

Source: Biomedtracker

Tetra Discovery Partners has appointed ***Richard M. Erwin*** vice president, clinical operations. With more than 25 years' experience, Erwin joins Tetra from Catalyst Pharmaceuticals, where he was executive director, clinical project management. He started his career at Amgen, where he was a clinical research associate. Before Catalyst, Erwin was involved in the development of a cholera vaccine developed by Silicon Valley's PaxVax. His previous experience also includes involvement in the product development leadership team for a global Phase III Alzheimer's program at Neurocrine Biosciences.

Brian health company, **IXICO**, has named ***Giulio Cerroni*** CEO – effective Feb. 6, 2017. Co-founder and current CEO, ***Derek Hill***, will continue to serve the company as an executive director. Cerroni carries over 30 years of international management experience and previously he was managing director of the genomics division of the international life sciences measurement and testing company, LGC Group (LGC). He has held a variety of senior roles at Thermo Fisher Scientific, Abgene, Anachem, ICN Biomedicals and Du Pont.

Philippe Monteyne has been appointed to **Aelix Therapeutics**' board of directors as an independent board member. Monteyne is a partner at Fund+ in Belgium and has also been a visiting professor of neurosciences at the Catholic University of Louvain in Belgium and vice president of R&D at Sanofi, France. Before this, he was senior vice president, head of development and chief medical officer at GlaxoSmithKline Rare Diseases and had held various executive positions at GlaxoSmithKline Biologicals.

Orphan disease focused company, **Minoryx Therapeutics**, has named ***Patrick Aubourg***, ***Marc Engelen***, ***Florian Eichler*** and ***Gerald Raymond***, to its scientific advisory board. Aubourg is a professor of pediatrics at the Medical University Paris-Sud, head of the Pediatric Neurology Department at the Hospital Bicêtre and director of Inserm Research Unit UMR1169 at the Medical University Paris-Sud/Paris Saclay University. Eichler is an associate professor of neurology at Harvard Medical School (US), assistant in neurology at Massachusetts General Hospital, director of the Leukodystrophy Clinic and director of the Center for Rare Neurological Diseases. Engelen is a trained neurologist specializing in pediatric neurology at the Academic Medical Center (AMC) in Amsterdam. He is a member if the medical staff in the department of neurology and the department of pediatrics. Finally, Raymond is a pediatrician, geneticist, neurologist and is currently working at the University of Minnesota Masonic Children's Hospital.

Karolinska Development AB's portfolio company, ***Promimic AB***, has appointed ***Magnus Larsson*** CEO. Larsson will be succeeding Ulf Brogren, who will be relocating to the US to lead the company's new sales operation in North America as head of sales. Having spent 15 years in the international dental implant industry, Larsson brings his experience in sales and marketing to Promimic. Most recently he was director, global market development at Dentsply Sirona Implants, Mölndal, Sweden.

Decibel Therapeutics has expanded its leadership team, naming ***John Keilty*** chief data science officer, and has also appointed three new board members. ***Troyen A. Brennan***, executive vice president and chief medical officer, CVS Health; ***Roger H. Brown***, president, Berklee College of Music; and ***George A. Scangos***, CEO, Vir Biotechnologies Inc. have all joined the company's board of directors. Keilty joins Decibel from Third Rock Ventures, where he was general manager of platform operations. Before this he was vice president of information technology and informatics at Infinity Pharmaceuticals.

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