Bayer's Zieler On The Power Of Real World Data

Zieler tells why real world data is "very powerful" as more stakeholders look beyond just randomized clinical trial data (p4)

Expert View

If the year of the Monkey is a jumpy ride filled with uncertainties, the coming year of the Rooster will be certain to bring more changes to the pharma sector (p20)

Stockwatch

The warm fuzzy feeling in life sciences in the week before the J.P. Morgan Healthcare Conference was rudely threatened (p21)

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'Between A Rock And A Hard Place,' Court Issues Injunction To Halt Praluent Sales

Regeneron and Sanofi have opportunity to appeal or to reach resolution with Amgen after district judge delays imposition of permanent injunction for 30 days in PCSK9 patent case.

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Finding that Amgen Inc. has suffered irreparable harm from Sanofi and Regeneron Pharmaceuticals Inc.'s marketing of their PCSK9 inhibitor *Praluent* (alirocumab), a competitor to Amgen's *Repatha* (evolocumab), and that monetary damages are inadequate, a district court judge issued a permanent injunction to block US sales of Praluent.

However, in her Jan. 5 order, Delaware District Judge Sue Robinson delayed imposition of the injunction for 30 days to allow defendants the opportunity to appeal and request expedited review of the ruling by the Federal Circuit, "and/or to encourage the parties to reach an appropriate business resolution." The judge noted that both parties have spent billions of dollars and over a decade of work to bring their respective products to market and each would suffer hardships if she ruled for the other. She also said that the public generally is better served by having a choice of available treatments.

"Therefore, the court finds itself between a rock and a hard place, i.e., being a patent holder and a verdict winner should be a meaningful factor in the balancing test, but taking an independently developed, helpful drug off the market does not benefit the public."

Regeneron and Sanofi announced that they will appeal the injunction, which prevents the marketing, selling or manufacturing of Praluent in the US during the term of two Amgen patents, both of which expire on Aug. 22, 2028. They will also appeal the jury verdict upholding the validity of the patents.

"It is our longstanding position that Amgen's patent claims are invalid and that the best interests of patients will be greatly disserved by an injunction preventing access to Praluent," Sanofi executive VP and general counsel Karen Linehan said in a release.

COMPETITION FOR INSURER CONTRACTS, FORMULARY POSITIONS

Amgen filed suit against Sanofi and Regeneron in October 2014 alleging infringement of patents covering Repatha. Prior to a jury trial the defendants stipulated to infringement of certain claims of the patents and in March a jury issued a verdict that the patents are valid.

On Jan. 3, Judge Robinson denied Sanofi and Regeneron's motions for a new trial

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IN THIS ISSUE

from the editor

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"Getting away with murder." Not a comfortable way to be branded by the incoming president of the US, even for an industry that has grown accustomed to being vilified. And pharma, an industry that for all its faults spends more time than most on improving the health of humankind, has always minded about being denigrated.

Has the pre-presidential "Twitter period" just been the lull before the storm? Or is his bark worse than his bite? How consistently will he see through his pledges, and how might he translate incoherent declarations into policy and action?

Many in the industry, along with investors more generally, had harboured a cautious optimism that Trump would (if nothing else) be good for business. He might help companies repatriate foreign cash by alleviating punitive taxation, or favour business interests more broadly.

With his vociferous if rather vague pronouncements this week about bidding, Trump shoved pharma and biotech stocks off a cliff, and to pour salt into the sector's wounds, prompted Bernie Saunders to tweet "Trump is right."

Never mind getting away with murder, pharma would be wise to watch its own back.

exclusive online content

New Drugs And Biologics Approved By US FDA In 2016
FDA's Center for Drug Evaluation and Research cleared 22 novel agents in 2016, and the Center for Biologics Evaluation and Research approved six new biologic products.
http://bit.ly/2jkPKk1

Interview: CrystalGenomics, First Korean Bioventure To 'Go All The Way'
After reaching milestones by launching a novel osteoarthritis drug and licensing out an AML candidate to a US partner, CrystalGenomics' CEO talks to *Scrip* about what else is in store for the South Korean bioventure in 2017 and beyond.
http://bit.ly/2iv9WzL

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Bayer And Google: Teaching Old And Young Dogs New Tricks

Getting a 150-year-old pharmaceutical company up-to-speed with digital technologies is not an easy task – but a 2016 partnership with Google has helped to propel Bayer's digital integration, says chief digital officer Jessica Federer.

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Bayer AG's head of digital, Jessica Federer, defines digital health as the "bigger picture," using technology alongside traditional health interventions. It's vital for pharma to evolve its digital technologies because "we're talking about behavior, analytics and integrated information approaches to help patients use medicines better," Federer said. Bayer's digital head spoke to *Scrip* in a recent interview, alongside Google's head of industry, healthcare, Stefani Klaskow, about the two companies' 2016 digital marketing partnership and greater plans for pharma digital business models this year.

Bayer and Google joined forces in 2016, forming a partnership initially focused on digital marketing. However, Bayer's Federer – the company's first chief digital officer – told *Scrip* that the two partners are learning important lessons from each other. "We are learning from Google how to be agile and they are learning stability from us," she said.

Klaskow, who joined Federer on a digital health panel at the 2016 FT Global Pharmaceutical and Biotechnology Conference, elaborated: "We learn a lot from the companies we work with. When Google used to have conversations with pharma companies we'd say things like 'move faster' and 'be more agile', and this didn't work. It's very easy for us to sit here as an 18-year-old company and say we can move faster – but we don't have a ton of infrastructure to work around. It's much harder for a 150-year-old company that is steeped in infrastructure and tradition to move that quickly."

Google has, in recent years, highlighted healthcare as one of its key development areas, so learning lessons from pharma giants is an important stepping stone for the tech leader. "We have learned a lot from our pharma partners on process and what it takes to last in this industry; we value that a great deal," Klaskow said.

Federer, who started her career at the US Department of Health and Human Services in the agency for healthcare research and quality, highlighted that through working with Google, Bayer has focused on growing its internal digital talent as well as developing programs and technologies. As a typically risk adverse industry, focused on safety and reliability, pharma has taken a while to catch up in the new and untested digital space. However, Federer noted that this is starting to change: "People are beginning to understand the risks of not acting in in the digital space: it has gone from risk management to opportunity management," she said.

Jessica Federer

Bayer's chief digital officer also noted that Google has been vital in helping Bayer train its teams across all functions – from digital marketing to legal and compliance. This training and development of digital talent within the pharma company will help it remain competitive as traditional business models continue to face turbulence in the pharma and biotech sector, Federer believes. "When you get the right people around the table together, suddenly you can do so much more. Until you have these leaders within the company that understand the digital space you can't move forwards. We now have the right team at Bayer," she said. "Bayer is not separating digital out into its own bubble, we are really trying to integrate it into how we work."

Klaskow added that at Bayer she has especially noticed the high level of commitment from the most senior parts of the organization for digital integration, compared with some other companies. "Bayer's management is really supporting and evangelizing that they need to move faster, they need to integrate – and that's across every discipline, we're not just talking about marketing or communications we are talking about R&D, manufacturing and human resources. Every function is understanding that digital needs to be a foundation to how they work," Klaskow said.

"We are working together with backbone functions such as legal and IT to make a company-wide change. This method takes a lot longer to put in place, but it is very sustainable," Federer added.

Google has several pharma partnerships ongoing, including arrangements with Novartis AG for the development of a smart contact lens; with Biogen Inc. for sensor software use in multiple sclerosis; and with Johnson & Johnson, which launched a new company – Verb Surgical Inc. – in 2015 in partnership with Verily Life Sciences (Google's parent company) for the development of robotics-supported surgical instruments.

DIGITAL INTEGRATION

Last year, Bayer created a digital market leadership team as part of its digital transformation – it sees the heads of digital marketing from pharma, consumer and crop science all working together. "Some might say, 'Why do they need to work together? They are from entirely different sectors.' But the platforms and the analytics we are using in each division are the same," Federer noted. "The data scientists are the same and the collaboration we have with Google goes across the board. This unity is something I want to see more of at Bayer."

However, Federer said there is still some way to go for the German company. "Whenever you look at things in a silo or talk about 'that division' or 'that team,' it shows that we haven't quite connected all the parts yet. But this takes time, you can't just push a button," she said.

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Bayer's Zieler On The Power Of Real World Data, Asia Pacific Outlook

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Claus Zieler, senior vice president and head of commercial operations, Bayer pharmaceuticals division Asia Pacific, tells Scrip why real world data is "very powerful" as more stakeholders including physicians look beyond just randomized clinical trial data. Zieler also underscores the German multinational's intent to give "special attention" to the fast-growing Asia Pacific region.

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The Asia Pacific (APAC) is a significant contributor to Bayer AG 's pharmaceutical earnings and Claus Zieler, senior vice president and head of commercial operations, Bayer pharmaceuticals division Asia Pacific, indicates that the German multinational is keen to sustain the momentum in the region. He maintains an upbeat tenor for a basket of products including *Xarelto* (rivaroxaban) and *Eylea* (aflibercept), for which Bayer recently ramped up its sales expectations, but prefers not to be drawn into specifics on any potential headwinds in the region as a result of the emerging geopolitical situation.

In an interview with *Scrip* in Singapore last month, Zieler also underscored the value of real world data in the backdrop of the encouraging findings of the XANAP study for Xarelto. XANAP is the first Pan-Asian, prospective, single-arm, observational study of patients designed by Bayer to evaluate the safety and effectiveness of the once-daily direct factor Xa Inhibitor for stroke prevention with non-valvular atrial fibrillation from over 400 sites across Asia in routine clinical practice.

ANJU GHANGURDE: *APAC is among the key markets of the future for Bayer and its demographics, aging population [by 2050, 1.2bn older people will call the region home], and growing expectations for healthcare all bode well. How is Bayer tweaking its priorities, strategy and allocation of resources in APAC in view of the trends in the region?*

CLAUS ZIELER: In 2015 Asia Pacific was about 25% of our revenue for the pharmaceutical division in Bayer. That's a fairly important weight within the global picture for the pharmaceutical division. IMS projections note that APAC is one of the geographies with the highest growth rates of about 7.5%, in stark contrast to some other regions. It points to the medical need in this region - patients needing treatment/better treatment. And it points to the aging population essentially creating that need - as people get older there are more chronic diseases, more non-communicable diseases and therefore the need for treatment of those diseases. Clearly Asia Pacific is an important region for pharmaceuticals in Bayer - a region where, with the forecasted growth rates, we will give special attention.

In Singapore, with the support of the EDB [Singapore Economic Development Board], we have collaborated with academic centers in a number of projects where we've looked at diseases specifically in Asia Pacific. These collaborations started with a focus on oncology - certain cancers that are particularly prominent in Asia Pacific - and last year we've taken the collaboration to the second stage. We are now looking also to heart and eye disease as areas where we want to look at the Asian setting; and in some instances, look at the genetic background in patients because that may vary from Asian to Caucasian patients.

The data collection that is going on, the number of trials that has tripled in the region since we've started that collaboration are all things that we have done to focus on Asia Pacific with our activities.

AG: *Would the evolving geopolitical situation – US President designate Donald Trump and the China equation etc. - mean enhanced volatility in the short term in Asia Pacific? Does Bayer anticipate any need for recalibration of its strategy in the region?*

CZ: We are focused on doing the things that we are good at - continuing with our R&D endeavors, getting the products we developed through the authority approvals to the market and getting the marketed products to the physicians and patients so that they are used properly and can provide value. I don't think we are in a position to comment and react to geopolitical changes. We will watch the landscape evolve and focus on what we are good at.

AG: *For five products - Xarelto, Eylea, Xofigo (radium Ra 223 dichloride), Adempas (riociguat) and Stivarga (regorafenib) - Bayer recently raised the estimated combined annual peak sales potential from "at least" €7.5bn previously to "more than" €10bn. How significant is APAC expected to be in driving this growth, especially given the demographics in the region?*

CZ: We raised our guidance in the recent investor conference and that's driven by growth worldwide. In 2015, Asia Pacific was around 25% of our global sales in pharmaceuticals, so we have a sizeable part of the business and also of the growth rates. We grew by more than 7% in Asia Pacific in 2015. It's fair to say that both in contribution as percentage of the business and in growth rate, Asia Pacific has carried its share in growing, and in growing with the five innovative launches.

AG: *So, you expect this kind of growth to be sustained for the five products in the Asia Pacific region?*

CZ: We are growing very fast and continue to grow very successfully with those products. "Sustained" is a question of what time frame you are looking at. If you are saying the next few years, then yes those are the products that will provide our business with growth.

AG: *Bayer recently outlined some encouraging findings from real world studies - XANAP and XAPASS - for Xarelto. What kind of impact do you expect such insights to have on prescription patterns in the APAC region, especially in markets like Singapore, Japan and South Korea?*

> 'APAC is an important region for pharmaceuticals in Bayer – we will give special attention'

Real world evidence studies have a tremendous importance in showing how the drugs that we develop and test in clinical trials perform in real life after coming to market. The XANAP study is an excellent example of a very well designed study – the first prospective real world study in this disease setting where we can show for Xarelto the rates of stroke and bleeding are even lower than in the phase III trial - in the East Asia cohort of the phase III trial.

XANAP showed low incidences of stroke and major bleeding of 1.7% and 1.5% per year respectively. In Phase III ROCKET AF East Asia, the incidences of stroke and major bleeding were 2.6% and 3.4% per year respectively. [Rocket AF refers to the rivaroxaban once daily oral direct factor Xa inhibition compared with vitamin K antagonism for prevention of stroke and embolism trial in atrial fibrillation].

In real life, the effectiveness of the drug is even better than in the clinical trial. Similarly, the side-effect rates are lower; it shows in real life the drug is really working. It's doing what it's supposed to do. It reassures us about the effectiveness and safety of the drug. Having those data from the real world setting is, of course, very powerful because when you a develop a drug in phase III you have very strictly controlled clinical trial protocol, which may or may not correspond later on to the way the drug is used in real life. So, having real world data reassures us by providing that extra data set that in real life we see similar effects and side effect rates as we saw in the highly controlled clinical trial setting.

AG: *Do you see such studies, in general, impacting reimbursement going forward?*

CZ: I can't speculate on what will or will not be used but I do think that more and more, not only doctors in their prescribing decisions, but also authorities will take into account the entire data set that is available for a drug and not only the randomized clinical trial data.

AG: *Are similar studies proposed for products like Stivarga for which Bayer has filed for supplemental regulatory approval for use in second-line advanced liver cancer in the US, EU and Japan?*

CZ: Stivarga is already approved in more than 90 countries worldwide for metastatic colorectal cancer (mCRC) and more than 80 countries worldwide for gastrointestinal stromal tumors (GIST). The compound has shown a statistically significant and clinically relevant benefit in three different tumor types where there were no approved therapies before in the respective line of treatment: in two pivotal Phase III studies in mCRC (CORRECT and CONCUR), one pivotal Phase III study in GIST (GRID) and one pivotal Phase III study in hepatocellular carcinoma (HCC) (RESORCE), with the latter being the basis for the global filings in HCC now. The compound has also been investigated in a large Phase IIIb study in mCRC (CONSIGN) which showed consistent efficacy and safety results to the pivotal Phase III studies in mCRC.

In the case of Stivarga, it was investigated and has shown benefit in areas where there were no proven therapies before. Regorafenib, the active ingredient in Stivarga, is the only systemic treatment shown to provide survival benefit in HCC patients progressing on sorafenib treatment. All previous second-line trials of novel agents have failed; thus, no effective systemic therapies after progression on sorafenib are currently available. The regulatory filings of Stivarga in HCC are thus an important step as they bring us closer to a much needed second-line option in HCC.

> 'Having data from the real world setting is very powerful; it reassures us by providing that extra data set'

AG: *Any new milestones since the Integrated Translational Oncology Network - Bayer's collaborative oncology research initiative in Singapore - took off, especially in areas like liver and gastric cancer?*

CZ: The collaboration that we've had in Singapore with the academic centers, with support of the EDB, is now nine years old. In those nine years, the first five were dedicated to projects in the oncology area. That has produced several publications on certain cancer types in the Asia Pacific; it has also produced the first phase I study that Bayer has conducted in Asia Pacific and a tripling of the number of clinical trials in Singapore in 2015 from about six in 2007. Those are the tangible outcomes.

In the meantime, we've taken the collaboration to a second stage where we've expanded the scope from only cancer to also include cardiovascular and eye disease. We are pursuing projects in that enlarged scope. The recognition that we get in the academic community for having continued with the program beyond the first stage is very high. There's a recognition that Bayer has entered into something for the long run.

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Lilly Management Reorg Brings In Shaw To Oversee Bio-Medicines

Shaw is the former US President of rival Novartis and a rising figure in big pharma. She will take over the role previously held by Ricks, who became CEO Jan. 1. Conterno will assume President USA role.

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Eli Lilly & Co.'s new Bio-Medicines president will be Christi Shaw, the former US president of Novartis AG and a rising figure in pharma. Shaw will take over the role held by David Ricks, who became Lilly's CEO – succeeding longtime CEO John Lechleiter – on Jan. 1.

The appointment was part of a broader leadership reorganization announced Jan. 5 as the company kicks off a new year with a new leader at the helm. Ricks said the changes would maximize the potential of the company's late-stage pipeline and newly launched medicines.

Shaw will be an experienced addition to Lilly's commercial leadership, especially when it comes to executing on the launch of the IL-17A blocker *Taltz* (ixekizumab), a potential blockbuster for the treatment of psoriasis. At Novartis, Shaw oversaw the launch of the rival IL-17A blocker *Cosentyx* (secukinumab), which grew into a fast blockbuster and was considered one of the most successful launches of 2015.

Shaw is one of a few high-profile women within the ranks of big pharma's top leadership

Cosentyx generated $301m in the third quarter, while Taltz, which just launched in the second quarter of 2016, generated $32m in the third quarter. Taltz was approved by FDA in February. Shaw also oversaw the launch of Novartis' heart failure medicine *Entresto* (sacubitril/valsartan), which many investors considered disappointing.

The drug experienced substantial pushback from payers, but Shaw gained notoriety for negotiating some of the most high-profile value-based reimbursement agreements with payers to be announced in the US. Her experience working in this experimental but growing area of reimbursement policy in the US will also be valuable at Lilly as payer pushback on pricing mounts.

Shaw is also one of a few high-profile women within the ranks of big pharma's top leadership at a time when gender equality in the sector has gained some attention. GlaxoSmithKline PLC appointed the first female CEO of a top tier big pharma last year: Emma Walmsley will succeed Andrew Witty April 1.

Shaw announced her resignation from Novartis in April for family reasons. She later appeared on Good Morning America to discuss the decision to leave her high-powered job to care for her older sister undergoing treatment for multiple myeloma.

Now Shaw's appointment to a new top industry spot is a return for the executive, who started her pharma career at Lilly in sales and marketing from 1989 to 2002.

In addition to the appointment of Shaw to lead Bio-Medicines, Lilly also announced Lilly Diabetes president Enrique Conterno will be promoted to Lilly USA president, overseeing all pharmaceutical commercial operations for the region. Conterno will succeed Alex Azar, who has decided to leave the company. Lilly Oncology president Sue Mahony will continue in her role.

Additionally, the company said that beginning on Feb. 1, its Diabetes, Oncology and Bio-Medicines business areas will assume commercial responsibility for their products in China – in addition to the US, Japan and Canada. Lilly's Emerging Markets business will combine with Europe to form Lilly International, which will be led by Lilly International president Alfonso (Chito) Zulueta, who has led the emerging markets business for three years.

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Gilead Pays Phenex $100m Milestone As NASH Candidate Progresses

With hepatitis C wrapped up, NASH is becoming the focus of liver disease R&D. Gilead, which has a number of NASH programs, has paid Phenex $100m for clinical progress with an in-licensed candidate for NASH and other liver diseases.

Phenex Pharmaceuticals AG has received a significant cash infusion from Gilead Sciences Inc. as a milestone payment for its GS-9674 drug candidate targeting nonalcoholic steatohepatitis (NASH) that will help the company advance its pipeline – but the biotech is interested in areas where it will need further big pharma partnerships.

Phenex received a $100m milestone payment from Gilead for its GS-9674 drug candidate targeting nonalcoholic steatohepatitis (NASH). GS-9674 is a novel, synthetic, non-steroidal Farnesoid X Receptor (FXR) agonist which was originally developed by Phenex and then sold to Gilead in December 2014. The deal covering Phenex's FXR program was valued at $470m.

"This milestone payment is in addition to a further undisclosed milestone from the same program earlier this year for GS-9674 entering Phase I studies," Thomas Hoffmann, CFO of Phenex, noted, which has meant that "for the last three years, Phenex shows high profitability."

The company's "outstandingly strong cash position" means it can afford to evaluate "radical" novel approaches to building up a drug discovery platform in liver and gastrointestinal (GI) diseases as well as in oncology, Hoffman said.

Gilead has now paid Phenex "roughly half of the overall sum" of the deal value, Claus Kremoser, CEO of Phenex, told *Scrip*.

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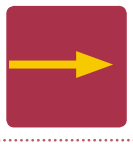

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J&J Innovation's Latest Deal Spree Includes CB-1 Antibody For NASH

Option to acquire a company developing a CB1-targeted antibody for non-alcoholic steatohepatitis gets Johnson & Johnson into the race. Janssen's James List explains how the NASH venture fits into J&J's growing efforts in metabolic disease.

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In unveiling its latest round of collaborations, Johnson & Johnson Innovation LLC announced a collaboration with an option to acquire with Bird Rock Bio on a Phase I antibody targeting cannabinoid receptor 1 (CB1) that could mean the pharma's entry into the crowded non-alcoholic steatohepatitis (NASH) space.

J&J revealed a spate of 15 collaborations underwritten by its innovation arm Jan. 5, in advance of next week's JPMorgan Healthcare Conference.

The agreement with Bird Rock enables J&J's Janssen Pharmaceuticals Inc. to collaborate on a Phase I trial of namacizumab, which it also sees as a potential therapy for diabetic kidney disease. After the Phase I data readout, Janssen has the option to acquire the privately held, La Jolla, CA-based biotech. Backed by 5AM Ventures, Versant Ventures, Apposite Capital and Aravis, Bird Rock also has a second antibody candidate, gerilimzumab, entering Phase II in rheumatoid arthritis.

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J&J's interest in namacizumab illustrates both its broad interest in addressing metabolic disease and the promise it sees for the antibody due to its ability to address three main drivers or outcomes of NASH – fat accumulation in the liver (steatosis), inflammation, and fibrosis or cirrhosis, James List, global therapeutic area head for cardiovascular and metabolism, told *Scrip*.

"There's a wealth of experimental data indicating that modulating CB1 signaling addresses each of these three pathways of pathology, so it's particularly well suited as a potential therapeutic for NASH," he said. List cited the potential for a differentiated therapy as part of what attracted J&J, as well as "the promise of really intercepting and successfully treating diseases."

With its additional therapeutic potential in diabetic kidney disease, namacizumab could become a seamless fit with Janssen's metabolic disease portfolio, led by its diabetes drug *Invokana* (canagliflozin), List added.

Janssen has "a large and growing interest across the various areas of metabolism," List said, from type 2 diabetes to an ongoing Phase III program for Invokana in diabetic kidney disease to obesity "and with this deal we're also expressing our interest in this epidemic of NASH," he added.

"So this is a perfect alignment of a potential novel therapeutic for a target that gets at basic pathology, which is what we like to do," List continued. "We like to intercept disease pathways and at the same time it potentially plays clinically into large pieces of unmet need on the metabolic spectrum, and that's NASH and diabetic kidney disease."

The exec added that it is too early to speculate on whether namacizumab might be positioned as monotherapy in NASH or as part of a combination regimen, which is the direction in which many disease experts expect NASH treatment to lead, but the antibody "shows great promise of being of a cornerstone of NASH therapy if the clinical data live up to its promise," he said.

RECENT SURGE IN NASH DEAL-MAKING

A wide range of companies – large, small, established, start-ups – are pursuing NASH drug development via a host of targets and modalities. Most advanced are Intercept Pharmaceuticals Inc.'s *Ocaliva* (obeticholic acid), a farnesoid X receptor agonist previously approved for primary biliary cholangitis, and Genfit SA's elafibranor, a peroxisome proliferator accelerator receptor (PPAR) alpha/delta agonist, both in Phase III.

While the originators are taking both of those assets forward, deal-making in the NASH space has reached a fever pitch. Last September, the Phase III-ready cenicriviroc, a dual inhibitor of CCR2/CCR5, was the star of Allergan PLC's $1.7bn buyout of Tobira Therapeutics Inc. Allergan augmented that deal with the near simultaneous acquisition of Akarna Therapeutics Inc. and its preclinical NASH candidate for $50m.

Meanwhile, Novartis AG recently bought out Conatus Pharmaceuticals Inc. and its Phase II caspase inhibitor emricasan for $65m in cash and debt, plus up to $650m in earn-outs, while Gilead Sciences Inc. and Bristol-Myers Squibb Co. – both established in liver disease with successful hepatitis therapies – have worked their way into the NASH competition with targeted deal-making. Most recently, Gilead paid $400m to acquire Nimbus Apollo Inc. and its ACC inhibitor program for NASH, while Bristol paid $100m up front in November to license Nitto Denko Corp.'s siRNA candidate for the disease.

Genfit's elafibranor is the most-advanced unpartnered NASH candidate – Intercept is partnered with Japan's Sumitomo Dainippon Pharma Co. Ltd. for development and commercialization of Ocaliva in Asia. Among Phase II NASH candidates, 10 currently are not partnered, according to Biomedtracker, although half of those are held by more established biopharmas such as Novartis, Gilead, Shire PLC and Novo Nordisk AS.

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No Dominant Sponsors In US FDA's 2016 Novel Approvals Class

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No company received more than two approvals among the 28 novel agents approved in 2016 by US FDA's drug and biologics centers combined.

FDA's novel agent approvals in 2016 are fewer than in the past three years, but they are also more evenly distributed.

No sponsor "won" the year's approval count. Six companies had two approvals apiece among the 22 new molecular entities and novel therapeutic biologics approved by FDA's Center for Drug Evaluation and Research and the six novel biologics from the Center for Biologics Evaluation and Research.

In 2015, a year that saw more than twice as many novel approvals as 2016, Novartis AG had the most approvals with four from CDER, while its divested vaccine operations produced two CBER approvals for other companies. Allergan PLC and Amgen Inc. followed with three approvals apiece.

The most prolific companies in 2016 included usual big pharma suspects like Roche subsidiary Genentech Inc., with two new expected blockbuster oncologics, the PD-L1 inhibitor Tecentriq and targeted hematologic cancer agent Venclexta, developed with AbbVie Inc. Staying in the big pharma category, Merck & Co. Inc. received approval for the hepatitis C combo Zepatier and anti-C. difficile agent Zinplava, and Eli Lilly & Co. also grabbed two approvals, with the oncologic Lartruvo and psoriasis therapy Taltz.

Mid-sized specialty pharmas also had a good showing. Biogen's investment in neurology paid off with the clearance of Zinbryta for multiple sclerosis and an early approval for the spinal muscular atrophy treatment Spinraza after one of FDA's fastest reviews ever.

Blood disorders specialist CSL Behring received approval from CBER for two new recombinant coagulation factors, Afstyla and Idelvion. Shire PLC's acquisition of Baxalta Inc. brought Cuvitru, an immune globulin approved by CBER, while Shire's ophthalmics business received approval of new dry eye drug Xiidra.

FIRST-TIME SPONSORS

Seven companies received their first approval from FDA in 2016. All seven of those products were reviewed by CDER. The emerging companies favored small, concentrated markets: five of the first-time sponsor approvals hold orphan drug designations.

Sarepta Therapeutics Inc.'s first drug cleared by FDA, Exondys 51 for the orphan genetic disease Duchenne muscular dystrophy, was easily the most controversial approval issued by the agency during the year, featuring disagreements among senior agency staff.

Clovis Oncology Inc. burst onto the cancer stage with two candidates for 2016 approval, Xegafri for non-small cell lung cancer (NSCLC) and Rubraca in an orphan ovarian cancer population, but only Rubraca was approved. Clovis withdrew Xegafri in advance of a complete response letter.

Intercept Pharmaceuticals Inc. is entering the commercial arena with approval of Ocaliva for an orphan disease, primary biliary cholangitis (PBC), although the company has its eye on a much bigger market, non-alcoholic steatohepatitis (NASH), for label expansion. Elusys Therapeutics Inc.'s anthrax antitoxin Anthim, in contrast, ideally will never be needed by many people; its primary market is government stockpiles.

FDA approved two new PET imaging agents in 2016, both from first-time US sponsors. Blue Earth Diagnostics Ltd.'s Axumin is the company's first product worldwide, while Advanced Accelerator Applications SA (AAA) has a broad PET portfolio in Europe. AAA's orphan-designated Netspot is the company's first US approval; another AAA application, for the radiopharmaceutical Lutathera, received a complete response letter.

Published online 5 January 2017

[Editor's note: Please see our sister publication, the Pink Sheet, for additional analysis of FDA's class of 2016 novel drugs and biologics.]

GSK Spin-Out NeRRe Raises £23m For NK Antagonists

New cash will fund further clinical testing of NeRRe's two neurokinin receptor antagonists for cough and hot flashes.

NeRRe Therapeutics Ltd., which is developing a portfolio of neurokinin (NK) receptor antagonists for the treatment of conditions caused by neuronal hypersensitivity, has raised £23m ($28.4m) in an oversubscribed Series B financing round.

New investors Fountain Healthcare Partners, Forbion Capital Partners and Orbimed joined existing investors Advent Life Sciences and Novo A/S.

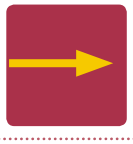
The funds will be used by NeRRe to generate Phase II data on orvepitant, its lead oral NK-1 antagonist, as a potential treatment for chronic cough; and to advance NT-814, a dual NK-1,3 antagonist, into Phase II trials as a potential non-hormonal treatment of post-menopausal vasomotor symptoms (hot flashes).

NeRRe was founded in 2012 as a spin out from GlaxoSmithKline PLC, which transferred its NK antagonist portfolio, including clinical data, toxicity, safety and formulation packages, and all associated intellectual property to NeRRe. GSK retains a minority stake in the firm, but no rights to the assets.

Other companies formed through the spin-out of GSK neuroscience assets include Convergence Pharmaceuticals (acquired by Biogen Inc. and Autifony Therapeutics Ltd.

NeRRe's CEO Dr. Mary Kerr was global franchise head of GSK's immune-inflammation and infectious disease portfolio until joining NeRRe in 2015, when she took over from Dr. Emiliangelo Ratti. Ratti and NeRRe's CSO/COO Dr. Mike Trower were both formerly senior neuroscience leads at GSK before co-founding NeRRe.

sukaina.virji@informa.com, 5 Jan 2017



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Ogeda Seeks Financing After Successful PhII For Non-Hormonal Menopause Drug

Ogeda SA's G-protein coupled receptor (GPCR) therapy, fezolinetant (ESN364), has met its primary endpoint in a Phase IIa trial for the treatment of menopausal hot flashes – vital progress towards providing women with a rapid, non-hormonal treatment option, says the company's CEO Jean Combalbert. The positive data are also good news for Ogeda as it seeks more investment from sources outside of Belgium to advance its drug candidate into larger studies. Per the Women's Health Initiative Study, it is noted that chronic use of HRT should be avoided due to important safety concerns including the increased risks of cancer and cardiovascular events. Currently though, the most popular approved therapies for menopause are all estrogen and progesterone-based products such as Novartis AG's *Vivelle* (estradiol) and Bayer AG's *Angeliq* (drospirenone and estradiol). The late-stage development pipeline for menopausal therapies also follows suit. According to Informa Pharma Intelligence's Biomedtracker database, there are two Phase III drugs in development for menopause – EndoCeutics Inc.'s Femivia and TherapeuticsMD Inc.'s TX-001HR – both of which act on estrogen receptors.

lucie.ellis@informa.com, 4 Jan 2017

Otonomy To Challenge Multi-Dose Ear Drops With Otiprio Expansion Plans

San Diego-based Otonomy Inc.'s ear infection treatment *Otiprio* (ciprofloxacin otic suspension) has shown positive results in a pivotal Phase III trial in acute otitis externa, or swimmer's ear, top-line data show. The results are strong enough for the company to file for expanded US approval of the product in the first half of this year, the company says, and its share price rose by 10.8% to close at $17.95 on Jan. 5. President and CEO Dr. David Webber said the clinical cure rates following a single administration of Otiprio were comparable to ITT results with commonly used antibiotic ear drops that require two or three doses per day for a week. "This trial reinforces Otiprio's unique profile as a single-dose product administered by a physician thereby eliminating the risk of patient non-compliance with the use of multi-dose, multi-day ear drops. Furthermore, the fact that approximately 70% of patients in this trial were treated by non-ENT physicians supports the utility of Otiprio outside the ENT specialist audience." Analysts at Biomedtracker agreed: "These positive data should ensure a smooth approval process as Otiprio seeks a label expansion for swimmer's ear. While current treatments with antibiotic drops require several administrations to the affected ear each day for seven days, Otiprio requires only a single administration thus improving patient compliance." Otonomy first launched the product in March 2016 for the treatment of pediatric patients with bilateral otitis media with effusion undergoing tympanostomy tube placement (TTP), but so far it has only brought in limited revenues ($300,000 in the third quarter of 2016). The company attributed the slow start to the time needed to build awareness among physicians and secure formulary approval and reimbursement. Otiprio delivers the antibiotic in a thermosensitive suspension that exists as a liquid at or below room temperature and gels when warmed – this allows it to be administered as a single dose during the TTP procedure. For otitis externa patients, the formulation allows the dosing burden on patients to be greatly reduced, improving compliance, and the company expects to expand its use beyond specialist ENT doctors.

alex.shimmings@informa.com, 6 Jan 2017

Inotek Plummets On Glaucoma Phase III Failure

The first Phase III trial of Massachusetts-based Inotek Pharmaceuticals Corp.'s lead product, trabodenoson, has missed its primary endpoint of reducing intraocular pressure, sending the company's share price down by more than 71% to close at $1.75 on Nasdaq on Jan. 3. Company executives pointed to a stronger than expected placebo response as one explanation for the failure of the first-in-class, highly selective adenosine mimetic, which targets the A1 subreceptor. They are now awaiting the full data later this quarter before determining the next steps for the trabodenoson monotherapy program – the product is also in earlier-stage development as a fixed-dose combination with an older glaucoma therapy. The top-line data from the MATrX-1 study in 303 patients with primary open-angle glaucoma (POAG) or ocular hypertension (OHT) and an IOP ≥24 mmHg and ≤34 mmHg reveal that it did not achieve its primary endpoint of superiority in reduction of intraocular pressure (IOP) compared with placebo at all 12 time points tested over three months of treatment (at four time points during each of these days: 8AM, 10AM, 12PM and 4PM on days 28, 42 and 84). The 8AM time point did not achieve statistical separation with any dose, which, Inotek said, was primarily due to an unexpectedly high placebo response compared to that observed in Phase II as well as a meta-analysis of glaucoma trials published in the *Journal of Ocular Pharmacology and Therapeutics*. However, the 6%/2000 mcg QD dose got closest: it achieved statistical superiority to placebo at days 84, 42, 14 and was marginally superior at day 28.

alex.shimmings@informa.com, 4 Jan 2017

2016 – The Pharma Year In Review

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As we enter a new year, Scrip takes a look at the five biggest themes that got the most hits from our readers over the last 12 months.

2016 was a year of political surprises of such international impact that their aftershocks will be felt by the pharma and biotech industries for many years. But, for *Scrip*'s readers, more parochial stories were important too. Here we take look at what, for our readers, were the year's five biggest story themes.

COMPANY DOINGS

As ever, the comings and goings of the major companies scored well, with stories on changes in personnel, structure and focus finding an eager readership. Pfizer Inc., GlaxoSmithKline PLC, Novartis AG and Shire PLC all featured heavily.

To split or not to split? That was the question for Pfizer after its planned $160bn merger with Allergan was called off in April, putting an end to its plans to regain its pharma top spot, enjoy a lower tax rate and access its offshore billions.

After teasing during the first-quarter results presentation that such a split could happen quickly if the decision was taken, CEO Ian Read was more circumspect during the Q2 earnings call, and the company decided in September to remain consciously coupled, for the time being at least. But Read assured investors there was no expiration date on optionality, suggesting the company could always reconsider splitting up the business next year.

Pfizer's planned move into dermatology garnered many hits, as did changes in focus at other major firms including Novartis's decision to rejigger its pharma division to favor oncology, not to mention the surprise closure of its Cell Therapy Unit. Other companies overhauling their R&D structures were Boehringer Ingelheim GMBH and Takeda Pharmaceutical Co. Ltd., while the challenges faced by Novo Nordisk AS were another big draw.

The year's biggest merger turned out in the end to be Shire and Baxalta Inc.'s $32bn deal to form the largest company that focuses on rare diseases, which completed in June. And at the tail end of the year, M&A attention moved towards Actelion Pharmaceuticals Ltd., which appears to playing fast and loose with Sanofi and Johnson & Johnson.

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Meanwhile, personnel changes at the top of UK giant GlaxoSmithKline were keenly watched. The rise of Emma Walmsley CEO of GSK's Consumer Healthcare division to the top job succeeding Andrew Witty as CEO when he retires at the end of March was seen as making a decent enough crack in the glass ceiling. As for the gender pay gap: details of her remuneration package are due to be revealed in early 2017.

Outgoing CEO Witty's exit interview made for grim reading for those left behind; he told a few home truths to industry at the recent FT Global Pharmaceutical and Biotechnology Conference in London. The old reliable fall-backs for inefficient pharma business strategies – price-oriented silo mentalities and selling expensive medicines into the once voracious US healthcare market – are no longer viable, he said. The world has radically changed and more change is coming. And all the while, industry's productivity has plummeted. Witty was, however, less fazed by the coming of Trump.

PEOTUS TRUMP

Indeed, the immediate pharma reaction to the shock Trump victory in the US presidential election involved less rending of garments than was perhaps seen in some other quarters. Pharma's stocks rose early on Nov. 9 as the market looked forward to a more favorable climate than it had been expecting under a Clinton administration.

The potential upsides for the industry include the possibility of a tax holiday to repatriate some of the billions of dollars currently squirrelled away overseas, and a reduction in the 35% tax rate which contributed to this situation in the first place. Other positives included a better regulatory climate especially in early stage research, plus the removal of Clinton's threatened "assault on drug pricing" raised during the election campaign.

However, the relief is expected to be short-lived. Issues surrounding drug pricing are going nowhere – there are too many players wanting healthcare costs to come down and putting pressure on insurers to restrict formularies. Moreover, Trump's plans for the Affordable Care Act (whatever these will end up being) are less obviously good or bad for industry.

So much so, Allergan CEO Brent Saunders recently warned pharmaceutical manufacturers not to let the election of Donald Trump as president of the US result in a false sense of security across the industry when it comes to the public controversy over high drug prices.

'BREXIT MEANS BREXIT'

Pharma has had more time to mull over the issues raised by the UK's June referendum vote to leave the European Union.

Prior to the surprise vote, industry had been clear that it did not want the change: the CEOs of the two biggest UK companies, GSK's Witty and AstraZeneca PLC's Pascal Soriot, the ABPI, the BIA and EFPIA, among many other parties were all in agreement that remaining in the EU would be better for industry.

Concerns raised covered the loss of cross-border business and research collaboration, the loss of EU research funding, and delays in in the availability of new drugs, all of which could discourage inward investment by international drug firms.

But "Brexit means Brexit" and with the UK prime minister Theresa May insisting that Article 50 will be triggered by the end of March, the rhetoric has shifted towards the pragmatic.

Even so, the upheavals and uncertainties brought by Brexit are so wide-reaching that it is difficult to know how to make the most of any opportunities that might arise, even for a life science sector accustomed

to adapting to rapidly changing circumstances. While we wait to see how hard a Brexit it will be, the only thing that is certain is more uncertainty.

IT'S A SCANDAL

Scandal stories that broke during the year were not just clickbait for *Scrip*'s readers: the fate of Martin Shkreli and stories of various price hikes for common drugs were big in the mainstream media too (*Shkreli: The Musical,* anyone?). Taken together, they may provide some answer to what remains industry's biggest existential question: why does nobody like us?

Steep price rises for certain drugs began to hit the headlines in 2015, notably with Valeant Pharmaceuticals International Inc.'s *Isuprel* and *Nitropress*, but Shrekli's decision to raise the US price of Turing Pharmaceuticals AG's toxoplasmosis drug *Daraprim* by more than 5,000% later that year really lit the touch paper.

This year, pricing controversies have centered around Mylan Pharmaceuticals Inc.'s EpiPen, the price of which has risen from $100 in 2008 to $600 in 2016.

Valeant may have begun offering hospitals discounts for its drugs in May, but the reputational damage was already done. And when Hillary Clinton tweeted in August that there was "no justification" for price hikes for "life and death" drugs the impact on Mylan's share price and biotech indices was immediate.

Mylan CEO Heather Bresch continues to defend the company's decision to substantially raise the price of the life-saving allergy medicine and put some of the responsibility at other players in the distribution chain. Her excuse? That the company failed to recognize as it raised the price of EpiPen that health insurance had changed to such an extent that the price hike now impacts the ability of consumers with high-deductible plans to pay for the medicine.

What's more the issue shows no sign of fading. Just last month in the UK, Actavis fell foul of the UK Competition and Markets Authority for charging the National Health Service "excessive" prices for generic hydrocortisone tablets, shortly after it fined Pfizer and Flynn Pharma Ltd. a combined total of £90m for charging "excessive and unfair" prices for phenytoin sodium capsules.

PRIMUM NON NOCERE

Above all: do no harm. The first rule of medicine was dramatically broken early in the year when which one volunteer died and several others were hospitalized during a French Phase I trial of novel drug from Portugal-based Bial-Portela & CA SA. The experimental drug, an inhibitor of FAAH known as BIA 10-2474, was under testing for various neurological conditions including anxiety disorders, Parkinson's disease and treating chronic pain in multiple sclerosis.

Latest reports into the disaster seem to concur with Bial's stance that the toxicity of the dose used could not have been foreseen from previous studies, underlining perhaps the inherent risks for clinical trial patients.

In November, the EMA put out for consultation a draft revised guideline intended to minimize the risks involved with running first-in-human and other early clinical trials, taking into account the lessons learnt from the tragedy.

The last drug trial disaster in Europe occurred in 2006, when six healthy volunteers given an experimental drug in London ended up in intensive care suffering from multiple organ failures after taking an experimental medicine from German drugmaker TeGenero AG; this also led to changes to clinical trial rules.

Scrip's most-read R&D stories, including the failure of Bristol-Myers Squibb Co.'s *Opdivo* (nivolumab) in the key first-line NSCLC market and the less surprising failure of Eli Lilly & Co.'s solanezumab in early-stage Alzheimer's disease, are the subject of a separate article on p12.

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CONTINUED FROM COVER

and for a judgment as matter of law regarding the patents' written description and enablement.

Repatha and Praluent, which lower LDL cholesterol in a select group of patients, are the only therapeutics in the PCSK9 inhibitor market. Amgen filed for approval of Repatha on Aug. 27, 2014 and received approval in August 2015. Sanofi and Regeneron filed for approval in November 2014 and used an orphan drug priority review voucher to obtain FDA approval in July 2015.

In assessing irreparable harm, Robinson noted that Amgen alleged it has been forced to compete with the defendants for contracts with insurers and exclusive formulary positions, particularly since the defendants were first to market. And Amgen said it was further harmed by defendants' marketing of Praluent as "The First U.S. FDA-Approved PCSK9 Inhibitor." Sanofi and Regeneron argued that Repatha would have faced pricing pressures even without competition from Praluent.

Both drugs were priced at about $14,000 per year, a sum that has been criticized by payers and clinicians. As a result, both products have struggled to get off the ground in the US and Europe.

The PCSK9 inhibitors are approved for higher risk populations, such as patients with cardiovascular disease and genetic conditions predisposing them to very high cholesterol, like heterozygous familial hypercholesterolemia. But the sponsors hope to expend labeling with improved cardiovascular outcomes data from ongoing trials.

Repatha's US sales for the first three quarters of 2016 were $65m and $18m in the rest of the world. Praluent's net product sales for the same period were $75.7m.

Jefferies analysts said in a note that they estimate peak sales of $3.25bn for Praluent, with $750m peak tied to the current label and a further $2.5bn potential if the product gains a CV mortality claim in the future. Their estimated impact to Sanofi revenues and core earnings per share assumes that about 60% of peak sales would occur in the US in the long term and that Sanofi would be able to mitigate some of the profit impact through reduction of its sales, general and administrative expenses spend in the US.

In another note, Evercore ISI analyst John Scotti said Regeneron could take an 8% hit to its discounted cash flow if the permanent injunction stands, halting US sales of Praluent. He said Amgen would benefit from a 3% boost to its earnings per share for every $500m in additional annual Repatha sales, based on analyst estimates of sales for the PCSK9 inhibitors, which assume positive cardiovascular outcomes trial results this year.

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R&D Matters – The Five Top Research & Development Stories of 2016

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If you take the temperature of R&D productivity you get a good indicator of the health of the pharma and biotech industries, making new drug development stories a perennial favourite with Scrip readers. Here we take a look at the five biggest R&D stories this year.

The top R&D story of the year, in the eyes of *Scrip* readers, was the disaster that befell Portuguese company Bial-Portela & CA SA when one volunteer died and several others were hospitalized during a Phase I trial of its novel inhibitor of FAAH – known as BIA 10-2474 – for various neurological conditions. Indeed, this was one of the top stories of the year, and is detailed in the companion piece *2016 – The Pharma Year In Review* (see p10). But failures in other trials provided the more usual drug development tragedies for other companies and, by extension, the patients who lost a potential life-saving treatment option.

KEYTRUDA TO OPDIVO: 'CHECKMATE'

Chief among these was the surprise failure of Bristol-Myers Squibb Co.'s PD-1 inhibitor Opdivo in the much-anticipated CheckMate 026 study in first-line lung cancer.

The behemoth of the checkpoint inhibitor world missed the primary progression-free-survival endpoint in the trial, taking everyone by surprise and prompting a 16% dive in the company's share price on Aug. 5. Analysts didn't hold back: "clear disappointment and overall surprise," the "worst-case scenario" and "possibly the biggest surprise of my career" were just some of their responses.

Just a week earlier, at BMS's second quarter results call, the company had boasted an 80% market share for its product with $840m in sales from a range of licensed indications, including melanoma, second-line NSCLC, renal cell cancer, and Hodgkin's lymphoma. Back then, progress into first-line NSCLC was seen as the obvious next step to total market dominance and further riches.

Lung cancer is the largest market for the cancer immunotherapies and BMS had already built a strong lead over rival Merck & Co. Inc.'s *Keytruda* (pembrolizumab) in the second-line NSCLC setting, but the first-line setting is the jewel in the NSCLC crown.

In an attempt to catch up, Merck had been pushing Keytruda hard in first-line NSCLC and won an early victory in July when it became first to report data from a first-line lung cancer trial showing that Keytruda improved PFS and also overall survival in the first-line KEYNOTE 024 study. Its victory became complete in October when it sailed to early approval at the US FDA for this patient population, while the presentation of the full CheckMate 026 results at ESMO showed just how badly Opdivo had fared: it performed worse than the control. The data did not even provide BMS with a crumb of comfort of a trend towards an efficacy benefit in patients with greater than 50% PD-L1 expression, which some had hoped for.

To rub salt into the wound, at the same meeting Merck presented the first positive Phase II data from the KEYNOTE-021 study that suggest the combination of Keytruda with chemotherapy could become a new standard for treating first-line NSCLC patients who test negative for PD-L1, as well as being an option for some PD-L1 positive NSCLC patients.

In short, studies reported this year have precipitated a period of rapid change for the NSCLC market that is expected to last for several years as the arrival of Roche's PD-L1 inhibitor *Tecentriq* (atezolizumab) shakes up the market for second-line NSCLC patients and clinical data from other combinations start to read out.

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NO PCSK9 PILL, NO BOCOCIZUMAB

Pfizer Inc.'s decision not to move forward with the development of an oral PCSK9 inhibitor for the treatment of high cholesterol was another huge hit with readers.

In August, president-worldwide R&D Mikael Dolsten revealed the company's fears during the company's second-quarter sales and earnings that the product's efficacy just wouldn't stand up to its the injectable rivals, Amgen Inc.'s *Repatha* (evolocumab) and Sanofi/Regeneron Pharmaceuticals Inc.'s *Praluent* (alirocumab).

An oral pill would have had an interesting competitive position versus the injectable products, though its development was years off and the market dynamics for the PCSK9 blockers that have launched have so far been challenging, driven largely by payer pushback on price. The injectables cost roughly $14,000 a year.

The disappointment was compounded later in the year when Pfizer terminated late-stage development of its lead injectable PCSK9 inhibitor bococizumab. Pfizer said the decision was based on updated data from six Phase III trials testing bococizumab, including two studies testing the drug out to 52 weeks, which led the company to change its mind about the commercial potential of the lipid-lowering drug. The 52-week data showed an "unanticipated attenuation of low-density lipoprotein cholesterol (LDL-C) lowering over time, as well as a higher level of immunogenicity and higher rate of injection-site reactions with bococizumab than shown with the other agents in this class."

Pfizer had been hoping to get bococizumab to market shortly after its rivals released cardiovascular outcomes data on Repatha and Praluent – it is hoped CVOT data will expand the market for the cholesterol-lowering drugs which have struggled amid pricing controversies.

Analysts pointed towards issues with anti-drug antibodies against bococizumab as being the likeliest culprit for the drug's waning effects against LDL-C, something which does not seem to be affecting the older products. The loss of their nearest competitor now leaves these poised to reap the benefits of any success in their outcomes studies, due early 2017.

It also leaves Pfizer's CV pipeline all the poorer, although CEO Ian Read did say the company would continue to look for ways to strengthen its position in the field. How long and hard this search will be remains to be seen, however, with other pipeline areas like oncology and inflammation/immunology growing increasingly large.

SOLA AND THANKS FOR THE MEMORIES

Next of the list was the failure of Eli Lilly & Co.'s Alzheimer's anti-amyloid disease candidate, solanezumab, in the EXPEDITION3 study in November. The result may have been largely expected but it was still a disappointment for the field which has had little cause for cheer.

Sola's two previous Phase III trials EXPEDITION and EXPEDITION2 both failed but a pre-specified pooled analysis showed a statistically significant improvement in patients with mild disease, keeping hope for the product alive. In a final punt, Lilly decided to test the product in patients earlier in the course of their disease, and confirming the presence of amyloid pathology via PET screening or cerebrospinal fluid testing.

But still EXPEDITION3 did not meet the primary endpoint, a statistically significant slowing in cognitive decline among people with mild dementia due to Alzheimer's disease as measured by the Alzheimer's Disease Assessment Scale-Cognitive subscale (ADAS-Cog).

In the end, the results, including many secondary clinical endpoints, favored solanezumab, but the magnitudes of treatment differences were small, Lilly said. It was not enough, and the company confirmed that it would not pursue a regulatory submission for solanezumab.

But the game is not yet over for the amyloid hypothesis. The weak signal in the EXPEDITION3 and its sister studies still suggest a role for amyloid and are seen as positive for Biogen Inc.'s earlier-stage amyloid-clearing antibody product aducanumab – this product has a slightly different mechanism and caused a splash at the Clinical Trials in Alzheimer's Disease (CTAD) conference in San Diego in December.

CAR-T TO MARKET

Unsurprisingly, given the dominance of immune-oncology in the minds of R&D executives, the fortunes of the CAR-T products held the attention of readers in 2016.

In a year of changing fortunes for key players, Novartis AG and Kite Pharma Inc. are now vying for pole position in the race to market the first chimeric antigen receptor T-cell product after pioneer Juno Therapeutics Inc.'s most advanced CD19-targeting CAR-T therapy, JCAR015, was stymied by fatal cerebral edemas which resulted in the on, off, on-again clinical hold of its leading program, the Phase II ROCKET trial in acute lymphoblastic leukemia (ALL).

Juno's initial position was that the deaths were caused by the use of fludarabine in a preconditioning cyclophosphamide chemotherapy regimen and the agency lifted a July hold on research after the company revised the protocol to stop using that agent. But fatal edema continued, even though the company insisted the removal of the chemotherapy did reduce the treatment's toxicity, and a voluntary hold was put on the study in November.

In early December, Novartis and Kite revealed their plans to file BLA submissions at the FDA in early 2017 based on data presented during the American Society for Hematology (ASH) meeting in San Diego, for their products, CTL019 and KTE-C19. Both consist of each treated patient's own T-cells reengineered to express CD19 so that the T-cells will attack cancer cells expressing the antigen and both have breakthrough therapy designations which could see them reach the market by the end of 2017.

Kite said it has initiated a rolling BLA submission that the company will complete by the end of the first quarter of 2017 for KTE-C19 in relapsed or refractory aggressive non-Hodgkin's lymphoma (NHL) patients ineligible for autologous stem cell transplant. Kite reported positive interim data from the Phase II portion of its Phase I/II clinical trial ZUMA-1 in September.

Novartis meanwhile plans a BLA filing in early 2017 and will seek EU approval later in the year for CTL019 in the treatment of relapsed and refractory pediatric and young adult patients with B-cell ALL based on data from the global Phase II ELIANA clinical trial. Presented at ASH on Dec. 3., this showed that 82% of patients – 41 out of 50 children and young adults – achieved complete remission or complete remission with incomplete blood count recovery three months after infusion of the Novartis cell therapy with no minimal residual disease detected. The relapse-free rate among the responders was 60% six months after infusion.

PROGRESS FOR MIGRAINE

After all the bad R&D news, readers were keen to hear news of clinical trial success for a new class of treatments for migraine, the CGRP inhibitors, and the epic battle to market shaping up between the major players. The jury is still out on which of the four products in late-stage development looks best-placed to succeed on the market, making speed at the regulators of the essence.

The first to report Phase III data was for Amgen and Novartis's biologic erenumab (AMG 334) from the ARISE study in episodic headache patients in September. But on their tail are Alder BioPharmaceuticals Inc., Eli Lilly & Co. and Teva Pharmaceutical Industries Ltd., each with a monoclonal antibody in Phase III development that has shown impressive – and impressively similar – results in mid-stage clinical trials.

A second positive trial for erenumab reported in November in the STRIVE study in episodic migraine is keeping Amgen and Novartis on track to be first to file in 2017 – a timing advantage which could prove vital in a sea of very similar competitors. Analysts expect the products' respective side-effect profiles to come into play as each tries to differentiate itself against the others, and against the next wave of oral and intranasal CGRP products coming through the pipeline, particularly from Allergan.

There are no products yet approved specifically for the prevention of migraine, and patients with episodic migraines spend about 14 days each month with a debilitating headache. Increased levels of CGRP – or calcitonin gene-related peptide – have been reported in patients with migraine, making it a novel target for the disease.

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Early-Stage Biopharma Financings Kept Up Multibillion-Dollar Pace In 2016

Series A venture capital and seed funding rounds for biopharma firms in 2016 kept pace with the level of investment seen in 2015, excluding one major deal in 2015, laying the foundation for optimism regarding early-stage financings in 2017 for particularly innovative companies.

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Money flowed to startups around the world in 2016 at a pace similar to 2015, providing for a steady stream of new companies to fill an important part of the biopharma ecosystem, and global venture capital is expected to keep pouring into drug discovery and development in 2017 as well.

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Data gathered by *Scrip* and Informa Pharma Intelligence's Strategic Transactions database show that 148 Series A and seed rounds totaling $3.5bn were completed in the US, Europe and Asia through Dec. 15, 2016 versus 156 Series A and seed rounds totaling $4bn for all 12 months of 2015. Venture capital investors backed an average of 13 early-stage biopharma firms per month in 2016 with an average investment of $23.6m compared with a monthly average of 13 companies raising $25.6m each in 2015.

But there's a bit of an asterisk on the 2015 total, since Boston Pharmaceuticals Inc. launched in December of that year with an initial investment of $600m to acquire and develop clinical drug candidates; without that financing the average Series A round was just $21.9m that year. By contrast, the biggest Series A round in 2016 came at the end of year when Versant Ventures and Bayer AG joined together to invest $225m in the stem cell startup BlueRock Therapeutics in December.

Jonathan Gertler, co-founder, managing partner and CEO of Back Bay Life Science Advisors, said venture capital investment in biopharma and medtech companies may slow down somewhat in 2017, since at least one of the exits for VC investors – initial public offerings – has become a less likely option.

Fewer companies have been able to get through the IPO window in the US this year and newly public life science firms have been particularly squeezed by declining biotech stock sentiment – two factors that reduce the value of companies in VC portfolios and limit options for venture capitalists to seek returns on their investments, Gertler said.

"Every time you see a retreat in the public markets, you see somewhat of a ratcheting down in venture capital. They have to save money for their portfolio companies and they worry about the value of now-public companies in their portfolio. This will also further diminish the capital available at the earlier stage," he noted. "That said, I still see a lot of activity. I see a lot of interest in those companies that are getting funded. Overall, I see that the pool of capital diminished somewhat, but corporate venture capital still has a lot of interest in filling that gap."

TOP 10 SERIES A FUNDRAISERS GET VENTURE, CORPORATE SUPPORT

A look at the top 10 Series A rounds illustrate the global distribution of venture capital for early-stage and emerging biopharma companies in 2016 as well as the role of big pharma companies and corporate VC funds in financing innovation.

Evanston, Illinois-based Aptinyx Inc. closed its first round of funding in May with lead investor New Leaf Venture Partners joined by Frazier Healthcare Partners, Longitude Capital, Osage University Partners, Adams Street Partners, LVP Life Science Ventures, PathoCapital, Goudy Park Capital, Beecken Petty O'Keefe & Co. and Northwestern University.

Aptinyx is developing NMDA receptor modulators for neurological disorders – drug candidates that were spun out of Naurex Inc. after its acquisition by Allergan

2015 Versus 2016 Biopharma Seed & Series A Stats

	2015	2016 (THROUGH DEC. 15)
Number Of Financings	156	148
Per-Month Average	13	13
Dollar Amount Raised	$4bn	$3.5bn
Average Per Deal	$25.6	$23.6m
Largest Deal	$600m	$225m

PLC for $560m up front. Allergan is developing Naurex's NMDA receptor modulators to treat depression and has an option to license certain programs from Aptinyx.

"At the time we did the A round, our focus was on two things," said Aptinyx president and CEO Norbert Riedel, who held the same positions at Naurex. "No. 1 was to get investors that were experienced in our space of diseases of the central nervous system and that understand the importance of forming a company that wasn't just dependent on a single compound succeeding."

Second, Riedel told *Scrip*, "the financing we did for $65m was, by design, intended to take us to the middle or the second half of 2018, by which time we would have data from patients with neuropathic pain." A second compound could be in the clinic by the end of 2017.

Aptinyx had a significant advantage, in terms of the fundraising process, because Naurex previously reported data that showed that NMDA receptor modulators could be effective in depression.

"If we stay true to our mechanism and chemistry, we should see success with our other molecules as well," Riedel said. "The molecules that we worked on and sold to Allergan were peptides and everything we have done and pursued at Aptinyx are not peptides; they were developed with our small molecule chemistry."

FUNDRAISING KEY: NOVEL TECHNOLOGY THAT IMPACTS PATIENTS

Riedel noted that for an investor to back a new biopharma firm in a difficult financing environment, the company must have truly novel technology with the potential to make a big improvement in patient outcomes. The company also should be led by a proven management team that can outline a credible timeline for development of the startup's drug or device candidates.

New Leaf Managing Partner Liam Ratcliffe, a member of Aptinyx's board of directors, agreed with Riedel's assessment of what it takes to attract high-quality VC investors for a Series A round.

"A key part of the Series A is, 'Where do you get to with that investment?' It's about the science, the underlying support of the mechanism, and the quality of the team, but it's also about the plan – the time, the cost to get there and what data they are going to produce," Ratcliffe said in an interview. "What's the trade off in terms of the number and type of indications? Is it a big play or an orphan drug? The plan is a critical part, and what we need to know is – with that Series A round – do we have the data that will be interesting and compelling to the next round of financing or a potential acquirer?"

> Money flowed to startups around the world in 2016 at a pace similar to 2015, providing for a steady stream of new companies

He acknowledged that many Series A rounds these days are quite large by historical standards and that is by design, given the difficulty that life science companies have had in launching an IPO or finding a suitable buyer or partner.

"The market has changed dramatically in a short period of time. Our view has been to be thoughtful and conservative in terms of the size of the round," Ratcliffe said. "Aptinyx had a $65m Series A, but based on the science and the team that came out of Naurex after the deal with Allergan, we wanted to make sure the company had sufficient runway across the market's ups and downs. Rather than go lean in a short time to the next financing, we wanted to make sure the company has sufficient funding."

STRATEGIC INVESTING VERSUS INVESTING FOR A PORTFOLIO

Tom Heyman, head of Johnson & Johnson Development Corp. (JJDC) – the big pharma's venture capital arm – has a slightly different view than Ratcliffe and New Leaf, because his group backs startups and other private biopharma, medical device and consumer health companies when their technology or product is of interest to Johnson & Johnson. JJDC is less focused on a return on its investment and more interested in how the technology might fit in J&J's portfolio.

"We're strategic investors, not financial investors," Heyman said in an interview. "We invest in companies that over time we might be interested in onboarding into one of our sectors of J&J" via licensing, collaboration, option or right-of-first-refusal deals.

JJDC has been "extremely active" during the past two years, he noted, and has increased the investments it has made in both startups and follow-on funding rounds.

"I'm quite optimistic about our opportunities to invest in companies at the early stages. I'm not worried there will be a shortage of investment ideas," regardless of how the IPO market swings from month to month, Heyman said.

In fact, he noted that there's a lot of competition to invest in highly innovative companies. In addition to traditional venture capital firms and investment banks, private equity groups and family-owned funds have pursued particularly attractive life science investments aggressively.

"For things that are a little more difficult – things [like diabetes and Alzheimer's disease] with longer-term studies – that's a little more difficult to find investors. We normally get them done, but it takes more work and more time to get things done," Heyman said. "But investors for transformational opportunities are easy to find, and for anything that has the name 'immuno-oncology' attached to it, investors are not difficult to fund. Anything in the [central nervous system (CNS)] or cardiovascular disease is harder to do. The clinical development timelines are long, the studies are big, and the endpoints aren't clear."

And when investors see big failures in large indications, like Eli Lilly & Co.'s recently failed Phase III Alzheimer's therapy solanezumab, he added, "it reminds people that these are difficult and expensive areas."

But if early-stage companies stay focused on producing good results, "they only have to worry about one thing, and that's their next technical milestone, because from that all good things will flow."

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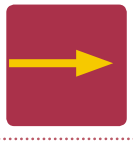

View 2016's Top 10 Series A Venture Rounds here: **http://bit.ly/2iMP0fT**

Slayback's 'Thoughtful' Generics Play Nets $60m KKR Investment

The New Jersey-based Slayback Pharma LLC has announced the closing of a $60m financing by the private equity firm KKR, putting the spotlight on investment and mergers and acquisition (M&A) appetite in the specialty space, especially injectables. Slayback, which works with its out-licensing partners to file ANDAs and 505(b)(2) applications with the US FDA for complex sterile and non-sterile dosage forms, expects the funding to help it expand and accelerate the development of its portfolio of products. Last year, Slayback announced the approval and launch of a generic version of Fresenius Kabi AG's Diprivan (propofol) Injectable Emulsion, an intravenous sedative-hypnotic agent indicated for use in the induction and maintenance of anesthesia or sedation, through its out-licensee Actavis. Sales and marketing rights for the product have been vested with Actavis, which will pay Slayback a share of the profits generated from the sale of propofol in the US and Canada. In December 2016, Slayback said that its outlicensee Sandoz (Fougera Pharmaceuticals Inc.) had launched a generic version of Valeant's herpes therapy, Zovirax Ointment (acyclovir ointment) 5%, in the US under a similar profit share deal. Interestingly, Slayback CEO Ajay Singh won his spurs at India's Dr Reddy's Laboratories, where he was vice president of strategy, portfolio and business development for the North American generics division. Singh's profile on Slayback's website claims that he was also part of the start-up team responsible for the biosimilar initiative at Dr Reddy's. Ali Satvat, a member of KKR who leads KKR's healthcare growth equity investing efforts, pointed to Slayback's development of "thoughtful" generic products and differentiated approach to the marketplace; the PE firm hopes to partner with Slayback to "build and scale" its product portfolio and help make healthcare more accessible, it said in a statement.

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Takeda Funds Celiac Asset As Prelude To Potential Acquisition

Takeda Pharmaceutical Co. Ltd.'s new alliance with the US startup PvP Biologics appears clearly designed to further strengthen the Japanese company's presence in the gastrointestinal area, one of its core therapeutic fields along with oncology and CNS. The celiac disease-focused collaboration also represents an early big win for PvP, a university spin-out formed in 2012 that could end being acquired by its new partner if its novel enzyme therapy lives up to early promise. Under the new agreement, San Diego and Seattle-based PvP will conduct all R&D activities through to Phase I proof of principle studies for KumaMax, a still preclinical stage, novel oral enzyme preparation. The recombinant product helps breaks down in the stomach the immune-reactive component of gluten - the cause of celiac disease - before it reaches the small intestine and causes inflammation of the lining. As part of the deal, Takeda will provide $35m towards PvP's expenses under a predefined development plan and also gains an exclusive option to acquire the privately held company upon receipt of a defined data package for KumaMax. The exercise of the option would entail an undisclosed fee plus subsequent development and regulatory milestones related to Takeda's global development and commercialization of the product.

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Novartis Spreads Cardiovascular Bets with Ionis Antisense Option Deal

Novartis AG has entered into an option agreement with Ionis Pharmaceuticals Inc. (formally Isis Pharmaceuticals) and its affiliate Akcea Therapeutics, Inc. to license two early-stage antisense treatments with the potential to significantly reduce cardiovascular risk in patients suffering from high levels of lipoproteins known as Lp(a) and ApoCIII. The two Ionis pipeline therapies included in the deal are AKCEA-APO(a)-LRx and AKCEA-APOCIII-LRx. The proposed deal includes a $75m upfront option payment as well as customary development, regulatory and commercial milestones and royalty payments to Ionis. Parallel to this option agreement, Novartis has also agreed a stock purchase with Ionis that will see it invest $100m into Ionis, with the potential of another $50m in the future. The deal is subject to customary closing conditions and regulatory approvals. Novartis will look to exercise its options to license and commercialize AKCEA-APO(a)-LRx and AKCEA-APOCIII-LRx following the achievement of positive Phase II data for both drugs. Novartis's head of global media relations, Eric Althoff, told *Scrip* that upon in-licensing the big pharma will initiate a global Phase III cardiovascular outcome study in a high-risk population and will be responsible for worldwide development and commercialization of both assets. Althoff added that "launch horizon is anticipated around 2023-2025." Novartis highlighted that both the Ionis therapies are "highly complementary" to Novartis' current asset ACZ885, which targets cardiovascular risk reduction by reducing residual inflammation in high-risk patients. According to Informa Pharma Intelligence's Biomedtracker database, AKCEA-APO(a)-LRx has completed Phase I trials in healthy volunteers and Ionis is expected to pursue the drug as a treatment for atherosclerosis; meanwhile AKCEA-APOCIII-LRx is in preclinical studies for dyslipidemia/ hypercholesterolemia.

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Microbiotica: Wellcome Spin-Out Exploits Unique Microbe Collection

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Emerging Company Profile: Microbiotica, a UK biotech spin-out from the Wellcome Trust Sanger Institute announced late last year, says it has unique capabilities in culturing and sequencing the human bacterial microbiome that will be of use to develop bacterial mixes for therapeutic use.

The first of Microbiotica Ltd.'s unique bacterial mixes will reach the clinic within the next two years, for a so-far undeclared indication, says company co-founder and CEO Mike Romanos. "We have a bacterial mix that is curative in animal models, so we should move into preclinical development within the coming year," he adds.

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Microbiotica Ltd is a microbiome-focused company that has just been spun out from the world-renowned Wellcome Trust Sanger Institute in Cambridge, the UK. It is concentrating on diseases where it believes addressing out-of-kilter bacterial populations could have a therapeutic effect.

Romanos believes Microbiotica has strong and unique capabilities in several areas including bacterial culture, bio-informatics, genome sequencing and disease models that puts it at least on a par with more established microbiome-focused companies.

"Over the past five to 10 years, Microbiotica co-founder Trevor Lawley and his group have taken a lead in understanding the relationship between bacteria populations and disease. They have cultured and sequenced bacteria found in the human gastrointestinal tract, many of which were previously thought to be unculturable," Romanos said in an interview.

This has resulted in a unique collection of isolated gut microbes and their genomic sequences that allows the researchers to compare and contrast the bacteria present in the gastro-intestinal tracts of diseased patients with those of healthy individuals, and to come up with bacterial mixes that could correct the microbe imbalance. Thousands of bacterial strains from the human gut have been cultured and sequenced, and is believed to be the world's largest culture collection of intestinal bacteria.

"We have bacteria banked and ready to put into medicines, and humanized disease models consisting of animals colonized with human bacteria, that can be used to evaluate potential therapies," Romanos said. "We have found that you can get a desired therapeutic effect in these animal models using bacteria from our collections."

> The company executive would like to get away from fecal transplants

Another arm of Microbiotica's research is based around the idea that some patients might respond differently to immuno-oncology agents based on the bacteria found in their guts. "If we can identify patients likely to respond, and those that don't, maybe we can correct the lack of a response in some patients to immune-oncology agents by the addition of bacteria," Romanos remarked.

What the company executive would like to get away from is any focus on fecal transplants. "Yes, in patients with Clostridium difficile-associated diarrhea, fecal transplants can be curative. But mixed results have been seen in the clinic," he noted.

There are around a dozen other companies active in developing various agents in the microbiome field, including Rebiotix Inc. that has RBX2660 in Phase IIb studies in C difficile-associated diarrhea, and Seres Therapeutics Inc. with SER-109, that is in Phase II and has attracted the Swiss multinational Nestle SA as a research partner. Other companies with an interest in microbiome-related products include Shire PLC with VP20621 in Phase II, MicroBiome Therapeutics LLC with NM504 in Phase II and Second Genome Inc. with SGM-10109 in Phase I.

Microbiotica was set up with £4m ($4.9m) in funding from the local investment firm, Cambridge Innovation Capital, and £4m from the UK technology transfer expert, IP Group plc, announced Dec. 19, 2016. The two investors will each appoint a director to Microbiotica's board.

The company's next steps include the recruitment of several senior-level executives and the establishment of laboratories and offices close to the Sanger Institute's laboratories, according to Romanos. Microbiotica will also concentrate on defining and manufacturing bacterial cultures to be used in its therapeutic bacterial mixes.

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From the editors of *Start-Up*.

Microbiotica Ltd

Location: Wellcome Genome Campus, Hinxton, Cambridge, UK
R&D Focus: the human microbiome.
Disease Area: not disclosed.
Founded/Disclosed: 2016.
Founders: Trevor Lawley, CSO; Mike Romanos, CEO; Professor Gordon Dougan.
Employees: 10 to be recruited in the next six months.
Financing: £8m in set-up funding.
Investors: Cambridge Innovation Capital; IP Group plc.

Alexion's Investigation Reveals 'Inappropriate' Conduct, Nothing Illegal

Alexion Pharmaceuticals Inc. finally posted a long-delayed 10-Q earnings statement for the third quarter of 2016 after completing an internal investigation of *Soliris* (eculizumab) sales that involved "inappropriate" – but not illegal – business conduct influenced by top executives. New Haven, Connecticut-based Alexion did not name any names after the stock market closed on Jan. 4; that's when it revealed that an investigation of Soliris sales practices had concluded. Interim CEO David Brennan said the company "initiated remedial actions to maintain a strong internal control environment" in response to the investigation's findings, and noted that Alexion is "committed to setting a tone at the top that is fully aligned with our ethical standards and values." Brennan, an Alexion board member and former CEO of AstraZeneca PLC, took the helm of the troubled biopharma company after Alexion said CEO David Hallal and chief financial officer Vikas Sinha left for "personal reasons" and "to pursue other opportunities." Vikas was immediately replaced by former Honeywell CFO David Anderson. The C-suite shakeup occurred about a month after Alexion revealed its internal investigation. The Nov. 9 disclosure of the investigation followed speculation by Leerink's George Porges during the prior week that the company's delayed form 10-Q filing with the US Securities and Exchange Commission (SEC) was an ominous sign of news in the offing. However, the analyst said in later reports that he did not expect a finding of severely improper activity nor did he anticipate a substantial restatement of earnings. Porges's crystal ball proved to be accurate in terms of Alexion's findings with the analyst noting in a Jan. 5 report that "the outcome from the investigation is very much consistent with our expectations, and is materially less than the 'worst case scenarios' imagined by many investors." The Audit and Finance Committee of the Board of Directors reviewed allegations by a former employee regarding certain Soliris sales – namely "pull-in" sales, i.e. when an Alexion employee urged a customer to order the drug for patients before those individuals would normally order the product. The practice allowed Alexion to record Soliris sales in an earlier quarter, thereby boosting quarterly sales figures for the drug, which is approved in the US to treat paroxysmal nocturnal hemoglobinuria (PNH) and atypical hemolytic uremic syndrome (aHUS). The Audit and Finance Committee found that the pull-in sales were not great enough to require a restatement of any of Alexion's quarterly earnings, and the company noted that all of the sales were for patients who would use the drug, meaning there was no stockpiling of unwanted product.

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Neurocrine Eyes June Launch Date For Valbenazine In Tardive Dyskinesia

Neurocrine Biosciences Inc. is solely focused on preparing for a June launch of its tardive dyskinesia drug *Ingrezza* (valbenazine) now that the hurdle of a US FDA advisory committee review has been removed. Neurocrine execs said they have no reason to believe valbenazine will not be approved by the new drug application's (NDA) April user fee goal date even though FDA informed the company that it was cancelling a scheduled Feb. 16 review by the Psychopharmacologic Drugs Advisory Committee. During a Jan. 5 investor call on the cancelled meeting, company representatives discussed efforts currently underway to prepare for valbenazine's launch, including the hiring of a national sales team, payer meetings and interactions with patient advocacy groups. Neurocrine also has bolstered its executive management team in anticipation of the company's move from clinical stage to commercial entity by adding a former Sanofi and Alnylam Pharmaceuticals Inc. executive as president and chief operating officer. Valbenazine, a vesicular monoamine transporter 2 (VMAT2) inhibitor, could be the first drug approved in the US for treatment of tardive dyskinesia, a condition characterized by involuntary, repetitive movements of the face, trunk or extremities. The condition is estimated to affect approximately 500,000 people in the US. Neurocrine has been in a race with Teva Pharmaceutical Industries Ltd. to be the first to market with a VMAT2 inhibitor for the condition. However, Teva is first pursuing approval of its candidate, deutetrabenazine, for treatment of chorea associated with Huntington's disease. That NDA received a complete response letter in May, and the company has resubmitted the application with an April 3 goal date. Teva was targeting a late 2016 NDA submission for deutetrabenazine in tardive dyskinesia. Neurocrine submitted its valbenazine NDA in August. The application is undergoing a priority review, with an April 11 user fee goal date. The company has long anticipated an advisory committee review of the drug, which is a new molecular entity, and FDA formally announced plans for a panel review in a Dec. 27 Federal Register notice.

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Cellectis Files IND For Talen-Edited 'Off-The-Shelf' CAR-T Candidate

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Cellectis has filed an IND for US testing of its TALEN-edited CAR-T immune-oncology therapy UCART123. Servier has already begun clinical testing with Cellectis' lead program, UCART19, in Europe. The product is licensed to Pfizer in the US.

Cellectis SA of France hopes to begin clinical testing in the first half of this year with its gene edited product candidate in patients with acute myeloid leukemia (AML) and blastic plasmacytoid dendritic cell neoplasm (BPDCN). This is the first IND filing for a gene edited allogeneic product candidate in the US.

UCART (Universal Chimeric Antigen Receptor T-cells) are 'off-the-shelf' allogeneic products, which means their production can be industrialized and standardized with consistent pharmaceutical release criteria, over time and from batch to batch, according to Cellectis.

UCART123

UCART123 targets CD123, an antigen expressed at the surface of leukemic cells in AML, as well as on leukemic and other tumoral cells in BPDCN.

"Following a Pre-IND meeting with the FDA in August 2016 and a NIH-RAC public hearing in December 2016, filing this IND is an important regulatory milestone for the company," said Stephan Reynier, chief regulatory and compliance officer, Cellectis.

Clinical development will be conducted at Weill Cornell Medical College and the MD Anderson Cancer Center.

UCART19

In 2015, Servier SA exercised an option to license Cellectis' lead program, UCART19, and then immediately shared it out by licensing US rights to Pfizer Inc. The deal came on the back of news that UCART19 had been used to treat a child in the UK under a special license from the country's MHRA because no other therapies were available for refractory relapsed acute lymphoblastic leukemia (ALL) following mismatched allogeneic stem cell transplantation. The patient went into full remission.

In June 2016, Servier began a Phase I trial of UCART19 in pediatric acute B lymphoblastic leukemia (B-ALL) at University College London (UK). The trial is sponsored by Servier "in close collaboration with Pfizer," according to Cellectis, which received an undisclosed milestone payment.

If successful, this 'off-the-shelf' approach could put real pressure on other players in the CAR-T space such as Novartis AG, Kite Pharma Inc. and the troubled Juno Therapeutics Inc.

Novartis and Kite plan to file their CRISPR edited CD19-targeting CAR-T therapies for US approval early this year but Juno has had two clinical holds put on its lead program owing to unexplained deaths.

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Lucky Rooster? A Stellar Year Ahead For Chinese Pharma Investment

If the year of the Monkey is a jumpy ride filled with uncertainties, the coming year of the Rooster will be certain to bring more changes to the pharma sector and immuno-oncology, high-end devices and combining artificial intelligence with next-generation genomics are attracting large amount of hot cash inflow.

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The usually harsh winter has been gentle to healthcare investment in China. More companies are betting on healthcare while shrinking investment in sectors. Zhongwei Capital, for one, has total 30 funds dedicated to health with CNY 1b funding for each. The focus areas are health services, medical device and smart health.

Qiming Venture Partners, which has both U.S. dollar- and Chinese Yuan-based funds totaling $2.7bn under management, has seen its portfolio firm Berry Genomics moving forward toward a China's A Share stock market listing via a reverse merger with a Shenzhen-listed Chengdu firm.

Qiming with roughly 40% of its investment on healthcare looks to bridge Chinese firms and U.S. health companies. The VC currently has 60 portfolio companies.

Back by the capital injection, more Chinese healthcare companies are stepping out and shopping for deals overseas.

The coming JP Morgan global healthcare conference for one, to be held Jan. 9-12 in San Francisco, will attract a large crowd of pharma executives from China. Beijing-based PE firm E-Capital is organizing a roadshow with 25 domestic-listed healthcare companies participating on the sideline of the conference, noted Irene Hong, managing partner of the firm.

PRESSURE MOUNTING

The going global trend, encouraged by the government to expand Made-in China overseas, also traces to mounting pressure on home turf.

On Christmas eve and days before the new year, a news report run by China's state owned CCTV shocked the drug-making sector which has witnessed many changes for the past year of 2016.

In the news, a reporter went undercover in hospitals in Hunan province and Shanghai city, and discovered a common practice of physicians taking kickbacks in exchange for drug prescriptions.

The drugs exposed by the runs are from both domestic and multinational drug makers with widely prescribed anti-infectives, hypertension treatment in the focus.

Such drugs are sold in the hospitals with inflated prices, several times higher than their ex-factory prices, due to the kickbacks given to the physicians, noted the report.

In one case, the kickbacks accounted for as much as 40% of the drug price, and one physician received four envelopes containing the kickbacks in as short span of three minutes from different sales reps.

The news has stirred up a controversy that has long been an eyesore in China's healthcare system, which has a below-average public healthcare investment, supporting a universal coverage that covers over 95% of the 1.3bn population.

To make up for the shortage of public fiscal support, hospitals rely on drug sales for revenues and so do physicians for incomes.

Coupled with a missing leverage role of the public payer, the results have been a popular practice of Daijinxiaoshou, or drug sales based on cash kickbacks.

Indeed, the CCTV news also revealed that some physicians preferred drugs with higher percentage of kickbacks to those with lower ones.

Not surprisingly, China's regulators, the National Health and Family Planning Commission reacted to the news with a call to root out corruption, by rolling out Sanming Model of healthcare reform.

The model is marked by its aligning medicines with treatment and payer. Health authorities at Sanming, located in the southwestern Fujian province, have piloted monitoring physicians drug prescriptions, especially large-selling drugs including supplements, nutrients and products with high kickbacks and less clinical benefits.

A large-scale crackdown on kickbacks and pressure to lower drug prices are projected to be in store for drug makers. That will push sizable companies seek buying overseas assets or collaborating for innovative new drugs, insiders say.

HOT AREAS

Immuno-oncology and high-end consumables are expected to be the mostly-sought areas for investment in 2017, noted Li Wengang, partner of Zhongwei Capital.

Following the lead of Suzhou-based Innovent Biologics Inc., more domestic companies are developing anti-PD1 and PD-L1 assets, however, newcomers should develop assets beyond PD-1 and PD-L1, Li pointed.

With the help of emerging cell-line screening technology developed by 3D Med, a Beijing-based startup, more domestic firms will develop own immune-oncology assets, Li projected.

Bio-degradable stents, pace makers will also attract hot investment due to an increasing demand for such devices to treat cardiovascular patients.

Smart health such as cancer diagnosis and treatment using artificial intelligence is also getting traction. Connecting AI with next-generation genomics (NGS) is what U.S. sequencer maker Illumina Inc. is looking for in China, said Zhao Ruilin, Illumina China GM.

China will be playing a significant role in clinical transformation and recreational genomics, given its size, Zhao told attendees at annual Technode China Conference, held in Beijing Nov. 8.

"It makes sense to apply AI with big data in China," Zhao said, citing Zhengzhou Medical University Hospital being one of the largest hospital in the world, with 2,000 beds.

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From the editors of *PharmAsia News*

Awkward Developments Pricking J.P. Morgan Bubble

The warm fuzzy feeling in life sciences in the week before the J.P. Morgan Healthcare Conference was rudely threatened by clinical trial results from Halozyme and Heron, and negative financial preannouncements from Heron and Teva.

ANDY SMITH

The biotech industry may have been hoping for a slow news week before the annual J.P. Morgan Healthcare Conference, to avoid investors being scared away from California. The rumors of blocks of vacant hotel rooms in downtown San Francisco being released in mid-December and what feels like a general downgrading of 2017 expectations from investment bank analysts were not enough to dampen the rise of the NASDAQ Biotech Index (NBI). The latter finished the first trading week of the year up just under 4.5% against the S&P 500's 0.6% rise. Cynics might point to the ability of determined and incentivized market participants to influence a stock market or index in the short-term, but drug pricing and clinical trial results are likely to counterbalance investors' thoughts as they review their biopharmaceutical holdings during and after the conference.

The value of the word "positive" in clinical trial announcements is falling rapidly as it becomes associated with contentious and mixed data sets, and p-values of eggshell-thin robustness. Halozyme Therapeutics Inc.'s announcement of the results of its Phase II open-label study of the combination of its recombinant human hyaluronidase and Celgene Corp.'s *Abraxane* (nab-paclitaxel) in pancreatic cancer patients appeared to be the latest step down in value.

I was expecting the ensuing debate to be polarized between those social media commentators who focused on the reasonable amount of data that was not "positive" and the sell-side analysts who were keen to support an impending share issue by their banking colleagues. In the event, the analyst reports I read were more critical than I had expected, with those from J.P. Morgan pointing out the commercial relevance of the logical and better progression-free survival hazard ratio in stage 1 compared with stage 2 patients, noting that these earliest diagnoses are the smaller patient population.

The analysts from Citigroup took last week's gold star for insight when they said the results were "quite mixed, and ultimately leave [the already started] Phase III as a risky trial." They went further by reminding me (at least) that the study had been complicated by a clinical hold in stage 1 patients, the retrospective use of the diagnostic and a shorter duration of treatment in stage 1 compared to stage 2 patients, any one of which could potentially confound the study. The positive momentum of the week before the J.P. Morgan Healthcare Conference – that will undoubtedly be used to raise money for many companies during and after the meeting – was strong enough to outweigh the intense social media criticism of the study plus a downgrade by Citigroup. Halozyme's stock price ended the week up 34%.

Last year's J.P. Morgan Healthcare Conference was preceded by the analysts from two investment banks expressing their concern about the fragility of the sales growth of Vertex Pharmaceuticals Inc.'s cystic fibrosis franchise. That concern proved remarkably predictive of Vertex's repeated guidance cuts and misses of analysts' consensus estimates throughout 2016 and their negative pre-announcement on the cusp of this year's conference. Two new negative pre-announcements from Heron Therapeutics Inc. and Teva Pharmaceutical Industries Ltd. marked the premature start of fourth-quarter earnings season that would otherwise commence with Celgene's financial guidance on Jan. 9.

HERON HIT

Heron attempted to soften the blow of a cut in expectations for its recently launched anti-emetic drug *Sustol* (granisetron) by also announcing some "positive" top-line results from the Phase II study of its post-surgical pain combination HTX-011 (bupivacaine and meloxicam) in 152 abdominoplasty patients. Only the detailed results for 20 patients in the 400mg middle dose arm and 21 placebo patients were reported. The analysts from Cowen described the trial results as "encouraging" but couched them with the same "totality" of the data phrase that Amicus Therapeutics Inc. used to describe its Phase III study which recently left the FDA unconvinced. With the missed endpoint of pain up to 24 hours in the study and its 2017 Sustol sales guidance of $15m-$25m against a consensus of $50m after its recent launch in the face of established generic palonosetron, the Cowen analysts' description of Heron as a "magnet for controversy" seemed apt. Despite the 13% share price spike on the "positive" results announcement Heron's share price ended the first trading week of the year just over 1%.

Teva waited until the last day of the first trading week of the year to announce that the weakness in its generic drug business that was first reported in the third quarter of 2016 was here to stay. Both the biggest generic pharmaceutical companies – Teva and Mylan NV – appeared to laugh in the face of the generic drug price deflation pressure that had diminished the financial performances all of the smaller generic companies including Endo International PLC and Valeant Pharmaceuticals International Inc. right up until November 2016 when, to borrow the lyrics of Ellis Paul, it hit them like a southbound train. That train does not appear to be stopping in 2017 because after lowering its full-year 2016 guidance in November Teva last week took a hatchet to its sales and earnings expectations for 2017 and continued to exclude any impact of generic *Copaxone* (glatiramer acetate). A similarly rosy picture was painted by Johnson & Johnson in 2016 when, like Teva, it assumed the absence of generic competition to one of its biggest branded drugs – *Remicade* (infliximab) – in its full-year guidance, right up until the day after Pfizer Inc. announced the *Inflectra* (infliximab) launch. The deals and collaborations announced on the first day of the conference should result in that warm fuzzy feeling but continued financial pressures will provide a longer-term chill.

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

Selected clinical trial developments for the week 30 December 2016 – 5 January 2017

LEAD COMPANY/PARTNER	COMPOUND	INDICATION	COMMENTS
Phase III Interim/Top-line Results			
Sun Pharmaceutical Industries Ltd.	*Seciera* (cyclosporine A)	dry eye disease	Emerald; primary and secondary endpoints met, in confirmatory Phase III study.
Agile Therapeutics Inc.	*Twirla* (low-dose levonorgestrel and ethinylestradiol) patch	contraceptive patch	SECURE; mixed results addressing a complete response letter, but filing expected in first half 2017.
Inotek Pharmaceuticals Corp.	trabodenoson (INO-8875), an adenosine mimetic	glaucoma	MATrX-1; missed primary endpoint with a high placebo response, further data expected.
Opko Health Inc./Pfizer Inc.	*Lagova* (MOD-4023), long-acting HGH-CTP	short stature	Study 005; missed primary endpoint, further analysis underway.
Otonomy Inc.	*Otiprio* (ciprofloxacin) otic suspension	acute otitis externa	Met primary endpoint, significant cure rate.
Pfizer Inc.	adalimumab (PF-06410293), biosimilar	moderate to severe rheumatoid arthritis	REFLECTIONS (B538-02); equivalent efficacy to Humira.
AEterna Zentaris Inc.	Macrilen (macimorelin)	short stature	CROSSOVER; failed to achieve its objective.
Phase III Initiated			
Ardelyx Inc.	RDX7675	hyperkalemia	In around 300 patients.
Dermira Inc.	olumacostat glasaretil, topical	acne	CLAREOS-1,-2,-3; reduces sebum production
GeNeuro SA/Servier SA	GNbAC1 (MAb against MSRV-Env)	multiple sclerosis	ANGEL-MS; Phase IIb extension study
Opko Health Inc./Pfizer Inc.	*Lagova* (MOD-4023), long-acting HGH-CTP	short stature	Study 006, in children, of weekly dosing.
Dr. Reddy's Laboratories Ltd.	DFN-15	migraine	In migraine patients with and without aura.

Source: Biomedtracker

Pharmalink AB has named ***Maria Carell*** chair of the company's board of directors, succeeding ***Hilde Furberg***, who has been elected vice chair of the board. With a background in operating, acquiring and developing healthcare and life science companies, Carell was previously CEO of Exeltis USA Inc. Before this, she was president of Meda US and executive vice president of Meda North America and South Pacific at Meda Inc. Prior to Med, she was president and CEO of a global medical device company, Q-Med Ab.

E-Therapeutics has appointed Amgen Inc.'s current executive director of corporate development, ***Raymond Barlow***, CEO. Once Barlow assumes his role as CEO on or before May 1, 2017, he will be appointed to e-Therapeutics' board of directors. Barlow has previously held roles at Zeneca as a member of its pharmaceutical R&D's technology access and strategic alliances team and following the merger with Astra, he became global manager in the discovery and development function. During his ten years at AstraZeneca, he held various roles including senior business analyst and director of corporate development; and later moved into the biotech sector working in senior business development roles for Microscience Ltd and Emergent Solutions Inc. He joined Amgen in 2012 after spending a couple of years at Crucell.

Cleave Biosciences has promoted ***Kanya Rajangam*** from vice president of clinical development to chief medical officer. Rajangam joined Cleave in 2015 and has a decade of oncology drug development experience. Before joining the company, she worked at Onyx Pharmaceuticals where she was involved in the clinical development and global regulatory submissions of a multiple myeloma drug. Previously, she was associate medical director at Exelixis.

David Fellows, who was previously retinal therapeutics company **Oxular Limited.**'s non-executive director, has now been appointed chair of the company's board. He replaces ***Nigel Pitchford***, who will continue on Oxular's board as a director. Fellows brings ophthalmology and organizational leadership experience to Oxular and is currently CEO of NightstaRx Limited. Previously, he was vice president of Johnson & Johnson's vision care franchise, and before this he was at Allergan for 25 years where he held various sales and marketing roles.

Digital heath focused **Adherium Ltd.** has appointed ***Scott Fleming*** senior vice president of business development, Europe – effective immediately. He will be succeeding ***John Tarplee***, who stepped down from the role at the end of 2016. Fleming is a founding member of the digital drug delivery movement and has 25 years experience in strategy, device development, sales and marketing. He co-founded MicroDose Therapeutx in 1997, where he developed the first digital piezo driven dry powder inhaler, which was then licensed to big pharma.

Zhenping Zhu has joined **3SBio Inc.**, a biotech company based in China, as president of research and development and chief scientific officer. Before this position, Zhu was executive vice president, global biopharmaceuticals, Kadmon Corporation, and president of Kadmon China. Previously, he was vice president and global head, protein sciences and design at Novartis.

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