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Pharma Industry Holds Tight As Disorderly Brexit Approaches

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The looming prospect of a disorderly Brexit at the end of March is spreading fear within the pharmaceuticals sector and life sciences industry, where the development of drugs and other products depends heavily on the political and regulatory conditions of a country and often require planning years in advance, while the provision of drugs to patients often requires tight timetables.

A disorderly Brexit became more likely Jan. 15 when the UK parliament overwhelmingly rejected UK Prime Minister Theresa May's proposed EU withdrawal agreement.

With just a month and a half left before the UK's scheduled departure from the European Union, and the government acknowledging that it has no "Plan B" in place, a "hard Brexit" looms larger than ever.

STOCKPILING MORE IMPORTANT THAN EVER

The pharma industry, conservative by nature, has been increasingly vociferous about its concerns over a disorderly departure by the UK from the European Union.

To their credit, most drug makers have been preparing for a bumpy Brexit, drafting continuity plans to address the whole range of potential Brexit scenarios while stockpiling medicines and transferring marketing licenses held in the UK for thousands of drugs over to mainland Europe, at considerable cost.

Sanofi UK & Ireland has been stockpiling medicines for months in preparation for a possible hard Brexit. *(Also see "Sanofi Top UK Exec Plans For Hard Brexit, Blasts 'Poor Access' To New Drugs " - Scrip, 30 Jul, 2018.)*

Hugo Fry, managing director for **Sanofi** UK & Ireland, told *Scrip* that "following the parliamentary vote, our position has not changed. We are continuing to ensure we have everything in place for a no deal scenario and are working to increase UK stock, where global supply allows, in line with the UK government's specific guidance." He did not elaborate.

Mike Thompson, CEO of the the Association of the British Pharmaceutical Industry (ABPI) said in response to the continued stalemate over Brexit that "with time running out, we hope Parliament will come together and quickly find a solution to the stalemate and reassure patients that medicines will not be disrupted come March 2019." He added that a "no deal" withdrawal would prove to be "extremely challenging" for the industry.

The UK BioIndustry Association (BIA) will be holding its powder dry until Jan. 18 when it will be holding a webinar on the subject.

However, its chief, Steve Bates, is on record in December as saying that "a 'no-deal' Brexit would mean the biggest disintegration of the complex regulated medicines market in Europe in terms of regulation, cross border movement of goods, comparative pricing, and intellectual property."

The life sciences industry contributes some £30.4bn to the UK's GDP and is the country's biggest R&D spender, with the current level standing at £4.2bn.

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

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from the editor

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As our cover story highlights, pharma is among many industries having to contend with major challenges in the political and regulatory sphere. As the eventual outcome of the UK's 2016 referendum on exiting the EU remains deeply uncertain despite the rapidly approaching deadline, in the US the regulatory framework is also being impacted by the government shutdown, which has endured for more than a month.

In Europe, companies have been preparing as best they can for whatever Brexit eventualities may emerge, although they warn that the impact in particular of the UK leaving the EU without a deal will have a major impact on numerous aspects of the pharmaceutical industry and medicines supply and regulation.

In the US, the FDA has tightened its belt but for now continues activities including advisory committee meetings drawing on carryover user fee funds. A large proportion of staff have been furloughed or are working unpaid, while regulatory submissions requiring fee payments will not be accepted until the impasse is resolved.

Although global politics seem to be increasingly chaotic, the biopharma universe is thriving. Naturally there are setbacks, but the momentum is strong for the development of innovative therapeutics. More drugs are making it to market, and the industry is moving from a theoretical embrace of data science to concrete actions to improve efficiency and productivity at many levels. You can read more about what Takeda is doing in that area as it prepares to integrate Shire on p9-10. Details of Novartis's latest data partnership are on p12, and the company's new R&D chief opens up further on p21-23.

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In A Record Year For US FDA Approvals, Pfizer Came Out On Top

MARY JO LAFFLER & BRIDGET SILVERMAN

Leading the pack of sponsors in the US FDA's banner year of novel drug and biologic approvals was **Pfizer Inc.** – and its four approvals are double what any other big pharma put forward in 2018.

Pfizer has spent years trying to build up its cancer business, and its 2018 novel approvals certainly reflect progress. All four of its new molecular entity (NME) approvals were for cancer drugs: the hedgehog inhibitor *Daurismo* (glasdegib) for acute myeloid leukemia, the ALK inhibitor *Lorbrena* (lorlatinib) for non-small cell lung cancer, the PARP inhibitor *Talzenna* (talazoparib) and the EGFR inhibitor *Vizimpro* (dacomitinib).

The four NMEs for Pfizer in 2018 are also double the NMEs it had approved in 2017, and those two were double the single NME approved in 2016. Several of the other top five pharmas (by 2017 pharma sales) matched Pfizer's two NMEs in 2017 – **Novartis AG**, **Roche** and **Merck & Co. Inc.** – but in 2016 Pfizer's single NME approval came behind two for Roche and two for Merck & Co.

But over the last three years, Pfizer's seven NMEs outstrips the other top tier pharmas. Merck & Co. followed with six and Roche with five, while Novartis totaled three and **Johnson & Johnson** just two.

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To read the rest of this story go to: https://bit.ly/2R3dpWp

inside:

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Worries over a hard Brexit extend beyond jobs and profits.

The head of the European Federation of Pharmaceutical Industries and Associations (EFPIA) said that "with the prospect of the UK leaving the European Union in a disorderly manner without a deal, there are very real, tangible and immediate threats to patient safety and public health in both the UK and across Europe."

A disorderly Brexit became more likely Jan. 15 when the UK parliament overwhelmingly rejected UK Prime Minister Theresa May's proposed EU withdrawal agreement

EFPIA Director General Nathalie Moll in a statement called on Brexit negotiators to agree on a series of actions, including steps to avoid disruption to the supply of medicines – notably blockages caused by transport delays at the border and where the development, manufacture, packaging, safety testing and regulation of the medicine no longer benefits from mutual recognition.

CONTINENTAL CONCERNS RISE TOO

Businesses on the European continent are also growing increasingly alarmed.

The head of Germany's confederation of industries (BDI Bundesverband der Deutschen Industrie) Joachim Lang said businesses on both sides of the English Channel have been left hanging in mid-air by the British political process.

In an article headlined "Hysteria Has Won Out - No Time Left For The Hangover", Lang lambasted British parliamentarians, and said the fall-out would hit businesses throughout the European region.

"A chaotic Brexit is drawing dangerously closer. The top priority now must be to avoid a hard Brexit."

"Responsibility for this lies purely and simply with the government and the opposition in London," Lang concluded.

Published online 16 January 2019

The Gene Therapies Are Coming – And Ways To Pay For Them

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As a new wave of gene therapies edges closer to the market, drug makers and payers are exploring new ways to pay for the expensive, potential one-time treatments. Alternative payment models for gene therapies and other expensive curative medicines were a big topic of interest at the J.P. Morgan Healthcare Conference in San Francisco Jan. 7-10, as the reality of paying for many multi-million-dollar treatments sets in.

The biggest announcement came from **bluebird bio Inc.** CEO Nick Leschly, who revealed a payment proposal for the company's late-stage gene therapy *Lentiglobin* (lentiviral beta-globin gene transfer) that allows payers to pay for the drug over five annual installments of 20% of the cost. In a presentation to investors Jan. 8, he said bluebird is targeting a price under $2.1m, even though the company's conservative assumptions of the therapy's value are more like $3m-$4m.

Bluebird said payers would only have to pay the annual installments if the therapy works, based on a threshold of reducing blood transfusions. The company also committed to keeping price increases limited to the Consumer Price Index (CPI).

The news is a landmark of sorts as it is the first time a drug maker has proposed an annual installment plan for a gene therapy over five years. **Spark Therapeutics**, which launched the first gene therapy in the US – *Luxturna* (vortigene neparvovecrzyl) – last year, also came to the market with innovative reimbursement proposals, including rebates based on near-term and long-term endpoints at 30-90 days and 30 months. *(Also see "The First US Gene Therapy Maker Innovates On Pricing And Reimbursement" - Scrip, 3 Jan, 2018.)*

Bluebird's proposal adds urgency to finding answers to questions about how such a payment model will be implemented in an insurance system that isn't structured to handle payments over time. It also raises the question if bluebird's proposal will become the model for other gene therapies, at least in the near-term.

Lentiglobin is under review in the European Union now for transfusion-dependent beta-thalassemia and is expected to be approved in the US in 2020 for that indication. It is also in development for sickle cell disease.

Bluebird may have beaten peers to the punch with a payment plan, but **Novartis** is also likely to bring novel approaches to the table. The company is expected to be the first to the US market with a new gene therapy, AVXS-101 for spinal muscular astrophy (SMA), in mid-2019. *(Also see "Keeping Track: Pfizer's Talzenna Ensures Record Year For Novel US Approvals; Novartis Submits SMA Gene Therapy" - Pink Sheet, 21 Oct, 2018.)* Other drug makers also have gene therapies in late-stage development, including **Sarepta Therapeutics Inc.** for Duchenne muscular dystrophy, **BioMarin Pharmaceutical Inc.** for hemophilia and **BioMarin Pharmaceutical Inc.** for the rare disease adenosine deaminase severe combined immune deficiency (ADA-SCID).

The topic is certainly something Novartis CEO Vas Narasimhan has been thinking a lot about. He also confirmed Novartis is talking to payers about annual payments for AVXS-101. "I think we are prepared and planning on bringing out amortization models that would allow health care systems and payers to pay over time for these therapies based on the outcomes that they would deliver," he said during a drug pricing Q&A at the J.P. Morgan meeting.

"The industry needs to put forth those models and then the payer systems need to adapt to be able to use those models, and that is a very different conversation, because that requires a significant shift in data systems," Narasimhan said. Broad structural change by insurers will probably only happen when enough gene therapies hit the market to force a change, he predicted.

A FIVE-YEAR THRESHOLD?

Among the biggest questions are how to measure value for a potential one-time

cure and over what length of time, particularly given the lack of long-term durability data on gene therapies.

For bluebird bio, the five-year payment plan leaves a lot of value on the table, if the therapy proves durable. It could also bring risk if it doesn't. "It's capped at five years and the rest, six years through life, is given back to the system," Leschly said.

But the five-year timeframe could help get payers to the negotiating table. Harvard Pilgrim Health Care is one insurer that has been talking to bluebird. Chief Medical Officer Michael Sherman said in an interview he thinks the five-year timeline is fair.

Harvard Pilgrim has been one of the more transparent and innovative insurers when it comes to trying new reimbursement models. The company was the first to sign on to Spark's value-based reimbursement agreement for Luxturna and has been proactive working with drug makers on other more traditional VBR deals.

Sherman said determining how many years a drug maker should essentially take credit for, if these gene therapies do ultimately have long-term durability, is a big uncertainty.

"There's not a scientific answer. That's somewhat of a philosophical or policy answer," he said. "What I do know is that if you cure a two-year old with appendicitis and they live 70 years, you don't say that it is worth 70 times $150,000, or $10m, and then pay that for the appendectomy."

"I do think five years, to many of us, for no scientific reason, just a gut feel, feels like it is a fair number and that is what bluebird is working off of," Sherman said.

He said he approved of Bluebird's approach so far. "I applaud bluebird for coming to the table and thinking very proactively, putting out a framework for how they are going to think about that price and based on what factors over what number of years," he said. "I think they are showing a lot of leadership."

Bluebird said payers would only have to pay the annual installments if the therapy works, based on a threshold of reducing blood transfusions

Sherman also said he is talking to other gene therapy makers about strategies for payments over time.

Sarepta CEO Doug Ingram also talked about upending the traditional reimbursement model in an interview at J.P. Morgan. He said the company is already talking to payers about alternative payment models ahead of the potential launch of its micro-dystrophin gene therapy for DMD in late 2020.

"What we have found so far is that payers are very willing to engage and actually appreciate the opportunity to do that," he said. "I think we will find solutions."

"The real issue is going to be the idea of absorbing the cost in one year of therapy that is going to benefit somebody over decades," he added. "That is just a structural issue and we're going to have to work on that together."

Sangamo Therapeutics Inc.CEO Sandy Macrae was also optimistic. "It will be solved," he predicted in an interview, though he said changes might be embraced more readily in Europe, where single-payer government health care systems tend to view total health care costs versus the more siloed US insurance market.

"But we've already had conversations with some of the payers here and they get it," he said. Sangamo is partnered on a gene therapy for hemophilia A with **Pfizer**.

Another challenge that needs to be sorted out is how reimbursement would be handled under an installment plan if the patient changes insurers. That's where Harvard Pilgrim's Sherman said his company is exploring a pilot program with other insurers in Massachusetts in collaboration with MIT's New Drug Development Paradigms (NEWDIGS) collaborative to come up with affordability models for gene therapies that would be shared among payers in the state.

"The idea would be to work with any gene therapy company that is interested," he said.

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How Lilly Aims To Make Sure Good Drugs Don't Get Lost In Translation

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Eli Lilly & Co. is focused on bringing more first-in-class drugs to market. That's why, Senior Vice President and Chief Scientific Officer Daniel Skovronsky said, the company is investing in technology and teams to make sure good drugs don't get lost in translation and fall behind competing products.

Lilly launched 10 new drugs during the last five years, but many hit the market behind at least one competitor, including some high-profile third-in-class products – the CDK4/6 inhibitor *Verzenio* (abemaciclib) for breast cancer and the CGRP inhibitor *Emgality* (galcanezumab) for migraine headache prevention. *(Also see*

"CDK4/6 Inhibitor Market Snapshot: New Drugs Jockey For A Piece Of The Multi-Billion Dollar Pie" - Scrip, 19 Jun, 2018.) and *(Also see "Migraine Market Gets Competitive With Second, Third CGRP Inhibitor Launches" - Scrip, 9 Nov, 2018.)*

"Our goal is to have transformational medicines," Skovronsky told *Scrip* in an interview during the J.P. Morgan Healthcare Conference Jan. 7-10 in San Francisco. "We are not satisfied with me-toos or second or third [entrants]. We want things that are first and big changes – step changes – from what's currently available."

In oncology, in particular, he said, first-in-class therapies that offer dramatic improvements versus approved options are necessary to satisfy patients, physicians and payers.

Lilly recently has made significant investments in big acquisitions of biopharmaceutical companies with an eye on buying novel, first-in-class drug candidates. *(Also see "Lilly Ready For More Risk When It Comes To Early Deals" - Scrip, 19 Dec, 2018.)* Representative transactions include the $1.6bn buyout of **Armo BioSciences Inc.** in 2018 and the $8bn purchase of **Loxo Oncology Inc.** announced this year at J.P Morgan. *(Also see "Lift-Off For Lilly In Cancer Genetics With Loxo Buy" - Scrip, 7 Jan, 2019.)*

However, since Skovronsky noted that Lilly intends to source only about a third of its research and development pipeline from external sources going forward, the company also needs to improve the speed of its in-house R&D to bring more first-in-class products to market.

"There's probably two main aspects of improving our speed of translating a target in the labs to clinical data in humans," he said. "One is around technology and technological innovation, and the other is around business processes and how we make decisions. It's actually the second one that I predict will give us the biggest gains."

On the technology side, Lilly has invested in automation around its drug-making capabilities, including robotics to assist with antibody generation and chemical synthesis for the faster creation of large and small molecules, respectively.

"Things that were rather laborious and time-consuming can now be accelerated dramatically," Skovronsky said. "By driving automation and investing in IT as well as robots we can make molecules faster than ever before, so that's definitely saving time."

TECHNOLOGY GAINS ASIDE, ATTITUDES TOWARD RISK A BIGGER HURDLE

"The biggest barrier though, in the past, has not been our ability to make molecules, but it's been our willingness to test them," he continued.

There's always an additional experiment that can be done for a new drug target or product candidate that will generate more data to de-risk the asset, but sometimes competitors get to that point first and then companies – including Lilly – have to figure out how to speed up development of their own programs.

Skovronsky described such a scenario as "an uncomfortable position to be in," but noted that it's fairly common in big pharma, because – despite the inherent riskiness of biopharma R&D – people in the industry tend to be risk-averse when deciding whether to move a discovery program forward.

"Sometimes the risk we don't want to take is the type of risk that Loxo embraced, which is, 'Here's some great biology, which we really believe in. It's clearly going to work, but is there a commercial opportunity at the other side? I don't know, because it's 10 years away and hard to predict.' Sometimes it's that kind of risk that slows us down," Skovronsky said. "Sometimes it's the risk [like that at] Armo, which is everybody thinks IL-10 is immunosuppressant, but we have evidence in mice that actually in the tumor environment it boosts immune response, so sometimes it's a biology risk that you're willing to take."

"The biggest barrier though, in the past, has not been our ability to make molecules, but ... our willingness to test them," Skovronsky said.

MOVING TO A RISK-EMBRACING BUSINESS MODEL

With the goal of more frequently being the first to develop a new class of drugs, Lilly's R&D organization has adjusted its business processes to embrace those types of risks.

"We're not talking about risks to patient safety or quality or taking shortcuts in toxicology or anything like that, but rather embracing the kind of risks that biotech companies do to try something different that no one's done before, either because the commercial picture is cloudy or the biology has some question marks around it, but that's our job and that's how we create opportunity for patients," Skovronsky said.

Lilly has reengineered how it does early stage discovery, by setting up an investment committee that makes decisions about targets very early on and then puts teams in place that run like small companies within Lilly to champion each project. The teams were called "trailblazers" early in the experiment and the name has stuck.

"We put in a leader that very much functions like the CEO of a biotech company. She or he is usually a scientist, but also has a business interest and background," Skovronsky said. "They put together a lean team; they're given a scarce budget, but a secure budget – they don't have to worry about coming back a year later and saying, 'Is this still a good idea?'

– and their goal is to take it all the way from target to human data in about three years."

Lilly has transformed its entire early R&D portfolio to this method of operating and the company is seeing dramatic results.

"Projects are going much faster already to human data and I think this will be a competitive advantage for Lilly," Skovronsky said. "It's a bit of the best of both worlds – the sense of urgency and commitment to a project that biotech has, but then the resources and expertise that we as a large pharma company have."

DISMANTLING MULTIPLE COMMITTEE STRUCTURE TO EMULATE BIOTECHS

He noted that instead of each project having to pass through several committees that could stop the program at any time for any reason, each drug candidate has its own leader and board of directors with the goal of keeping it going unless the first set of human data don't justify further investment. Each program's committee includes senior executives from the larger Lilly organization.

"Our CEO sits on a couple of these, I sit on a couple of them, our chief medical officer sits on many of them, and they really function like the board of a biotech company," Skovronsky said. "They make sure we don't do anything that compromises safety or creates enterprise risk, but on the other hand [they are] empowered to help these teams move as quickly as they can and dispense with the bureaucracy that otherwise might arise at a big pharmaceutical company."

Several programs under this model are in the clinic, but they still are early enough in the R&D process that the molecules haven't been publicly disclosed yet.

"We've only been at it for about a year and a half now, but we've had a number of them that have graduated to clinical development, many of them quite recently," Skovronsky said, noting that about 30 programs are being prosecuted under this biotech-like model.

However, there has been some criticism of the strategy, primarily that the scientists involved are not being compensated in the same way as the CEO of a small biopharma company if their programs succeed in the clinic. In such an instance, the start-up might be acquired for millions of dollars, generating a big return for its founding scientists.

As for how Lilly can recreate that type of incentive system to keep its scientists focused on delivering the best result, Skovronsky admitted that "we can't and we don't intend to, but that's not actually what motivates the scientists. They want to make a difference for patients and they want to see their projects progress and get into humans. That's great motivation and our people are engaged, so that turns out not to be an issue."

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Lilly/Loxo Deal Came Together Quickly

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Eli Lilly & Co.'s $8bn acquisition of genetics-based cancer specialist **Loxo Oncology Inc.** happened quickly and without any other bidders involved, according to filings with the Securities & Exchange Commission outlining how the deal materialized.

Lilly raised its offer for Loxo just once from $230 per share to $235 per share before it was accepted by Loxo's board of directors, which opted not to reach out to third parties. The deal closed in just a matter of days over the Christmas holiday from a first offer Dec. 20 to a signed merger agreement Jan. 5.

Lilly and Loxo announced the acquisition on the opening day of the J.P. Morgan Healthcare Conference in San Francisco Jan. 7. *(Also see "Lift-Off For Lilly In Cancer Genetics With Loxo Buy" - Scrip, 7 Jan, 2019.)* The news, coming on the heels of a $74bn merger agreement between **Bristol-Myers Squibb Co.** and **Celgene Corp.**, set a positive tone for the pharmaceutical industry's big business meeting of the year, with investors hoping more deals will follow in 2019. *(Also see "J.P. Morgan 2019: Industry Throws A Bonanza, With An Elephant In The Room " - Scrip, 9 Jan, 2019.)*

The filing documents that Lilly sought to announce the acquisition at J.P. Morgan and encouraged Loxo to fit the timeline.

Notably, the deal wasn't competitive, although Loxo said it had reached out to as many as 15 biopharma companies to discuss a potential licensing deal for its second drug candidate LOXO-292 beginning in April 2018. That is the drug Loxo views as its most valuable asset, the filing says, even though it already has one drug, *Vitrakvi* (larotrectinib), on the market.

Vitrakvi was approved by FDA in November for the treatment of patients with neurotrophic receptor tyrosine kinase (NTRK) gene fusion-positive tumors. *(Also see "FDA Nod For Loxo/Bayer Tissue Agnostic Drug Marks Paradigm Shift In Cancer " - Scrip, 27 Nov, 2018.)* Vitrakvi is partnered with **Bayer** under a 2017 deal that gave Loxo $400m upfront. *(Also see "Loxo's Tissue-Agnostic Approach Brings $400m Upfront From Bayer" - Scrip, 14 Nov, 2017.)*

Loxo has gotten a lot of interest for developing cancer drugs based on genetic biomarkers rather than on the site of tumor origin, but the commercial potential of the drugs is uncertain, given the limited patient populations and requirements for testing.

Loxo CEO Joshua Bilenker first met with Lilly Senior VP-Oncology R&D Levi Garraway in April at the 2018 American Association for Cancer Research (AACR) annual meeting in Chicago, according to the filing. After releasing positive interim data from a Phase I study testing '292 in patients with RET fusion-positive tumors at the American Society of Clinical Oncology (ASCO) 2018 meeting, the company held more serious partnering discussions with five biopharma companies. But it wasn't until Dec. 10 when Loxo met again with Garraway in Stamford, Conn. that acquisition talks developed. The original offer of $230 per share came Dec. 20 after a meeting involving Garraway, Lilly's Head of Business Development Darren Carroll, Chief Financial Officer Joshua Smiley, Chief Scientific Officer Daniel Skovronsky and President-Lilly Oncology Anne White.

However, Loxo's board rejected the offer Dec. 21 as inadequate and opened the door for Lilly to conduct more due diligence if it would consider a higher offer. Loxo said it also discussed contacting third parties about making an acquisition proposal but decided not to until Lilly confirmed or increased its proposal, according to the filings.

A due diligence review and discussions continued over the holidays, with Lilly raising its offer for Loxo to $235 per share Dec. 30, representing a 75% premium to Loxo's closing share price on Dec. 28. In a telephone call with Bilenker, Lilly CEO David Ricks said the big pharma would not increase its offer further. Later that day, Loxo agreed to move forward with the merger.

The SEC filing also details Loxo's long-term financial projections, from revenue of $37m in 2020 to $1.93bn in 2033.

Now it will fall to Lilly to see if it can reach those targets and maximize Loxo's innovative cancer research more broadly.

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Loxo Links And Colorectal Cancer Data Put Array In M&A Spotlight

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The chances of **Array Biopharma Inc.** becoming the next M&A target for big pharma may have increased with more positive data from a late-stage trial of a triplet combination of its BRAF inhibitor *Braftovi* (encorafenib), MEK inhibitor *Mektovi* (binimetinib) and **Eli Lilly & Co./Merck KGAA**'s anti-EGFR antibody *Erbitux* (cetuximab) for colorectal cancer.

The Colorado-based company has announced updated safety and efficacy results, including mature overall survival (OS), from the safety lead-in of the Phase III BEACON CRC trial evaluating the combo in patients with BRAFV600E-mutant metastatic colorectal cancer (mCRC). The results, which will be presented at the ASCO 2019 Gastrointestinal Cancers Symposium in San Francisco on Jan. 19, showed that mature median OS was 15.3 months for patients treated with the triplet.

That length of OS "is unprecedented in this patient population and, for context, represents a substantial improvement compared to the observed historical published benchmarks of approximately four to six months for median OS with current standards of care in patients with BRAF-mutant mCRC," according to Axel Grothey of the West Cancer Center in Memphis and BEACON CRC lead investigator. He added in a statement that the updated data "further underscore the potential of this triplet for patients with BRAF-mutant mCRC who are in desperate need of effective new treatment options."

Array at head of potential M&A target pack

Updated median progression-free survival (of eight months) and updated confirmed overall response rate (48%) for patients treated with the triplet in the safety lead-in remained the same as previously reported. The combo was generally well tolerated with no unexpected toxicities and Array noted that the rate of grade 3 or 4 skin toxicities continued to be lower than generally observed with Erbitux in mCRC.

On the basis of these results, the randomized portion of the BEACON CRC trial was initiated, evaluating patients with BRAF V600E-mutant metastatic CRC whose disease has progressed after one or two prior regimens in the metastatic setting in one of three arms: triplet therapy, doublet therapy with Braftovi plus Erbitux, and investigator's choice of either irinotecan/Erbitux or FOLFIRI/Erbitux. The study is expected to be completed this summer and on a conference call, Grothey said that if the results were consistent with the safety lead-in data, he was confident about saying that the triplet would potentially set a new standard of care in the second or third-line setting.

Following consultations with the US FDA and the European Medicines Agency, Array chief medical officer Victor Sandor noted that the firm had initiated an amendment to the BEACON CRC protocol to allow for an interim analysis based primarily on confirmed ORR and durability of response endpoints, "which we believe could support an accelerated approval with

positive results." Array anticipates top-line results from the interim analysis in the next few months.

Array has already made its first steps into the commercial word after getting US approval in June last year for a combination of Braftovi and Mektovi to treat patients with unresectable or metastatic melanoma with either a BRAFV600E or BRAFV600K mutation, as determined by an FDA-approved diagnostic test. Third-quarter sales came in at $14m, which was deemed by analysts to be impressive given that the combo only became available in July, and the combo has a market share of around 10%.

THE LOXO LINK

Array has cropped up in M&A rumors since observers started to look at possible takeover targets in the precision medicine field following Lilly's announcement earlier this month that it intended to acquire **Loxo Oncology Inc.** for $8bn, representing a 68% premium. *(Also see "Lift-Off For Lilly In Cancer Genetics With Loxo Buy" - Scrip, 7 Jan, 2019.)*

That deal in itself is of great interest to Array in terms of royalties, given that it actually discovered *Vitrakvi* (larotrectinib), the Loxo tropomyosin receptor kinase inhibitor partnered with **Bayer** which got the green light in November from the FDA for the treatment of both adults and children with solid tumors that have a neurotrophic receptor tyrosine kinase (NTRK) gene fusion. It also discovered LOXO-292, a first-in-class oral drug, which is in Phase III for cancers including lung and thyroid that harbor abnormalities in the rearranged during transfection (RET) kinase and was singled out by Lilly as "the most substantial single component of the deal" with Loxo.

Array, which licensed back rights to Braftovi and Mektovi from **Novartis AG** in 2015 after the latter acquired the BRAF inhibitor *Tafinlar* (dabrafenib) and MEK inhibitor *Mekinist* (trametinib) from **GlaxoSmithKline PLC**, has partnered the doublet with **Pierre Fabre Group** for Europe, Asia and Latin America and with **Ono Pharmaceutical Co. Ltd.** in Japan and South Korea. It is also in line for royalties from **AstraZeneca PLC**'s selumetinib, a MEK inhibitor which is due to be filed in the US in the second half of 2019 for thyroid cancer, and **Roche**'s late-stage AKT inhibitor ipatasertib for triple-negative breast cancer.

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Takeda's Investments In Data Science Seek Improved Trial Outcomes, R&D Efficiency

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Takeda Pharmaceutical Co. Ltd. President of Research and Development Andrew Plump's teams will be focused on the integration of **Shire PLC**'s drug candidates into the Japanese pharma's R&D organization over the coming months, and the company's ongoing investments in artificial intelligence, machine learning and digital health may help ensure that the combined pipeline's programs are developed efficiently.

Plump insisted in an interview during the J.P. Morgan Healthcare Conference, conducted a day after Takeda closed its $61bn Shire purchase, that much of the work to rationalize Shire's R&D pipeline in the context of Takeda's strategic priorities has taken place during the past few years as the acquirer has trimmed its R&D organization. At almost the same time, Takeda launched an internal Data Sciences Institute to seek out data-based, practical solutions for improving clinical trial outcomes and R&D efficiency for its remaining pipeline.

Plump has said during the past few months that Takeda's ongoing efforts to streamline its R&D organization, while still growing its pipeline via external collaborations, has helped prepare the company to take on Shire's pipeline programs.

That doesn't mean that all Shire assets will remain Takeda's priorities; Plump told *Scrip* at J.P. Morgan that decisions to discontinue development of any programs will take place within the next six months. Whatever is left, however, could benefit from Takeda's investments in data science.

"Three years ago, or three-and-a-half years ago, we set up a group called the Data Sciences Institute … [with] more traditional quantitative sciences like biostatistics on one end expanding all the way into what we consider to be more cutting-edge data informatics and digital sciences – wearables, machine learning and AI capabilities, etc.," Plump said.

He noted that the group is a great tool for talent development and talent attraction as both traditional biostatisticians and AI or digital specialists come up with ideas on their own and in collaboration across disciplines to improve the way clinical trials are run.

"I think there's still so much we can be doing with the more traditional sciences; we're looking at trials in different ways, using adaptive designs of trials, Bayesian designs," Plump said. "Those can help hugely and that's not using new digital technology, that's just applying the kinds of things we already know. That helps with the cultural change in the organization, getting people to feel comfortable working differently."

Some of Takeda's more "pie in the sky" digital initiatives include real-time data capture in clinical trials through a system called "Platypus."

"It allows us in a clinical trial to bring quality-controlled data into the cloud in real time in a way that maintains the integrity of the trial; our clinical trial monitors and statisticians can look at that data in real time. What that allows you to do – it's almost limitless now in how you can track a trial, but in a way that doesn't confound results," Plump said.

MUNDANE, PRACTICAL SHIFTS COULD BRING TRANSFORMATIVE RESULTS

He used clinical trials to test depression drugs as an example of where data science could improve results, because the endpoints are variable and subjective, asking the patients and the treating

physicians to fill out forms rating their depression on a scale of 1-10. A patient's form and his or her doctor's assessment generally should line up, but if there are a lot of discrepancies between the two, then the trial may have problems.

"It could mean the physician's not good, the site's not good or the patients are fakers – who knows what it is? – but we can now, in real time, quality control sites that way," Plump explained. "Rather than having those data become part of our dataset that we evaluate against, therefore permanently attached to that trial and destroying the credibility of the trial, we can go in and institute proactive measures right at the beginning."

If such measures could ensure that depression drug trials are positive 80%-90% of the time instead of 50% of the time, that "transforms the cost structure of drug development and the speed of drug development. So, even though it's mundane and practical, it can be transformative," he said.

Platypus also gives Takeda the ability to aggregate data across trials and look at predictive modeling to find safety and efficacy trends that can help the company better understand a drug candidate and its potential indications across multiple settings.

The broad goal, Chugai says, is to enable earlier detection and treatment of any treatment-related issues to improve overall health outcomes.

"Another area that I think is fascinating and will be quite interesting is the digital wearable side, particularly in [the central nervous system (CNS)] where our measures are so crude, and I think we're going to find new ways of studying phenotypes in patients, and I don't think that that's far out. I think that's three-to-five years out," Plump said.

"Then, the last area is moving away from clinical trials and using real-world evidence to help to support new claims on our therapies – safety claims and I think efficacy claims, eventually," he added.

The US FDA is working on a framework for how to allow real-world evidence data to support applications for drug-labeling claims. *(Also see "Real-World Evidence: US FDA Framework Emphasizes Data Fitness And Study Quality" - Pink Sheet, 9 Dec, 2018.)*

"As with everything, there's a lot of hype, but what we're trying to do is separate the wheat from the chaff, and what we're trying to do is do it thoughtfully and not pretend that overnight this is going to change everything," Plump said.

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United Neuroscience To Move Forward Alzheimer's Vaccine After Promising Phase IIa

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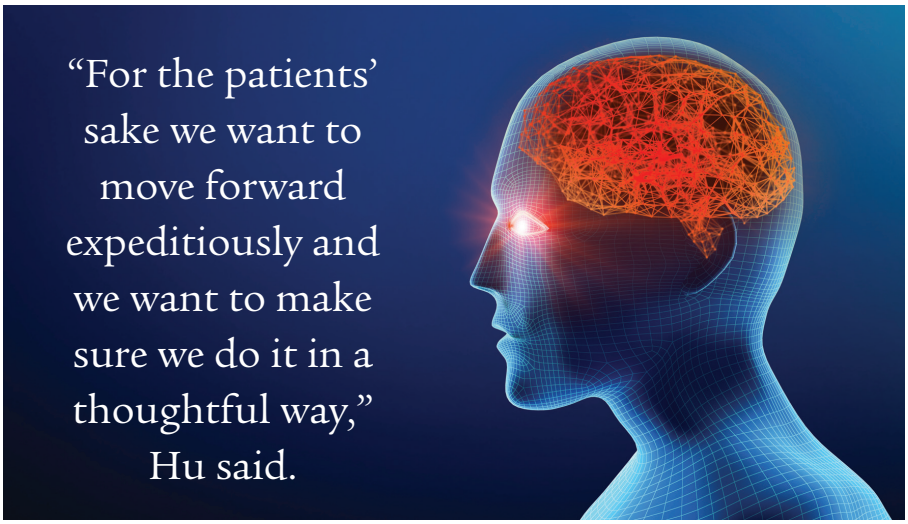

Private, Dublin-based biotech **United Neuroscience** says it plans to rapidly advance its active Alzheimer's vaccine immunotherapy UB-311 after reporting positive top-line results from a Phase IIa study of 42 patients on Jan. 16.

The company's lead candidate UB-311 is a novel synthetic peptide that targets beta amyloid in Alzheimer's disease, with the goal of preventing and treating plaque build-up. The Phase IIa double-blind, placebo-controlled study evaluated the safety and immunogenicity of prolonged dosing over 18 months with two different dosing regimens of UB-311 — one cohort was dosed every three months, one every six months and a third got placebo.

Execs have described the approach as being similar to flu shots, with antibody levels raised over a period of months, with lasting effects that are followed-up with a booster. The company reported Jan. 16 that the vaccine met the primary aims of safety and immunogenicity, with a 96% response rate, supporting previously reported Phase I data.

"What we found and what we are encouraged by is that we saw reproducible immunogenicity with high response rates across the board," CEO Mei Mei Hu said in an interview.

The vaccine was also safe and well-tolerated, she noted.

Results also suggest activity on secondary endpoints evaluated in the study, including amyloid PET burden, Clinical Dementia Rating-Sum of Boxes (CDR-SB), Alzheimer's Disease Cooperative Study-Activities of Daily Living (ADCS-ADL), Alzheimer's Disease Assessment Scale-Cognitive subscale (ADAS-Cog) and the Mini-Mental State Exam (MMSE).

However, while the company said the results pointed it the right direction, the study was not inpowered to show statistically significant improvements on these measures.

The data will be presented at upcoming medical meetings, including the International Conference on Alzheimer's and Parkinson's Diseases, March 26-31 in Lisbon, and published in peer-reviewed journals, the company said.

United Neuroscience noted in a statement that "the early results suggest a clinical response and support the continued and rapid development of UB-311."

Hu said that the company is evaluating a number of options.

"For the patients' sake we want to move forward expeditiously and we want to make sure we do it in a thoughtful way," Hu said.

The company is now moving participants into a long-term extension study. *Biomedtracker* analysts saw the data as positive, though early.

"Although this small Phase IIa study was not designed to demonstrate statistical significance, the 96% response rate and directionally positive results seen in the secondary endpoints measuring cognitive and functional outcomes, as well as clearance of underlying disease pathology are encouraging," Biomedtracker commented on the news.

Demonstrating safety over 18 months is critically important in light of adverse event problems with prior active vaccine candidates for Alzheimer's disease, the analysts added.

Elan Pharma (S.E.A.) Ltd. and **Wyeth**'s past efforts in developing the vaccine ANI1792 for reducing beta amyloid were derailed due to safety issues related to cases of encephalitis in clinical studies and the drug was dropped in 2002. Hu noted that it is reassuring that encephalitis was not seen in the Phase IIa study of UB-311. "It's a very clean profile," she said. Beta amyloid has long been the central focus of drug development for Alzheimer's, but efforts so far have failed as clinical trials advanced.

Anti-beta amyloid antibody failures include **Pfizer Inc./Johnson & Johnson**'s bapineuzumab and **Eli Lilly & Co.**'s solanezumab. . Three BACE inhibitors failed in 2018 – J&J's's atabecestat, Lilly/**AstraZeneca PLC**'s lanabecestat and **Merck & Co. Inc.**'s verubecestat.

Biogen Inc. reported mixed mid-stage results for its anti-amyloid antibody BAN2401, but is continuing development while also pursuing development of a range of other mechanisms.

Hu acknowledges that there have been a lot of failures in the Alzheimer's space, but that the company views those as opportunities for everybody else to learn.

In addition to supporting further development of the UB-311 vaccine, United Neuroscience sees the latest data release as supportive of its *Endobody* technology platform in other indications.

The company is focused on developing vaccines that it says will train the body to work against proteins made in the body, which the immune system normally resists attacking because they are defined as self.

United Neuroscience's UB-312, which targets alpha-synuclein in the brain, is nearing Phase I for Parkinson's disease and multiple system atrophy, and the company has a tau-targeted candidate in preclinical development for Alzheimer's disease and chronic traumatic encephalopathy.

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Novartis's Data-Centric R&D Strategy Adds Pact With UK-based Big Data Institute

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Building on its aim to become a more data-centric, digitally enabled innovator, Switzerland's **Novartis AG** has allied itself with Oxford, UK-based artificial intelligence specialist the Big Data Institute (BDI) to improve its drug development by making it more efficient and more targeted.

By using artificial intelligence and advanced analytics, the duo expect to transform how ultra large and multiple datasets are analyzed, combined and interpreted and to identify early predictors of patient responses to treatments for inflammatory diseases, such as multiple sclerosis and psoriasis.

"This has the potential to transform how we design and conduct our clinical development programs of the future," said Novartis drug development chief John Tsai

> "John Tsai, Novartis's head of global drug development and chief medical officer, said "this has the potential to transform how we design and conduct our clinical development programs of the future."

FLAGSHIP PROGRAMS

The alliance will make use of anonymized data from around 5 million patients from the UK and international partner organisations, together with anonymized data captured from relevant Novartis clinical trials.

Announcing their five-year partnership on Jan. 18, Novartis and BDI said it promised "to lead to the ability to predict how patients will respond to existing and new medicines" by identifying patterns in data, often across multiple data sources and types such as imaging, genomics, clinical and biological. No financial details were disclosed.

They will focus initially on two flagship programs within Novartis's global drug development organization.

Gil McVean, director at the University of Oxford's Big Data Institute, said "one focus is on multiple sclerosis where we're particularly using neuro-imaging data combined with information from clinical trials from the drug that Novartis has developed.

"The other is around a cluster of disorders where there's a common target which seems to be hugely effective in treatment but where there is also lots of uncertainty about the types of disease, which sub-types of disease, or about variations of response from individuals," McVean said in a video clip posted on the BDI website. He did not elaborate.

R&D PRIORITIES

The alliance also allows for knowledge exchange, and access to a broader network of scientific talent across the two organizations.

The R&D partnership reflects priorities outlined by Vas Narasimhan when he took over as Novartis CEO in February 2018 and declared a strategy of investing in differential technologies to deliver more breakthrough innovation and "pivoting to become a data-centric, digitally enabled organization." *(Also see "New Dawn At Novartis As Narasimhan Demands Breakthroughs" - Scrip, 24 Jan, 2018.)*

UK LIFE SCIENCE STRATEGY

That strategy is also mirrored in Novartis's plans to relocate its UK headquarters to a new life sciences and technology cluster in London from its current base in Frimley, Surrey, by January 2020. *(Also see "Novartis UK Moves To London To Seek Its Life Sciences Digital Fortune" - Scrip, 30 Nov, 2018.)*

"This partnership with the BDI is aligned with the UK's Life Sciences Industrial Strategy and offers the opportunity to expand our understanding and capabilities in data science at scale," said Mark Toms, chief scientific officer at Novartis UK. *(Also see "UK Industrial Strategy Offers 'Substantial' Life Science Investments Through New Sector Deal" - , 27 Nov, 2017.)*

"As a leading medicines company driven by data and digital, Novartis expects the collaboration with the BDI to enhance its capabilities in data science and analytics," Toms said.

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Verona Investors Gasp As Lead Asset Misses Main Endpoint In COPD Trial

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Verona Pharma PLC's newly-named *ensifentrine* (formerly RPL554) showed add-on benefit in maximally bronchodilated COPD patients in a three-day Phase II trial - but the fact the first-in-class, inhaled, dual inhibitor of phosphodiesterase 3 and 4 missed its primary endpoint caused investors to sell shares in the UK-listed biotech.

Verona on Jan. 14 released top-line results from the brief study evaluating the effect of two different doses - 1.5 mg and 6.0 mg, twice daily - of nebulized ensifentrine (RPL554) when used on top of **Boehringer Ingelheim**'s inhaled long-acting muscarinic antagonist/long-acting beta2 agonist *Stiolto Respimat* (tiotropium/olodaterol).

The trial targeted patients whose lung function is not sufficiently improved by LABA/LAMA or ICS/LABA/LAMA therapy, a patient group with few remaining treatment options.

Patients in the study, conducted at sites in the US and in the UK, already receiving inhaled corticosteroid (ICS) therapy were allowed to continue to receive a stable dose of ICS throughout the study, thus providing additional data on what the clinical stage company described as "triple therapy" use.

After a 7- to 14-day washout period in advance of dosing and between study arms, patients received three days of treatment with each of two dose strengths (1.5 mg or 6.0 mg) of nebulized ensifentrine or placebo twice daily.

MISSED PRIMARY ENDPOINT

The primary endpoint of peak forced expiratory volume in one second (FEV1) after morning dose on day three of treatment was not met with statistical significance. Verona noted, however, that the ensifentrine 1.5 mg morning dose improved peak FEV1 by 46 milliliters (mL), compared to placebo.

Importantly, Verona said, peak FEV1 after evening dose on day three showed "statistically significant" improvement compared to placebo with both doses, with ensifentrine 1.5 mg showing a 130 mL improvement and ensifentrine 6.0 mg showing an 81 mL improvement.

PLUS POSITIVE 'SPIN'

"This is just a three-day study, but we saw considerable effect on FEV1 and residual volume and we believe this will translate into

longer treatment," Jan-Anders Karlsson, CEO of Verona Pharma, told an analyst call in connection with the trial data. "Also, the anti-inflammatory effect produced a large improvement in symptoms, which is what these patients are looking for," he said.

Verona believes the three-day short study with nebulized ensifentrine provides clarity on its future development.

> "Despite the tone of the press release and conference call, these data are largely negative."
> - Datamonitor Healthcare analyst Chris Mulligan

"We are very pleased to have seen such an effect both in the morning by adding to what we previously thought was maximum bronchodilation, but there clearly is opportunity to improve on that; we had an even larger effect with the evening dose and based both by FEV1 and residual volume, this should give lasting effect throughout the night," the CEO told the analyst call.

"Based on these data we believe that the large additional effect on lung function, both FEV1 and residual volume that was shown in this short study, will translate into significant symptom improvement in these patients when they are treated over longer periods of time. We believe that ensifentrine will have a truly meaningful impact on these patients with severe symptoms and few other treatment options," Karlsson said.

"We believe this is a very attractive commercial opportunity, especially for a first-in-class nebulized treatment in the US," he added.

LEAVE ANALYSTS MIXED

Some analysts took a sanguine view about the missed primary endpoint. Jefferies' Peter Welford said in a note to investors that "whilst the lack of statistical significance could dominate the headlines, we believe the incremental +46mL FEV1 benefit with 1.5mg morning dose of ensifentrine (RPL554) on top of double, or even triple, standard of care is promising."

"We understand that the FEV1 magnitude of benefit conferred by LAMA/LABA therapy alone was impressive. This likely made showing additional bronchodilatory benefit challenging, in our view, so the fact ensifentrine did further boost FEV1, whilst also improving residual volume (RV) in a small 3-day trial is encouraging and is supportive of its novel mechanism," Welford concluded.

But *Datamonitor Healthcare* analyst Chris Mulligan was not very impressed by the three-day trial, describing its design as "unorthodox."

He noted that while investigators were keen to highlight the improvement in FEV1 and residual volume seen in the 1.5 mg dosing group, a key point is that the trial missed its primary endpoint of improvement in FEV1 after the morning dose on day 3 due to a lack of statistical significance.

"In addition to missing the formal endpoint, there were a number of issues with the trial design and the data presented that were not adequately explained," he said. "Most significantly, the trial showed a negative dose response with FEV1 and residual volume data for the 6 mg group being similar to placebo at most time points, and less than that seen for the 1.5 mg group."

The lack of a robust dose response also cast doubt over the reproducibility of the data and thus the success of any subsequent trials, Mulligan said.

"The trial was unorthodox in that it was a 3-day trial with lots of tightly packed time points. I think the issue is that the investigators spoke about the evening and morning time points as if they are comparable, but they are not," Mulligan told *Scrip*.

While a greater improvement over placebo was seen at the evening time point versus the morning, variation in the dosing and sampling means that the timepoints are not strictly comparable, Mulligan said.

"Firstly, patients took a once daily dose of their LABA/LAMA medication in the morning and a twice daily dose of RPL554, once in the morning and once in the evening. This means that the post dose measurement in the evening was approximately 12 hours post the last LABA/LAMA dose."

"Secondly, the morning measurements were taken 1.5 hours after dosing and the evening measurement were taken 0.25 hours after dosing. Both these factors mean that the response observed in the evening measurement is likely to be exaggerated."

"Despite the tone of the press release and conference call, these data are largely negative," Mulligan concluded.

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Merck's Keytruda Shows Utility In Subset Of Esophageal Cancer

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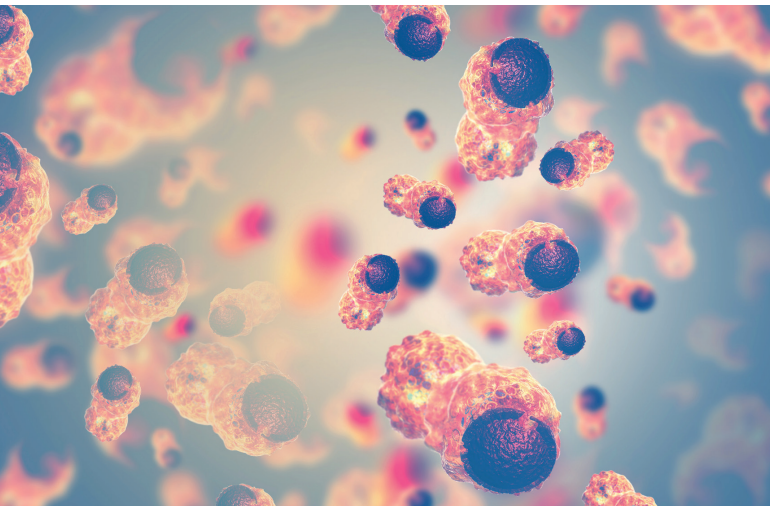
Merck & Co. Inc. plans to seek supplemental approval for its anti-PD-1 therapy *Keytruda* in second-line esophageal cancer based on successful data from a Phase III study testing pembrolizumab monotherapy versus physician's choice of chemotherapy, after the trial showed statistical significance in improving overall survival in patients whose tumors express PD-L1.

The trial was designed to be deemed successful if it proved any of three primary hypotheses pertaining to overall survival compared to control. While the trial reached statistical significance in the PD-L1-positive patients, statistical significance was not achieved in patients with squamous cell carcinoma (SCC) or adenocarcinoma who progressed after standard therapy or in

the overall intent-to-treat population. Keytruda did show a positive numerical trend for both of those hypotheses, Merck Head of Global Clinical Development Roy Baynes told *Scrip*, narrowly missing statistical significance in the SCC/adenocarcinoma patients.

[Editor's Note: This story has been updated to correct an original report that the trial failed to meet its primary endpoint for overall survival. Proving any of the study's three primary hypotheses sufficed as a successful trial.]



Partial data from the open-label KEYNOTE-181 study was released on Jan. 14, while a fuller dataset will be presented at the 2019 Gastrointestinal Cancers Symposium on Jan. 17. KEYNOTE-181 is just one of several studies Merck has initiated investigating Keytruda in the gastrointestinal setting, including the ongoing KEYNOTE-590 of Keytruda plus chemotherapy in first-line esophageal cancer.

Merck cited seven ongoing studies in the GI setting at the American Society of Clinical Oncology conference in 2017. Detailing its overall strategy for the drug, Merck cited a three-wave strategy, with gastric cancer listed among the second-wave indications for Keytruda and esophageal as one of 10 possible third-wave opportunities.

KEYNOTE-181 enrolled 628 patients at a 1:1 ratio to either Keytruda or a physician's choice of paclitaxel, docetaxel or irinotecan chemotherapy in patients with advanced or metastatic esophageal cancer or esophagogastric junction carcinoma whose disease had progressed despite prior therapy. In 222 patients whose tumors had a PD-L1 combined positive score (CPS) greater than or equal to 10, patients treated with Keytruda showed a 31% reduction in risk of death compared to the control group patients. Merck noted that this is the first time an anti-PD-1 agent has demonstrated a survival benefit in second-line esophageal cancer.

The median overall survival of patients receiving Keytruda in the PD-L1-positive patients was 9.3 months, compared to a median OS of 6.7 months in patients receiving chemotherapy. Merck added that the 12-month survival rate in these patients was 43% for patients getting Keytruda, versus 20% for the control group.

In an analysis of the data, *Biomedtracker* said the higher OS combined with Keytruda's superior safety profile compared to chemotherapy supports approval "as a new second-line standard of care" in esophageal cancer patients who test positive for PD-L1. Biomedtracker gives Keytruda a 38% likelihood of approval in esophageal cancer, unchanged on the latest data, three percentage points above average for a Phase III esophageal cancer candidate.

In a Jan. 15 note, Morgan Stanley analyst David Risinger noted the positive data but did not adjust his sales projections for Keytruda, as the US ramp-up in lung cancer will remain the product's primary revenue driver. Morgan Stanley estimates that Keytruda will post sales of $7.1bn for full-year 2018, rising to $9.9bn in 2019 (about 1% higher than consensus estimates) and continue growing to a peak of $15.6bn in 2023.

STATISTICAL SIGNIFICANCE MISSED ON OTHER PRIMARY HYPOTHESES

Merck also reported that a histologically selected group of 401 patients in KEYNOTE-181 with squamous cell carcinoma or adenocarcinoma showed a clinically meaningful improvement in median OS of 8.2 months for Keytruda patients versus 7.1 months for control, but that this finding did not meet statistical significance.

Meanwhile, the overall intent-to-treat population showed a directionally favorable effect in OS, the company said, but with OS of 7.1 months in both the treatment and control arms, these data also did not meet statistical significance.

Secondary endpoints of progression-free survival and objective response rate were not assessed. Merck said the study will be submitted to the US FDA and other regulatory agencies for review.

Keytruda's safety in KEYNOTE-181 was consistent with that seen in previous trials of the drug, Merck noted, with a 64.3% treatment-related adverse event rate for patients getting Keytruda and an 86.1% rate for control arm patients.

During the company's briefing at the J.P. Morgan Healthcare Conference on Jan. 8., Merck Research Laboratories President Roger Perlmutter cited both esophageal and non-muscle invasive bladder cancer as two settings where Keytruda data were upcoming. Overall, Merck said it is testing Keytruda in 65 studies involving more than 9,000 patients – including those with esophageal and gastric cancer and hepatocellular carcinoma.

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J&J's Erleada Gives Chase To Xtandi For Non-Metastatic Prostate Cancer With Approval In Europe

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Astellas Pharma Inc. and **Pfizer Inc.**'s *Xtandi's* grace period being the only treatment for men with non-metastatic castration-resistant prostate cancer (nmCRPC) in the EU is shortly to come to an end after just three months with the approval of **Johnson & Johnson**'s subsidiary **Janssen Pharmaceutical Cos.**'s *Erleada* (apalutamide) in the same indication, for men who are at high risk of developing metastatic disease.

Janssen told *Scrip* that the company was "working with reimbursement authorities in local markets to ensure availability as soon as possible", while the price of apalutamide, an androgen receptor antagonist, "will be decided at a national level following discussions with local reimbursement bodies".

Erleada received FDA approval for nmCRPC in February 2018, followed shortly after by approvals in Canada, Australia, Argentina and Brazil. In the US, its monthly price is around $11,000 per month, which is comparable to Xtandi.

In Europe, Xtandi (enzalutamide) has been approved in the EU for prostate cancer since 2013, and was additionally approved in the nmCRPC indication in October 2018. But this will be Erleada's first foray into the EU market, and its lack of first-mover advantage leave analysts lukewarm over its prospects.

"Xtandi's long-standing presence in the market and physician familiarity will definitely give it a major commercial advantage over Erleada," *Datamonitor Healthcare* analyst Hardik Patel told *Scrip*.

Erleada is banking on its clinical edge. Trial results show the Janssen product may have a "slight advantage in efficacy in this particular setting", Patel said. In the Phase III SPARTAN trial, treatment with Erleada led to a 24.3-month improvement in median metastasis-free survival (MFS) over placebo. In comparison, in the Phase III PROSPER trial, treatment with Xtandi led to a 21.9-month improvement in median MFS over placebo.

Datamonitor Healthcare forecasts Xtandi to make $138m in the nmCRPR indication in the five major EU markets in 2019, falling to $100m in Europe by 2026. Comparatively, Erleada is forecast to make just over half this, $55m in 2026.

These figures take into account off-label use of Xtandi in the nmCRPC setting, which had a significant amount of sales in the indication before approval. These figures also consider the potential launch of another androgen receptor modulator, **Bayer AG**'s darolutamide in nmCRPC. "The estimated launch of both products for the same setting in a similar timeframe definitely obstructs them from garnering higher uptake individually," Patel told *Scrip*.

Data from the ARAMIS Phase III study showed darolutamide significantly extended metastasis-free survival (MFS) compared with placebo, the primary endpoint. The drug candidate has been given fast-track designation by the FDA. A second Phase III study with darolutamide, ARASENS, in metastatic hormone-sensitive prostate cancer is underway. *(Also see "Positive Phase III For Darolutamide In Prostate Cancer Could Improve Options For Orion" - Scrip, 24 Oct, 2018.)*

SPARTAN STUDY

Erleada's EC approval is based on data from the pivotal Phase III SPARTAN study, which assessed the efficacy and safety of apalutamide plus androgen deprivation therapy (ADT) versus placebo plus ADT in patients with nmCRPC who had a rapidly rising prostate specific antigen (PSA) level despite receiving continuous ADT.

Findings from the study showed that apalutamide plus ADT, significantly reduced the risk of developing distant metastasis or death (metastasis free survival) by 72%, compared with placebo in combination with ADT. The median MFS was improved by over two years (40.5 months vs. 16.2 months) in patients with nmCRPC whose PSA is rapidly rising.

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Financial Transparency Concerns Over Patient Groups Advising NICE

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The relationship between the pharmaceutical industry and patient groups is again under the spotlight in the UK following research by the *BMJ* which reveals a lack of disclosure concerning the financial interests of charities involved in the assessments of new drugs by NICE.

The study investigated the prevalence of financial interests among patient organizations contributing to health technology assessments at NICE in England and Wales and the extent to which the cost-effectiveness watchdog's disclosure policy ensures that committees that decide whether drugs should be made available on the NHS are aware of these interests. Researchers used a number of sources, including accounts, annual reports and websites of patient groups, as well as payments declared by pharmaceutical companies and Disclosure UK's database.

Some 53 patient organizations contributed to 41 NICE technology appraisals pub-

lished in 2015 and 2016 and of that number, 38 (72%) had accepted funding from the manufacturer of a technology or a competitor product in the same or previous year that they had contributed to the appraisal.

The researchers also examined evidence of pharmaceutical industry funding for each occasion that a patient organization contributed to technology appraisals and found that specific interests were present in almost four out of five occasions, 92 out of 117 cases.

After a review of written and oral declarations of interests, the study's authors found that NICE's decision-making committees were aware of less than a quarter of specific interests (30/144; 21%). For nearly two-thirds of the specific interests not known to committees (71/114; 62%), disclosure by patient organizations was not required by NICE's policy.

In a *BMJ* editorial, Jeremy Taylor chief executive of National Voices (the national coalition of health and care charities in England), wrote that the study contained "some interesting data, a fair analysis and some reasonable recommendations," with the main one being that NICE should review its disclosure policy, but " I'm less sure that it tells us anything really new." He went on to claim that the authors "make a point of telling us that they went in search of a smoking gun. They wanted to see if specific patient organisation interests of which NICE committees were unaware had nevertheless materially affected NICE decisions. They couldn't show such an effect."

Taylor acknowledged that "it would be better for decision making, public trust and organizational reputations if patient groups improved their disclosure of payments from pharmaceutical companies. This is not new. One has to ask why it remains an issue."

He argued that charities in the UK "are robustly regulated and care deeply about their reputations and independence," and added that the patient organization/pharma link is "a niche concern of certain researchers and journalists, and somewhere down the priority list for hard-pressed charities." As the *BMJ* report noted, some patient groups are very small and will have limited capacity, for example to engage with the journal's researchers on detailed questions about their finances, Taylor went on to claim.

In the UK, disclosure of payments to third parties is rigorously governed by the Association of the British Pharmaceutical Industry code but "charities are not subject to a reporting discipline of equivalent bite," Taylor wrote. He also said that in general he was against more regulation for charities, but aligning NICE requirements more closely with those of the Scottish Medicines Consortium or with certain European regulators "might be a good way forward."

He concluded by saying the authors are right to acknowledge the importance of having patient voices at the decision making table in HTA processes, stating that "conflicts of interest are hard to avoid. They should be disclosed and managed… but interests should not be the occasion for delegitimizing and excluding patients and their representatives. No decision about me without me."

Responding to the *BMJ* research, Gill Leng, deputy chief executive and health and social care director at NICE, told *Scrip* in an email that "we aim to maintain a high standard of integrity in the way we conduct our work. Ensuring that organisations and individuals declare potential conflicts of interests, in accordance with our policies is central to how we develop guidance and is essential in maintaining public and professional confidence in our work. This study is an important contribution in making sure that we achieve this aim."

A spokesperson for NICE said that its declarations of interest policy "is based on international best practice, and reflects the fact that we take very seriously the need to reduce potential bias in our decision-making." She stressed to *Scrip* that the agency had already decided to review this policy in the spring "but will give careful consideration to the authors' recommendations in deciding what changes need to be made to our current arrangements."

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All Gifts Out As IFPMA New Code Of Practice Raises Ethical Bar

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In its first revision in seven years, the International Federation of Pharmaceutical Manufacturers and Associations' code of practice has been amended to include a blanket ban on gifts and promotional aids for prescription medicines, and the move from a rules-based approach to one based on values that IFPMA believes will better guide business behaviors and interactions between its members and the healthcare community at large.

"We are placing a global ban on gifts for any company that is a member of IFPMA, and for all those firms that are members of our regional and national associations," said Thomas Cueni, Director General of IFPMA, suggesting that it would help increase shareholder value.

"This new revised Code is more principles-based and seeks to embody a deeper and broader appreciation of business integrity," Cueni said in a forward accompanying the 42-page revised code of practice, downloads of which are on IFPMA's website.

"With the new Code, we are setting the bar higher," Cueni added.

"This new revised Code is more principles-based and seeks to embody a deeper and broader appreciation of business integrity"

UPDATING THE CODE

Initially introduced in 1981, the IFPMA Code of Pharmaceutical Marketing Practices was the first international self-regulation mechanism in the biopharmaceutical industry.

Updated and revised over the decades, the IFPMA Code has offered a rules-based compliance framework for areas such as clinical research, fees for services, and support for continuing medical education.

The last Code revision in 2012 saw its scope extended beyond marketing practices to cover all interactions with healthcare professionals, medical institutions and patient organizations.

The Code's latest revision slaps a global ban of gifts and promotional aids for prescription medicines wherever IFPMA member companies operate, thereby bringing the rest of the world in line with current European and US guidance.

Any exceptions based on the custom of gifts to mark significant national, cultural or religious events have also been now been removed, such as mooncakes given in connection with the Chinese Mid-Autumn Festival, or condolence payments.

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AZ Management Shake-Up Sees CMO Bohen Exit

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The management changes at the top of **AstraZeneca PLC** are continuing apace with highly regarded chief medical officer Sean Bohen being the latest to leave a week after the UK major unveiled a reorganization.

There has been no official statement but a company spokesperson confirmed to *Scrip* that Bohen would be moving on to pastures new. He joined AstraZeneca in September 2015 as CMO and executive vice president of global medicines development from **Genentech Inc.** where he was instrumental in bringing a large number of new medicines through late-stage development, in particular for cancer.

Sean Bohen

There is no specific timescale for Bohen's departure but the spokesperson noted that he would remain as CMO until AstraZeneca completes the transition to the new structure laid out last week by CEO Pascal Soriot. That move will see the formation of four new development and commercial units which are being set up to align the company's R&D and commercial operations more closely.

The change in structure includes the creation of two therapy area-focused R&D units: one for biopharmaceuticals – ie, its cardiovascular, renal & metabolism (CVRM) and respiratory areas – headed up by Mene Pangalos, and another for oncology, which will be led by José Baselga, who recently resigned under controversial circumstances as physician in chief at Memorial Sloan Kettering Cancer Center in New York.

The restructuring has inevitably led to other AstraZeneca executives looking for opportunities elsewhere. Earlier this month, Bahija Jallal, former head of the company's Medimmune unit, announced she was leaving after more than 12 years to take on the role of CEO at **Immunocore Ltd.**, while the chief of global product and portfolio strategy Mark Mallon has taken over as CEO of **Ironwood Pharmaceuticals Inc.** after 24 years of service. *(Also see "Jallal To Lead Immunocore, Building On Partnership She Forged At MedImmune" - Scrip, 4 Jan, 2019.)*

In October, Ludovic Helfgott, AstraZeneca's global head of CVRM announced that he had accepted a role with **Novo Nordisk AS**. He will join the Danish group in April as head of its biopharma business, which comprises Novo's hemophilia and human growth hormone franchises.

This catalog of departures does not appear to reflect any problems at AstraZeneca but rather, as Soriot said last week, "we are entering what we expect will be a period of sustained growth for years to come, which is why we have decided to more closely align our R&D and commercial operations." He added that

the new structure would "support growth and sharpen the focus on our main therapy areas, speeding up decisions and making us more productive."

The future of Soriot himself was the subject of speculation two years ago when he was linked to a possible move to Israeli drugmaker **Teva Pharmaceutical Industries Ltd.**. He said at the time that he had plans to leave and repeated his commitment to AstraZeneca again last week when announcing the reorganization.

If he so desires, Bohen will not struggle to find a job as he has been a key player, along with Pangalos, in helping AstraZeneca stock its late-stage pipeline with drugs that have gained approval and made an impact in their respective markets, notably in oncology. Notable successes under Bohen's watch have been the lung cancer drug *Tagrisso* (osimertinib), the immunotherapy *Imfinzi* (durvalumab) and the PARP inhibitor *Lynparza* (olaparib) and his own focus on oncology will make him an attractive candidate for companies in the industry's hottest area.

Rumors about the possible departure of Bohen began following an investor note from Tim Anderson at Wolfe Research issued at the end of last week stating that he would likely be departing in 2019, coinciding with the structural changes. He noted that that "investors generally like Dr Bohen, and his hiring in 2015 away from Genentech was viewed as a big upgrade for AstraZeneca."

Anderson went on to say in the Jan. 11 note that it was not clear that Bohen's upcoming departure was widely known by investors, "and it probably contributes to some of the recent share price weakness with AstraZeneca, especially as it comes on the heels of two other recent departures (Mallon and Jallal)." As to whether "these departures foretell an R&D crisis at the company, or some sort of imminent bad news," he added "not likely, in our view. However, the optics of having respected leaders leave a company are never good."

The analyst went on to say it appeared that the key driver for the reorganization was to try and speed up product development, saying the current structure was reminiscent of **Roche**'s dual system. The Swiss giant's Pharma Research & Early Development (pRED) operates independently from Genentech Research and Early Development (gRED) and Roche's **Chugai Pharmaceutical Co. Ltd.** R&D arm in Japan.

AstraZeneca's new structure, Anderson wrote, "seeks to do away with this by integrating discovery and development efforts, to make the R&D process more seamless and shorten cycle times."

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Can Vivus Get Away Without Outcomes Study Of Obesity Drug Qsymia?

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Vivus Inc. is discussing results from a retrospective study of claims data for its obesity drug *Qsymia* with the US FDA, in hopes that the results may be incorporated into labeling and "reduce or modify the need for a cardiovascular outcomes study," the company said Jan. 14.

Approved by the FDA in 2012, Qsymia (phentermine/extended release topiramate) is cleared for use with diet and exercise for chronic weight management in adults with a body mass index of 30 kg/m2 or more or 27 kg/m2 or more and at least one weight-related comorbidity, such as hypertension or diabetes.

The limitations of use section of labeling advises that the effect of Qsymia on cardiovascular morbidity and mortality has not been established and that the safety and effectiveness of Qsymia in combination with other products intended for weight loss, including prescription and over the-counter drugs and herbal preparations, have not been established.

A study of medical claims data that the company says supports Qsymia's safety profile in people taking the combination compared with those who were former users will be printed in the February issue of the *Journal of Clinical Endocrinology & Metabolism*; initial results were published online earlier.

Vivus submitted a request in early 2017 for a labeling change to focus on short-term rather than chronic use, but a user date of Nov. 28 for the supplemental filing passed with no action.

"We intend to include these findings in our ongoing discussions with the U.S. Food and Drug Administration related to our requested label modification for Qsymia. The requested modification would allow for the safe and effective short-term use of Qsymia and could potentially reduce or modify the need for a cardiovascular outcomes study," the company said in its Jan. 14 announcement about the results.

In clinical studies, an elevation in heart rate had been detected for patients on the combination compared with patients on placebo, but the company suggested that the beneficial effects on weight, blood pressure, lipids and glycemic measures offset that effect.

The elevation in heart rate raised concerns during a meeting of the FDA's Endocrinologic and Metabolic Drugs Advisory Committee in 2012. However, panelists reviewing the drug were reassured that a post-approval cardiovascular outcomes study would be mandated and gave the drug the go-ahead. A long-term outcomes study to assess the risk for cardiovascular events was one of 10 post-marketing requirements attached to the approval.

Upon approval in 2012, the agency issued a statement advising against the use of the drug in patients who recently had unstable heart disease or stroke and regular monitoring of heart rate. A long-term outcomes study was never started.

NO DEFINITIVE CONCLUSIONS IN RETROSPECTIVE CLAIMS STUDY

The retrospective study examined the records of more than 500,000 patients, comparing risk for major adverse cardiovascular events (MACE) of current users to those who stopped taking the

medication, using records from Truven Health MarketScan Databases, which include commercial and Medicare claims. The study was funded by Vivus and carried out by RTI Health Solutions. Researchers looked at phentermine (PHEN) with topiramate (TPM) as separate components taken together, the PHEN/TPM fixed combination (Qsymia), and PHEN and TPM individually.

They used discharge status and medical billing codes to evaluate the rates of MACE, defined as hospitalization for acute myocardial infarction or stroke or in-hospital cardiovascular-related death, between 2012 and 2015.

"Most patients initiating PHEN/TPM (76%) were fixed PHEN/TPM users. Compared with the unexposed cohort, patients initiating PHEN/TPM were older and more likely to have a recorded history of obesity. In addition, patients initiating PHEN/TPM were more likely than the unexposed cohort to have hypertension, hyperlipidemia, diabetes, and sleep apnea," the article noted.

Researchers reported that the MACE rates among current users of PHEN/TPM, fixed-dose PHEN/TPM, and PHEN were lower than those among unexposed former users, whereas the rate of MACE among current users of TPM was greater than among unexposed former users. There were fewer than 10 events in total for those on phentermine/topiramate or formerly on this regimen, so the results are difficult to interpret.

Phentermine/topiramate was not associated with a higher cardiovascular risk, but because there were so few MACE events during 3,245 person-years of follow-up, it is not possible to "draw a definitive conclusion from the data," the company reported.

However, the agency tends to be fastidious about cardiovascular outcomes trials (CVOTs). Furthermore, Vivus' statement includes a comment from co-author Peter Kowey, Jefferson Medical College in Philadelphia, that "the confidence intervals for this observation were broad, indicating that the data were imprecise and compatible with a considerable range of possible effects."

Investors appear encouraged, however. The company's stock price opened at $3.31 and closed at $4.45 on Jan. 14. On Jan. 15, it closed up by 2.9% at $4.58.

SALES STILL VERY LOW

Vivus' Qsymia has struggled with slow sales from the get-go and the company has long floated the idea of less expensive safety studies as an alternative to an outcomes study. Vivus reported only $9.7m in sales for Qsymia for the third quarter, down from $9.9m in the year-ago period.

When Qsymia was first launched, a number of Wall Street analysts thought the product was going to be worth up to $2.5bn, but obesity drugs have failed to gain traction.

The federal government views obesity as a lifestyle disease and this has influenced reimbursement. Consequently, it's largely a cash pay drug, CEO John Amos explained during a Jan. 9 presentation at the Biotech Showcase, held in San Francisco in parallel with the J.P. Morgan Healthcare Conference. Vivus is selling the drug for about $100 per month, which market research suggests is appropriate for an out-of-pocket expense for obesity, he added.

Cardiovascular outcomes trials are required for all new obesity drugs and diabetes drugs.

Eisai Co. Ltd. and partner **Arena Pharmaceuticals Inc.** reported in August that their obesity drug *Belviq* (lorcaserin HCl), a 5-hydroxytryptamine serotonin 2C receptor agonist that also was approved in 2012, was not associated with a higher risk of cardiovascular events in the CAMELLIA-TIMI 61 CV outcomes study.

Although a randomized, prospective outcomes study was requested for regulatory purposes, usage of the fixed-dose combination of phentermine and topiramate is low and "performance of a randomized study of medications in a post-market setting is difficult, especially for CV event outcomes," Ritchie and colleagues said in the article about the retrospective study.

"With low drug uptake and rare outcomes, a retrospective observational database study is an efficient method to generate information on the safety of fixed-PHEN/TPM in usual clinical practice in a much shorter time than would be possible with a prospective study," the article states.

The FDA has acknowledged that observational studies using databases are effective for gathering safety information in clinical practice in a much shorter time frame, the article notes.

"The present study was also prespecified via protocol and conducted in accordance with both regulatory and international society guidelines for observational database studies," Ritchie and colleagues said.

"It included outcome measures previously validated within claims data. In an era in which regulators are calling for increased use of real-world evidence for regulatory decision-making, the present database analysis has provided timely data on a large number of patients in a manner that is actionable," in the sense of ruling out the doubling of MACE risk for patients on phentermine with topiramate. "Furthermore, the insights gained from the present study were obtained within several months, rather than over several years," the authors said.

The article also notes that while the fixed-dose combination is approved for chronic long-term use, the average duration of use for current users in the study was only 2.1 months, similar to the amount of time phentermine and topiramate are used individually.

"These durations of use were shorter than those in the premarket clinical trials but presumably reflect actual clinical patterns of use and might further decrease any concerns about the risk of CV outcomes," the article says.

In an interview, CEO Amos explained that in the real world patients go through cycles where they use the drug for a period, lose weight and then go off it, believing they are able to maintain a new healthier lifestyle, including good eating habits, but then they may find they need to use a pharmaceutical again.

The efficacy reflected on the label is "pretty tremendous," and the company is trying to identify better ways to utilize the product to help deal with the obesity epidemic, the exec said.

Even though the just-published claims data are not definitive, Vivus believes a long-term outcomes study is not necessary. In addition to studies evaluating use for up to two years showing no harm, the company has been monitoring safety closely through a Risk Evaluation and Mitigation Strategy (REMS) and there has been no safety signal. "This is a safe product – it is not a new chemical entity, it's phentermine and topiramate and both of those products have been available on the market from well before the '90s. There is a body of evidence and body of safety data out there regarding these products," Chief Medical Officer Santosh Varghese told *Scrip*.

Published online 15 January 2019

Novartis R&D Chief Tsai On 2019 Goals, Priorities, BD And Digital Advances

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Novartis AG Head of Global Drug Development John Tsai is in the interesting position of having stepped into the job previously filled by the man who is now the CEO, Vas Narasimhan. But reporting directly to the former head of R&D is an unusual privilege, Tsai said in an interview with *Scrip*, and the two are aligned on a shared mission to move Novartis toward advanced therapy platforms and breakthrough medicines.

Tsai sat down with *Scrip* at the J.P. Morgan Healthcare Conference in San Francisco Jan. 7 and talked about a wide range of topics, from how he came to accept the job while working for **Amgen Inc.** to business development priorities and what it means for Novartis to embrace new digital technologies. He stepped into the role May 1, after having only taken over as chief medical officer at Amgen a year earlier. Tsai previously worked for many years at **Bristol-Myers Squibb Co.**, where he was global head of clinical development for marketed products and global clinical operations.

Making the sudden leap to Novartis wasn't easy, he said, especially since it required moving to Basel, Switzerland after he had just relocated to Southern California. But after meeting with Narasimhan at J.P. Morgan in 2018, he said the two couldn't stop talking and had an aligned vision for drug development.

"One of the visions we're very aligned on and Vas' vision and the vision for the company was around advanced therapy platforms, around embracing data and digital technologies to help us develop drugs and advance drugs," he said. "It's around the cultural change for the organization and giving back to society as well, changing the reputation of the organization."

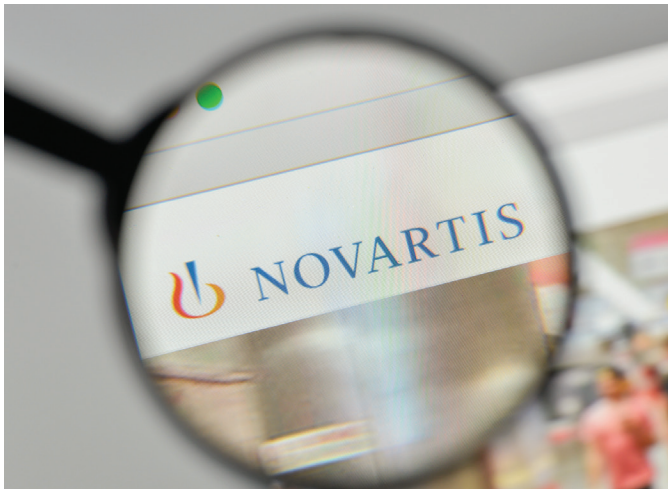
But while those are big overarching themes for the organization, Tsai said he still has the opportunity to direct the execution and operation of those themes within R&D.

Novartis held its first R&D day since the new leadership was put in place in December and outlined 11 near-term launches that could come in the next three years, drug candidates like fevipiprant, an oral treatment for severe asthma, and siponimod for multiple sclerosis. The company also revealed that it has refocused the pipeline, refining it from 430 products to 340.

BUILDING INNOVATIVE PLATFORMS

The big priority, according to Tsai, is pivoting to emerging platforms like gene therapy, targeted protein degradation and silencing RNA, while maintaining a solid late-stage pipeline across seven therapeutic areas.

"We have been very open to say 80% of our product portfolio is in the small molecules or large molecules. That's our core therapeutic areas that we develop in," he said. "But, 20% of that we actually look at what are the new breakthroughs in technology that will allow us to really change the trajectory of improving care for patients. This would be in the cell therapies, the gene therapies, the radio-drug conjugates. These are different from our traditional approaches."



Novartis is investing heavily in all three areas, building up in gene therapy and radiopharmaceuticals through business development, including the $8.7bn acquisition of gene therapy developer **AveXis Inc.** in April and the acquisition of two radiopharmaceutical companies, **Endocyte Inc.** in October for $2.1bn and **Advanced Accelerator Applications SA** for $3.9bn in 2017. *(Also see "Novartis Tunes Into Radiopharmaceuticals With Endocyte Buy" - Scrip, 18 Oct, 2018.)*

In cell therapy, Novartis was a pioneer with the launch of the first chimeric antigen receptor T-cell (CAR-T) therapy *Kymriah* (tisagenlecleucel), but the launch has been slow commercially, partly due to manufacturing issues.

INVESTING IN RADIO-DRUG CONJUGATES

Novartis appears uniquely invested in radiopharmaceuticals – or as Narasimhan coined it during his investor presentation at J.P. Morgan, radio-drug conjugates. The company already has one product on the market, *Lutathera* (lutetium Lu 177 dotatate), gained through AAA and approved for a rare, complex cancer, somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumors (GEP-NETs) – in which a radioactive component destroys the tumor cells.

"Do we think there is an opportunity in radio-drug conjugates? Absolutely. And I think it has turned out to be even better than we originally expected," Tsai said.

The company is exploring radio-drug conjugates in prostate cancer through a late-stage drug candidate acquired with Endocyte, and is also interested in studying the platform in combinations in cancer. "We are looking at how do we combine potentially chemotherapies or other agents with radiotherapy," he said. "I think it is just the beginning."

As for cell therapy, the company remains committed despite early hurdles with the launch of Kymriah, which generated only $20m in the third quarter. The company has eight clinical programs ongoing for Kyrmiah and a CAR-T BCMA candidate in Phase

CONTINUED ON PAGE 23

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

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

PIPELINE WATCH, 11–17 JANUARY 2019

Event Stage	Lead Company/Partner	Drug Name	Indication	Comments	Change To LOA (%)	LOA (%)
Phase III Published Results	Aradigm Corp.	Apulmiq (ciprofloxacin) Inhalation	Bronchiectasis	ORBIT-3,4; The Lancet Respiratory Medicine, Jan. 15, 2019	0	45
Phase III Published Results	Merck & Co., Inc.	Zepatier (elbasvir/grazoprevir)	Hepatitis C	DAHHS-2 (GT1, 4); The Lancet, Jan. 16, 2019	0	100
Phase III Published Results	DNDi/MSF	Liposomal amphotericin B, miltefosine	Leishmaniasis And HIV/AIDS	Encouraging Results In Ethiopia Study	0	100
Phase IIb/III Published Results	GlaxoSmithKline plc	Krintafel (tafenoquine)	Malaria	DETECTIVE (ex-US), GATHER; NEJM, Jan. 17, 2019	0	100
Phase II/III Published Results	Eisai Co.	E0302	Amyotrophic Lateral Sclerosis	Journal of Neurology, Neurosurgery & Psychiatry, Jan. 13, 2019	0	0
Phase II//III Trial Suspension	ASLAN Pharmaceuticals	varlitinib	Gastric Cancer, First-Line	ISO-CC-005; Positive Results	-35	0
Phase III Updated Results	Merck & Co., Inc.	Keytruda (pembrolizumab)	Esophageal Cancer, Second-Line	V203-AD; Positive Responses	4	42
Phase III Updated Results	Array BioPharma/Ono/Pierre Fabre	Braftovi (encorafenib)/ Mektovi (binimetinib)/ Erbitux (cetuximab)	Colorectal Cancer, Metastatic	Add-On To LAMA/ LABA; Mixed Results	2	39
Phase III Trial Initiation	Innovent Biologics/Lilly	sintilimab	Gastric Cancer, First-Line	ORIENT-16 (China); Plus Chemotherapy	-	0
Phase III Trial Announcement	Quantum Genomics Corp.	firibastat	Hypertension, Resistant	A Pivotal Study	0	13
Phase III Top-Line Results	ALK-Abello/Merck & Co	Ragwitek (ragweed allergens)	Allergic Rhinitis, Pediatric	SLIT Tablet, Met Primary Endpoint	0	100

Source: Biomedtracker | Informa, 2019

CONTINUED FROM PAGE 21

I development, as well as a large preclinical initiative. "We acknowledge that cell therapy is not as transparent or straightforward as what was originally thought," Tsai said. But he harkened cell therapy to where monoclonal antibodies were 20 years ago. "We go into it with eyes wide open and are very transparent to say it is a learning process for us, but I think the potential is huge."

In gene therapy, Novartis aims to have seven products in the clinic over the next year, including gene therapies for ophthalmic indications and Rett syndrome. FDA approval of AVXS-101, branded *Zolgensma*, is anticipated in mid-2019 for spinal muscular atrophy. It could represent a big test case for new payment models for what are hoped to be one-time cures for patients.

Tsai said Novartis is focused on building out these platforms and other emerging areas further through business development. "We look at it as opportunities for breakthroughs," he said, pointing to the AveXis acquisition as an example. "Some of them are much smaller than that. The ones that make the big headlines are the ones that are later. We also look early."

Tsai also works closely with Jay Bradner, president of the Novartis Institutes for BioMedical Research (NIBR), the company's drug discovery engine located in Cambridge, Mass., to determine what drugs will move into clinical development.

"The great thing about working with Jay is he knows that I'm agnostic as to whether that comes from an internal source or an external source," Tsai said. "My job is to develop the best pipeline that is available to us and to sustain a company of our size."

DATA AND DIGITAL

Rather than setting a goal of how many projects to move into clinical development, he said the team is focused instead on finding the big breakthroughs and accelerating their development.

"Particularly when you are a company of this size with 500 ongoing clinical trials, you tend to move many of the projects in similar speed, and this is where I think data and digital really comes in and allows us to begin to look at where the opportunities are," he added. The company is hoping investments in digital technology will yield faster and more cost-effective clinical trials.

The company recruited a chief digital officer, Bertrand Bodson, who joined the company in January 2018 to lead a company-wide digital strategy. Novartis has already launched some data initiatives, including a $100m investment to modernize two million patient years of clinical trial data dating back to 2001. The company is also exploring digital advancements for improving the efficiency of clinical trials and the underlying processes required to run clinical trials, like the collection of consent forms and case reports.

"This sound very simple, but what I can tell you is that when you work at various companies they use the same systems year after year after year and these systems are outdated by 10 if not 15 years," Tsai said. Novartis embarked on a $120m effort to upgrade its underlying systems beginning in 2017. Executing on all these fronts will keep Tsai and the R&D team at Novartis busy, but the test of success will be how exciting new technologies and platforms progress into new drugs for patients.

Published online 16 January 2019

APPOINTMENTS

Executive	To Company	New Role	From Company	Previous Role	Effective Date
Christine Moulton Clemson	AMAG Pharmaceuticals Inc	Vice President, Medical Affairs	Sage Therapeutics	Senior Medical Director	15-Jan-19
Richard Christopher	InVivo Therapeutics Corp	Chief Financial Officer and Treasurer	iCAD Inc	Chief Financial Officer	14-Jan-19
James Dillard	Perrigo Company plc	Chief Scientific Officer and Executive Vice President	Altria Group	Senior Vice President, Research, Development and Sciences and Chief Innovation Officer	14-Jan-19
Erin Quirk	Terns Pharmaceuticals Inc	Chief Medical Officer	Gilead Sciences	Vice President, Clinical Research	17-Jan-19
Susannah Cantrell	Tricida Inc	Chief Commercial Officer	Gilead Sciences	Vice President, Head, Global Commercial Strategy and Marketing, Oncology	17-Jan-19
John McDermott	Vascular Therapies Inc	Chief Executive Officer	Endologix	Chief Executive Officer	9-Jan-19
Omar Khwaja	Voyager Therapeutics	Chief Medical Officer	F. Hoffmann-La Roche AG	Global Head, Neuroscience Translational Medicine and Global Head, Rare Diseases	15-Jan-19

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