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Pharma Welcomes UK Incentive Plan To Tackle AMR

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The pharmaceutical industry says it is ready to play its part in meeting the challenge of antimicrobial resistance (AMR) after being buoyed by the UK government's launch of a major proposal that could offer drug makers a new payment model and incentivize more research in the area.

The government has published a 20-year vision and five-year national action plan for how the UK will contribute to containing and controlling AMR by 2040. It includes targets, such as cutting the number of drug-resistant infections by 10% (5,000 infections) by 2025, reducing the use of antibiotics in humans by 15% and preventing at least 15,000 patients from contracting infections as a result of their health care each year by 2024.

The plan is being launched by health secretary Matt Hancock at the World Economic Forum (WEF) in Davos. He claimed that AMR needed to be treated as a global health emergency, saying that "each and every one of us benefits from antibiotics, but we all too easily take them for granted, and I shudder at the thought of a world in which their power is diminished. Antimicrobial resistance is as big a danger to humanity as climate change or warfare. That's why we need an urgent global response."

This is not a new message but industry observers have been enthused by the part of the plan that will see England and Wales' cost-effectiveness watchdog NICE and NHS England explore a new payment model "that pays pharmaceutical companies based on how valuable their medicines are to the NHS, rather than on the quantity of antibiotics sold." The conventional business models that work for most pharmaceuticals have failed to motivate the development of new antibiotics and a WEF report published last year, put together in collaboration with the Wellcome Trust, noted that of a total $40 billion-a-year market for antibiotics, sales of patented antibiotics only constituted about $4.7bn.

Clinical trials of antibiotics are complex and costly and with such meagre returns on offer to date, the majority of big pharma players have exited the space. Now the UK government has explicitly stated its desire to address the market failure in antibiotics and hopes the proposals will incentivize companies to invest in the development of drugs that will treat high priority resistant infections.

The country's department of health noted that the way drugs companies are currently paid depends on the volumes they sell, meaning they have an incentive to sell as many as possible, at the same time as government is trying to reduce antibiotic use. It added that "low returns on investment in development means industry does not innovate enough and as a result, very few of the new drugs that are currently in the pipeline are targeted towards priority infections."

PHARMA 'READY AND WAITING'

There are hopes that this could change and the new plan got the thumbs-up from Mike Thompson, CEO of the Association

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from the editor

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Big ideas usually get an airing at the annual World Economic Forum in Davos, with business and health often among the themes. For Davos to be worth the carbon emitted by its private jetting attendees, the innovative thinking on display must translate into action.

When it comes to antimicrobial resistance, if all we needed was thought leadership, we'd have been home and dry a few years ago. That's why it was encouraging that UK health minister Matt Hancock's intervention in Switzerland included several concrete commitments, as well as a pledge to experiment with purchasing arrangements that de-link the price of antibiotics from the volume sold and to use the health technology assessment agency NICE to assess the value of such products (see cover story). This recognizes that current models mean antibiotic developers are unlikely to recoup their investment. It is promising not least because it could provide a way forward for other countries to follow.

On a different note, Davos also put the spotlight on productivity and work-life balance. Psychologist Adam Grant and economist and historian Rutger Bregman both highlighted evidence that reducing the working week appears to make staff more productive, less stressed and happier. Estate planning firm Perpetual Guardian in New Zealand, which employs around 200 people, has confirmed it will adopt a four-day week permanently after an initial trial. Could it work for your firm? With research foundation Wellcome having confirmed it is considering such a move, this might be a topic for pharma to mull in 2019.

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Clinical Trials In Review: Big Hits And Misses In 2018

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The biopharmaceutical industry lives and dies on the strength of clinical trials, where a hundredth of a point can be the difference between towering success and crumbling defeat.

Looking back at the past year in research and development, many trends held true. Certain areas of immuno-oncology continue to deliver, but expanding beyond the known possibilities is still a challenge. Alzheimer's disease remains outside of reach. But some areas have had resounding success, like acute myeloid leukemia and the first new flu drug in 20 years.

Cholesterol seems to be one field you can never count out. In 2017, **Merck & Co. Inc.** surprised everyone with a successful outcomes trial for its CETP inhibitor anacetrapib in REVEAL – a class that had been long written off. *(Also see "The Year's Clinical Trials In Review: Big Hits In 2017" - Scrip, 28 Dec, 2017.)* Those results may have been too little too late, as Merck has moved on from the program, but **Amarin Corp. PLC**'s successful cardiovascular outcomes trial for its purefied fish oil *Vascepa* might breathe new life into that business.

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To read the rest of this story go to: https://bit.ly/2DF6VcR

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of the British Pharmaceutical Industry. "We have been working closely with the government for the last two years and pharmaceutical companies are ready and waiting to start testing a new model to support antibiotics R&D in 2019."

Thompson added that the UK had "shown international leadership in raising the profile of this global health threat" and the government's plan "reinforces its commitment to finding solutions to the issues which have hampered the development of new medicines for so long."

Steve Bates CEO of the UK BioIndustry Association, said it is "really good" to see the country "taking a first-mover advantage on innovative pricing and reimbursement for AMR. Ensuring these incentives work for innovative small biotech companies and their investors is vital as we continue to see established players divesting from this area."

He added that since the UK market is only 3% of the global drugs market,and this being a worldwide problem, the biggest value of the move will be the country offering its "continued political leadership to inspire other countries to develop reimbursement mechanisms for drug developers in AMR suitable for their own health systems."

One of the companies hoping to benefit is **Destiny Pharma**, whose lead program, XF-73, is in clinical studies for the prevention of costly, post-surgical infections such as meticillin-resistant *Staphylococcus aureus* (MRSA). CEO Neil Clark said the Brighton-based firm "welcomes government recognition of the need for financial support for companies carrying out research and drug development for anti-infectives that address AMR and new financial incentives for pharmaceutical companies that distribute and sell them." *(Also see "Destiny Pharma's XF-73 Being Studied For Diabetic Foot Ulcers, Burns Too " - Scrip, 27 Sep, 2018.)*

Graham Dixon, CEO of **Neem Biotech**, a Welsh firm looking at new approaches to address infection, particularly in wounds and cystic fibrosis, told *Scrip* that "despite the huge global threat of AMR, until recently there has been little incentive for the pharma industry to invest in the innovation needed to combat this pending disaster." He added that "concurrently with our progress in developing non-traditional solutions to counter resistance mechanisms, including targeting bacterial virulence, we have always been cognizant that we would need to explore novel payment models that are beneficial to healthcare authorities, ensure continued access to effective medicines by patients and ensure we are incentivized to continue our research in this important field."

> "Antimicrobial resistance is as big a danger to humanity as climate change or warfare. That's why we need an urgent global response."

Glyn Edwards, CEO of another UK antibiotics specialist, **Summit Therapeutics**, commented that "the UK's AMR vision is exciting because it acknowledges the necessity to curb the inappropriate use of antibiotics, the need for improved collaboration between industry and governmental bodies and, importantly, it recognizes the need for innovation in the development of new antibiotics." He added that the firm supports the government's position "that a targeted approach could be part of the solution for developing medicines which could help future proof us against AMR. We eagerly await the detail."

Peter Jackson, executive director at the UK's public-private AMR R&D Centre at Alderley Park near Manchester, sent an email to *Scrip* noting that the government announcement "is the critical step that the world has been waiting for, and is very welcome for AMR researchers." He pointed out that it takes huge amounts of money to research and develop a new treatment, "but we want to use new antibiotics sparingly, so pharma companies are unlikely to recoup their R&D investment by selling these new life-saving drugs to the NHS as sales volumes will be severely curtailed."

Jackson noted that the global response to this dilemma so far had been to introduce so-called 'push' incentives – grants and other financial incentives awarded to drug developers to reduce their cost of early-stage R&D. Initiatives such as the US-based CARB-X, the Danish Novo REPAIR fund and the Swiss GARDP program "are priming the development pipeline with hundreds of millions of dollars of new cash targeted at supporting small-to-medium enterprises (SMEs) worldwide." *(Also see "REPAIR Is Trying To Fix The Antibiotic Gap Left By Industry" - Scrip, 12 Sep, 2018.)*

However, "the international community has also been calling for action to fix the broken antibiotics reimbursement model" by introducing 'pull' incentives that 'de-link' the revenues received by the pharma company from the volume of drug sold, Jackson added. The pull incentives "have been more elusive," he claimed, "and despite attempts such as the REVAMP proposal currently stalled in the US congress, none have yet been introduced." *(Also see "A Tamer 'Wildcard'? Antibiotic Exclusivity Would Have More Strings Attached In New Bill" - Pink Sheet, 4 Jul, 2018.)*

He said the news that NICE and the NHS are now working together with industry to trial a new reimbursement model "is a great breakthrough. This should point the way for other countries around the world to quickly follow suit and introduce their own incentives for antibiotics R&D," while at home it is a boost especially for SMEs "that are doing the majority of the research work in the UK. It is also an important signal to the private investment community to step back up to the mark and support companies engaged in AMR R&D."

Several of the projects at the AMR R&D Centre are targeting the most persistent and dangerous lung infections, caused by *Pseudomonas aeruginosa*," Jackson concluded. "Last year, there were over 70,000 cases of such life-threatening infections reported in the UK for patients on ventilators in hospital [and] just a 30% reduction in these infections could improve the prospects for over 20,000 patients and could also save the NHS an estimated £200m in intensive care costs every year."

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Lartruvo Phase III Fail Rocks Lilly Oncology Plans

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Following the excitement of its proposed acquisition of **Loxo Oncology Inc.** and its intensified strategic focus on cancer therapies, Lilly has been brought back to earth with a bang following the failure of already-approved *Lartruvo* (olaratumab) in a late-stage trial.

Lilly tumbles on sarcoma drug fail

The company has announced results from the Phase III ANNOUNCE study of Lartruvo in combination with doxorubicin in patients with advanced or metastatic soft tissue sarcoma (STS) which did not confirm its previously-seen clinical benefit compared to doxorubicin alone, a standard of care. Specifically, the study did not meet the primary endpoints of overall survival (OS) in the full study population or in the leiomyosarcoma (LMS) sub-group.

STUDY DETAILS

The results represent a setback for Lilly given that the Lartruvo/doxorubicin previously showed an OS benefit in STS in a 133-patient, US-only Phase II trial, which led to accelerated approval by the FDA and conditional marketing authorization by the European Medicines Agency at the end of 2016. Those green lights were contingent upon verification of clinical benefit in a confirmatory trial and Lilly said while it was working with regulators "to determine the appropriate next steps," it was suspending promotion of Lartruvo.

The company "was surprised and disappointed that Lartruvo did not improve survival," said Anne White, president of Lilly Oncology in a statement, adding that "we will carefully study the detailed data in an effort to better understand the different results between the two trials." For the moment, the drug is also being studied in a Phase II trial in advanced STS in combination with gemcitabine and docetaxel.

The failure of ANNOUNCE is also a blow to Lilly's finances and the firm is taking a pre-tax charge of $70-$90m in the first quarter. For the full year, it expects a $0.17 impact to earnings per share (EPS).

The contribution of Lartruvo to Lilly's coffers has not been insignificant, posting sales of $203m in 2017 and $221m in the first nine months of 2018. In an investor note, BMO Capital Markets analyst Alex Arfaei wrote that "this was a very surprising event," given that Lartruvo "was an important cancer drug for Lilly that was on track to reach $300m in 2018, and consensus forecasts were $500-$600m by 2022-2023.

MORE ACQUISITIONS?

He said that it was probable that Lilly would eventually pull Lartruvo from the market and BMO has removed the drug from its model, which lowers revenue and EPS guidance by 2-3%. However, Arfaei added that "while incrementally negative, this doesn't change our bullish thesis" on the company and given Lilly's strategic focus on oncology, "this increases the probability that Lilly will make more oncology acquisitions to improve scale."

Arfaei also stressed that the broker's model does not yet include the proposed $8bn Loxo acquisition, which came together very quickly indeed and without any other bidders involved, according to recent filings from the US Securities & Exchange Commission. Lilly raised its offer for Loxo just once from $230 per share to $235 before it was accepted and the deal closed in just a matter of days over the Christmas holiday from a first offer on Dec. 20 to a signed merger agreement on Jan. 5. *(Also see "Lilly/Loxo Deal Came Together Quickly" - Scrip, 17 Jan, 2019.)*

The speed at which Lilly secured the Loxo buy highlights the firm's desire to grow its oncology franchise and upgrade the pipeline as the company faces up to the effects of patent expiries on its lung cancer chemotherapy *Alimta* (pemetrexed). Last year it also acquired **Armo BioSciences Inc.** and its immuno-oncology asset pegilodecakin for $1.6bn.

The Lartruvo failure also highlights the issue of drugs winning quick conditional approvals after showing promise in earlier-stage trials but which is not backed up by Phase III studies. Investors were certainly spooked by the results from ANNOUNCE and Lilly's stock slipped 2% on Jan 18 to close at $116.59.

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Bristol Stuck In Waiting Game As Opdivo TMB Gamble Fails To Pay Off

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Bristol-Myers Squibb Co.'s withdrawal of a high-profile US FDA filing for use of its PD-1 inhibitor *Opdivo* with its CTLA-4 inhibitor *Yervoy* in first-line non-small cell lung cancer based on the tumor mutational burden biomarker in the CheckMate 227 study puts more pressure on pipeline assets from the newly acquired **Celgene Corp.** to pay off.

Bristol said on Jan. 24, as part of its fourth-quarter/year-end 2018 earnings report, that it has voluntarily withdrawn the filing ahead of the May 20 user fee date.

Tumor mutational burden (TMB) refers to the number of mutations in tumor cells and has been associated with response to checkpoint immunotherapies, but despite some intriguing findings it is not yet fully validated. *(Also see "TMB Biomarker Is A Winding Path Rather Than Straight Road" - Scrip, 14 Jun, 2018.)* PD-L1 expression is a more commonly used biomarker for the immuno-oncology (IO) space, though it has always been viewed as imperfect.

The multi-arm CheckMate 227 study is testing the IO combination of Opdivo (nivolumab) and Yervoy (ipilimumab) as well as Opdivo monotherapy vs. chemotherapy in first-line non-small cell lung cancer (NSCLC).

In Part 1a, the company tested the IO combination vs. Opdivo monotherapy vs. chemotherapy in patients with at least 1% PD-L1 expression, while Part 1b tested the IO combination vs. Opdivo/chemotherapy vs. chemo in PD-L1 non-expressers. Part 2 of the study tests Opdivo/chemotherapy vs. chemotherapy in all comers and features overall survival (OS) as the primary endpoint.

In February 2018, the company announced that with the blessing of the FDA it pooled two parts of the study – Part 1a and Part 1b – to assess TMB and would be using progression-free survival (PFS) in these patients as a primary endpoint. *(Also see "Bristol's Opdivo/Yervoy Bid Will Show Whether Tumor Mutation Burden Is Ready For Prime Time" - Pink Sheet, 5 Feb, 2018.)* PD-1 expressers in Part 1a would continue for assessment of the co-primary endpoint of OS.

The company went ahead with filing in high-TMB patients but announced in October that there would be a three-month delay related to its submission – at the FDA's request – of an analysis of OS, which showed similar hazard ratios for those over and under the TMB threshold of 10 mutations/megabase.

Bristol CEO Giovanni Caforio kicked off the company's earnings call by saying that following recent discussions with the agency, it believes it is "important to further characterize the interaction between the two biomarkers of TMB and PD-L1 in these patients in order to understand their relevance to overall survival in this setting."

And to do this, it needs data from Part 1a of the CheckMate 227 study, which will not be available during the review period of the application, though they are expected in the first half of 2019.

"I would like to emphasize that we continue to believe that TMB is scientifically important and we look forward to continuing to advance our research in this area," Caforio said.

Data from Part 2 of CheckMate 227 are expected in mid-2019. The company also is running the CheckMate 9LA study, which tests the Yervoy/Opdivo combination with chemotherapy in first-line NSCLC, but results for this trial have been pushed from late 2019 to 2020.

While Bristol encountered setbacks with its first-line NSCLC development, **Merck & Co. Inc.**'s competing *Keytruda* (pembrolizumab) forged ahead, having proven a strong OS benefit in combination with chemotherapy in the KEYNOTE-189 study in first-line NSCLC, with consistent results across levels of PD-L1 expression. *(Also see "Merck's Keytruda Enjoys Clean Sweep In Lung Cancer, At Bristol's Expense" - Scrip, 17 Apr, 2018.)*

William Blair analyst Matt Phipps said in a Jan. 24 note that the strong results for Keytruda and chemotherapy in NSCLC "undoubtedly remove a sense of urgency on the part of regulators."

TMB FILING WAS A LONGSHOT

BMO Capital Markets analyst Alex Arfaei said in a Jan. 24 note that the "decision to pull the Opdivo/Yervoy application in high-TMB patients should have been expected following recent data disclosures."

Wolfe Research analyst Tim Anderson described the TMB filing as a "Hail Mary" by Bristol to try and salvage a study. "BMY took a chance with this filing, despite a distinct lack of data by it and other companies showing an OS benefit," Anderson said.

The withdrawal of the filing raises more questions about the viability of TMB as a biomarker with the FDA. Asked about this during the earnings call, Chief Scientific Officer Thomas Lynch said he doesn't know what the FDA is thinking, but that he personally believes TMB will continue to be very important.

"I think the broad genomic profiling will continue to be important in the way we approach patients with cancer. I just think it's early days in trying to understand that," Lynch said.

The company believes it is important to understand the interplay of various biomarkers, including PD-L1 and TMB, and how they may work together, Lynch said.

The totality of survival data is needed and that will be available "hopefully reasonably shortly" when the Part 1a data come out, the exec said.

Wolfe Research's Anderson questioned the company's take, however. Bristol said it is withdrawing the filing, because additional data from Part 1 of CheckMate 227 falls outside of the time frame where the FDA would make its decision on the TMB application, but it's unclear why if the agency believed in the biomarker it wouldn't just issue a complete response letter as it awaited the data, Anderson said.

The analyst expects that Part 2 of CheckMate 227 is more likely to be positive than Part 1a or CheckMate 9LA, and that "even if results are not as strong as [KEYNOTE-189], this will still be enough to capture Opdivo at least some share in 1L lung, given the brand's

existing commercial momentum and the likely widely held view among prescribers that Keytruda and Opdivo are essentially the same in terms of their clinical profiles."

Morningstar's Damien Conover said in a Jan. 24 note that he expects supportive lung data from Part 1a and Part 2 of CheckMate 227 and CheckMate 9LA, but added that "strong data from Merck's Keytruda is likely to limit Opdivo's lung cancer share to close to 15% by 2022."

OPDIVO'S QUARTERLY SALES GROWTH FLAT

Keytruda started to overtake Opdivo in the second quarter of 2018. *(Also see "Amid PD-1 Uncertainty, Bristol Under Pressure For M&A Activity" - Scrip, 25 Oct, 2018.)* And late in 2018, **Roche**'s PD-L1 inhibitor *Tecentriq* (atezolizumab) was cleared for use with its VEGF inhibitor *Avastin* (bevacizumab) and chemotherapy, becoming the second checkpoint inhibitor-combo approved for first-line NSCLC. *(Also see "Roche's Tecentriq Becomes Second In PD-1/L1 Family To Gain First-Line Lung Cancer Approval" - Scrip, 6 Dec, 2018.)*

Bristol reported sales of $1.8bn for Opdivo in the fourth quarter, up 33% from the year-ago period, but flat compared to the third quarter ($1.79bn) and lower than expected. The company explained that sales were flat due to inventory draw-down from the third quarter and Medicaid rebates.

Bristol noted that Opdivo's share in second-line NSCLC remained stable at 30% and that the product continued to perform well in renal cell carcinoma and adjuvant melanoma, boding well for the future. Based on the strong momentum in the 2018 business, the company expects to see growth for Opdivo in the US and internationally in 2019, Caforio told the call.

Quarterly sales of the company's blockbuster anticoagulant *Eliquis* (apixaban) were also slightly lower than expected – due to higher discounting – though they were up 25% from the year-ago-period at $1.7bn.

Demand remains strong and Caforio stressed that Eliquis is the number one novel anticoagulant in the US; he said there is "considerable room for the market" to expand based on its superior profile in prevention of stroke in patients with atrial fibrillation.

Overall, Bristol's product sales rose 10% to $6bn in the fourth quarter. Caforio said he "could not be prouder of our very strong performance in the quarter, which wraps up a very good year for the company."

WAS CELGENE DEAL DRIVEN BY 'DESPERATION'?

Uncertainty about the lung cancer situation for Opdivo puts more pressure on the recently announced $74bn deal to acquire **Celgene Corp.***(Also see "Bristol Values Celgene's Hematology, Immunology Portfolio At $74bn, But Does It Price In Risk?" - Scrip, 3 Jan, 2019.)* The deal, unveiled in early January, provides a way for Bristol to meet demands to diversify past Opdivo and allows for $2.5bn in cost synergies, but investors have been concerned about the future for Celgene's blockbuster multiple myeloma drug *Revlimid* (lenalidomide), which is nearing the end of its patent life.

"The optics of the quarter were not great in the setting of the pending CELG transaction, with Opdivo sales coming in slightly

below consensus. This begs the bear case that Opdivo is finally starting to slow down (because of dynamics in the lung cancer setting) and that this is the driver of BMY buying CELG, out of desperation," Anderson said.

When the deal was announced at the beginning of the year, Bernstein's Ronny Gal flagged the risk for a negative decision on Revlimid dosing patents in February or March.

Chief Financial Officer Charles Bancroft sought to reassure investors during the call, noting that Bristol performed extensive due diligence on the Revlimid intellectual property situation.

Bancroft also stressed the value of the combined entity, with near-term launches of six new medicines and "the doubling of all our pipeline assets." (*See chart.*)

Five Phase III assets are positioned to launch in the next 12 to 24 months and a significant number of Phase I and Phase II assets will bolster the existing pipeline and provide complementary platforms such as cell therapy and protein homeostasis, Bancroft said.

The near-term growth is being driven by the Celgene assets, which include lisocaptagene maraleucel (liso-cel, JCAR017), an anti-CD19 chimeric antigen receptor T-cell (CAR-T) therapy that will be submitted for relapsed/refractory diffuse large B-cell lymphoma in the second half. It also includes bb2121, which Bristol sees as a best-in-class B-cell maturation antigen (BCMA) CAR-T. *(Also see "CAR-T Forecast: Celgene Follows, But Also Leads As Next Batch Of T-Cell Therapies Near Market" - Scrip, 3 Jan, 2019.)*

The company was asked during the earnings call about the commercial challenges facing CAR-T, given the high costs associated with hospitalization required for treatment.

Bristol's Chief Commercial Officer Christopher Boerner acknowledged that with today's CAR-T treatments patients need to remain in the hospital, often in the intensive care unit, for treatment as well as monitoring. One of the things the company finds exciting about liso-cel is that because there are no significant Grade 3/4 toxicities and the rate of cytokine release syndrome is lower than competing products, patients could potentially be monitored in the outpatient setting.

This would bring the overall cost of the therapies down, increase the value of the assets and expand the physician users out of large academic centers to community centers, he noted.

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Six Near-Term Product Launch Opportunities: Greater than $15B in Non Risk-Adjusted Revenue

luspatercept	U.S. and EU regulatory submissions expected in first half 2019 in 2L MDS and Beta-Thalassemia
fedratinib	Targeting patients who relapsed from or are intolerant to Jakafi in Myelofibrosis
liso-cel (JCAR017)	CD19 CAR-T with strong efficacy and a potentially differentiated safety and tolerability profile for R/R DLBCL
bb2121	Potential to be first-and possibly best-in-class BCMA CAR-T in Multiple Myeloma
ozanimod	U.S. NDA and EU MAA submissions for RMS planned for Q1 2019
TYK-2	Biologic-like efficacy in Psoriasis with upsidepotential to address multiple autoimmune diseases

Source: Bristol-Myers Squibb

Hanmi To Step Up Global Drug Development As Lilly Returns BTK Rights

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Eli Lilly & Co. has returned rights to the novel oral Bruton's tyrosine kinase (BTK) inhibitor LY3337641 (also known as HM71224) it had licensed in from originator **Hanmi Pharmaceutical Co. Ltd.** in 2015, in a move that was partly expected after the US giant decided to halt its Phase II trial of the molecule last year due to what it saw as weak data.

"After undertaking a thorough assessment of other development opportunities, including re-evaluation of all available clinical data, Lilly has elected to return LY3337641/HM71224 to Hanmi Pharmaceutical," Nicole Hebert, advisor at Lilly R&D Communications, told *Scrip*.

"As previously disclosed in February 2018, Phase II development of the molecule for rheumatoid arthritis was discontinued due to a low likelihood of demonstrating significant efficacy at the conclusion of the trial," she added. However, this decision does not impact Lilly's commitment to immuno-oncology, stressed the US firm, which noted it continues to invest in leading-edge clinical approaches across its immunology portfolio, in hopes of transforming the treatment experience.

"We've built a deep pipeline and are focused on advancing the science to find new treatments that offer meaningful improvements to support the people and the communities we serve," Hebert said.

Hanmi last year decided to end the development of another product, the EGFR inhibitor olmutinib, after both **Boehringer Ingelheim GMBH** and **ZAI Lab Ltd.** decided to return their respective rights.

'UNRELATED TO LOXO DEAL'

Although the Hanmi news comes shortly after Lilly's recent $8bn acquisition of **Loxo Oncology Inc.**, which also has an investigational BTK inhibitor (LOXO-305) in Phase I/II trials, Hebert stated that "this decision is not related to the Loxo announce-

ment as the asset is oncology-focused." Lilly suspended Phase II trials in rheumatoid arthritis of the novel Hanmi BTK inhibitor in February last year, as the interim results increased the possibility of not meeting efficacy targets, but also began additional tests to explore other indications.

Eventually however, "Lilly decided to return the rights to this molecule after reviewing all clinical data and the BTK inhibitor market situation," said Hanmi in a statement.

The Korean firm will receive all the clinical trial and development-related data from Lilly within 90 days of the return of rights, and will now independently review plans to develop the molecule for other potential indications. Hanmi will in addition retain the upfront payment of $53m it received from Lilly under the original deal.

R&D PROGRESS WITH PARTNERS, INDEPENDENTLY

The leading South Korean pharma firm added that it doesn't expect the new decision by Lilly to affect its development of other new drugs targeting global markets.

"Development of new global drugs can only be achieved through relentless challenges despite failures. We will speed up the development of 27 new drug pipeline assets in obesity/diabetes, immune disorders and the rare disease area so that we can begin to launch new drugs in two to three years," Hanmi declared.

It is stepping up efforts to rapidly commercialize new drugs under clinical development with global partners, as well as to independently develop these in markets outside Korea.

"We will speed up the development of 27 new drug pipeline assets in obesity/diabetes, immune disorders and the rare disease area."

One of its partners, **Spectrum Pharmaceuticals Inc.**, submitted a US regulatory filing approval for *Rolontis* (eflapegrastim), a long-acting G-CSF analog, in late 2018, which could be approved by the FDA as early as late this year. The novel, oral pan-HER inhibitor poziotinib, also licensed out to Spectrum, is set for Phase II interim results in lung cancer in the latter half of this year, based on which Spectrum is expected to file for US approval by early next year.

Hanmi is also aiming to develop poziotinib in China via its Chinese unit Beijing Hanmi. With a goal to launch the drug in this market in 2022, it plans to file for an IND to Chinese authorities in the first half of this year; China accounts for more than 40% of global lung cancer patients.

In addition, Phase III clinical trials of efpeglenatide (a Exd4 analog using Hanmi's proprietary LAPS sustained release technology, also known as SAR-439977), licensed out to **Sanofi**, and Phase II studies with HM12525A (JNJ-64565111, LAPS GLP/GCG), licensed out to **Janssen Pharmaceutical Cos.**, are also progressing smoothly, it said.

JPM HIGHLIGHTS

Three major R&D programs which Hanmi is progressing were highlighted at the recent J.P. Morgan Healthcare Conference in San Francisco, in obesity, NASH and oncology.

In obesity, a LAPS formulation glucagon analog HM15136, a potential best-in-class treatment, is showing good weight loss effect with oral antidiabetic combination synergy and minimal hyperglycemic events. Hanmi plans to complete a Phase I study in the second quarter of this year and begin Phase II in the fourth quarter.

In NASH (non-alcoholic steatohepatitis), a LAPS GLP-1/GIP/GCG tri-agonist, HM15211, is showing promising efficacy in NASH/fibrosis prevention and treatment with weight loss effect, and should enter Phase II in the fourth quarter.

In oncology, Hanmi's next generation FLT3 inhibitor is showing effective antitumor activity against a wide range of FLT3 mutations in acute myeloid leukemia. Hanmi received an orphan drug designation from the US FDA last year and is slated to begin a Phase I in the US and Korea in the first quarter.

The company disclosed it also plans to begin a global clinical trial of a new autoimmune disease therapeutic using its Pentambody platform technology, a next generation bispecific antibody platform developed by Beijing Hanmi.

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From the editors of PharmAsia News.

Why Roche Oncology Bet Big On Neoantigen-Directed T-Cell Therapy

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Roche's latest big bet in exploring and discovering the next generation of cancer immunotherapies rests on a large deal with **Adaptive Biotechnologies Corp.** to develop T-cell receptor (TCR) therapies tailored for each individual patient.

Roche and Adaptive announced a development and commercialization deal on Jan. 4, right before the J.P. Morgan Healthcare Conference kicked off in San Francisco. *(Also see "Deal Watch: Sanofi Retains Options To Two Bispecifics While Exiting Antibody Pact With Regeneron" - Scrip, 7 Jan, 2019.)*

Based in Seattle, Adaptive Biotechnologies has developed the *TruTCR* T-cell receptor discovery and immune profiling platform.

Roche is set to pay $300m upfront and more than $2bn in milestones to work with Adaptive Biotechnologies on the development, manufacturing and commercialization of bespoke T-cell therapies targeted at neoantigens, proteins generated by tumor-specific mutations. Per the deal, the engineering and manufacturing of these therapies will be the responsibilities of Roche.

While Roche hasn't been at the forefront of chimeric antigen receptor T-cell therapy (CAR-T), the Adaptive deal helps them further develop in a new avenue of personalized cellular therapy.

"Cell therapies vary in their specifics, but the general concept is the same," Roche explained. Like with CAR-T, with Adaptive's TCRs

a patient's T-cells are extracted, modified, multiplied and reintroduced. But CAR-T cells recognize proteins on the surface of all cells, whereas TCRs target tumor-specific proteins inside cells. The hope is that this will one day allow application of TCRs to a broader range of cancers – including solid tumors – than CAR-T because the targets are more specific, so there is less risk of affecting normal tissue.

"For neoantigen-directed T-cell therapies, this means genetically engineering a person's T-cells with receptors that recognize their own tumor-specific neoantigens. The big challenge, though, is choosing the right neoantigen to target for each patient, and the right receptor to target those specific neoantigens. Each person's T-cells carry an incredibly diverse and unique collection of receptor types that are generated to recognize foreign cells," the company noted.

"It's highly personalized, because the mutation that causes your cancer is going to be different than the mutation that causes mine," James Sabry, global head of partnering at Roche, commented in an interview at the J.P. Morgan meeting.

The "holy grail" for Adaptive Biotechnologies and the ultimate goal for the partnership is to develop bespoke therapies using a patient's own T-cell receptors targeted against a patient's particular neoantigens. But along the way, they plan to engineer off-the-shelf TCR therapies.

With the off-the-shelf TCR approach, DNA in the patient's tumor is profiled for immunogenic antigens and neoantigens that are shared among patients. Adaptive Biotechnologies then uses its library of T-cell receptors from healthy donors to develop an off-the-shelf therapy.

Roche stresses that the neoantigen-directed T-cell approach it is developing with Adaptive Biotechnologies involves genetic engineering of a patient's own T-cells with receptors that recognize their own tumor-specific neoantigens. A cell therapy is engineered and manufactured for each individual patient, based on the particular TCRs and neoantigens present.

Speaking about the off-the-shelf vs. fully personalized products the partners envision will be created through the deal, Adaptive Biotechnologies President Julie Rubinstein said that while a shared neoantigen is important for a group, it may still not be the best target for every individual patient.

"Ultimately, we believe we can find the best target for each individual patient and create a drug against the exact target that we think is actually driving the tumor," she said in an interview after J.P. Morgan.

The partners declined to give timetables on development for either hematologic malignancies or solid tumors, but Harlan Robins, cofounder and head of innovation at Adaptive Biotechnologies, told *Scrip* that they both are eager to move "as fast as humanly possible."

The deal is exclusive when it comes to development of therapeutics in oncology, but Adaptive will still be able to work with pharma partners on oncology research and diagnostics and is broadly free to develop cellular therapies for other diseases.

News of the tie-up preceded an action-packed J.P. Morgan meeting, held Jan. 7-10 in San Francisco. **Eli Lilly & Co.**'s $8bn take-out of **Loxo Oncology Inc.** and **Bristol-Myers Squibb Co./Celgene Corp.**'s merger dominated the biotech headlines. *(Also see "J.P. Morgan 2019: Industry Throws A Bonanza, With An Elephant In The Room " - Scrip, 9 Jan, 2019.)* The $74bn merger with Celgene will give Bristol, a big player in checkpoint immunotherapy, a foothold in cellular therapy for the first time. *(Also see "Bristol Values Celgene's Hematology, Immunology Portfolio At $74bn, But Does It Price In Risk?" - Scrip, 3 Jan, 2019.)*

"We feel though our deal is perhaps not as large on a piece of paper right out of the gate, it has the most game-changing potential in cancer therapy," Rubinstein said.

"In theory, if we can actually develop a patient-specific cellular therapy using the patients' own T-cell receptors, we can do that for all patients with any cancer," the exec said.

Roche's Multiple Approaches Across Targeted Therapies And Cancer Immunotherapy

Franchises		Targeted Therapies			Cancer Immunotherapies		
		Small molecules	ADCs	mAbs	Checkpoint Inhibitor	Bi-specifics	Vaccines
Heme	B-Cell (NHL / CLL)	3	1	3	1	3	
	AML	2	1				
	Hemophilia A			2			
	MM	2			2	1	
Breast / GYN	HR+	4			1		
	HER2+ (eBC / mBC)		2	2		1	
	TNBC	3		1			
	Ovarian, Cervical, Endometrial	1		1			
Lung / Rare Cancers	NSCLC	4		2	2	2	1
	SCLC				1		
	SCCHN			1			
	Melanoma	2					1
GI / GU	RCC			1	1	1	
	HCC			2			
	CRC	1		2	2	2	
	Pancreatic					1	
	Gastric			1	1		
	Bladder						
	Prostate	1					

Note: Includes all assets currently in clinic

Legend: 1+ Products 1 Product No Products

FITTING INTO ROCHE'S OVERALL ONCOLOGY STRATEGY

Sabry said the deal is part of an overarching strategy Roche has around what it thinks the next generation of immunotherapies will look like, with a heavy emphasis on personalization.

The oncology powerhouse was among the leaders in the revolution of checkpoint inhibitor immunotherapies. Roche's PD-L1 inhibitor *Tecentriq* (atezolizumab) has been a success in that it is approved for non-small cell lung cancer (NSCLC) and metastatic urothelial cancer and is in line for supplemental approvals in a range of other indications, including combinations. *(Also see "Roche's Tecentriq Becomes Second In PD-1/L1 Family To Gain First-Line Lung Cancer Approval" - Scrip, 6 Dec, 2018.)*

However, like other checkpoint inhibitor drugs, it has paled in comparison to **Merck & Co. Inc.**'s PD-1 inhibitor *Keytruda* (pembrolizumab), which has the strongest performance and labeling to date of the members of the class. *(Also see "Keytruda Is King, But Merck Faces Questions About Business Development" - Scrip, 25 Oct, 2018.)*

But as dramatic as the impact of checkpoint inhibitors has been, the response rate to PD-1/L1 checkpoint inhibitors is typically only up to about 30% and in some cancers there is very little efficacy at all.

In addition to the checkpoint inhibitor approach, Roche is exploring a variety of other ways to tackle cancer, encompassing bispecific antibodies, personalized vaccines and cellular therapies. (*See table opposite.*)

Since 2016, Roche has been working with privately-held **BioNTech AG** to develop novel messenger RNA (mRNA) cancer vaccines tailored to individual patients based on the particular neoantigens on their tumor cells, a deal that involved a $310m upfront payment.

The BioNTech and Adaptive Biotechnologies neoantigen-related strategic deals fit with the fundamental understanding that came with checkpoint inhibitors of the importance of immune system surveillance in cancer, as well as Roche's investment in personalized medicine, which was also illustrated through the 2018 acquisitions of the molecular information company Foundation Medicine and the cancer data specialist Flatiron Health. *(Also see "Roche Pushes Personalization With $2.4bn Foundation Buy-Out" - Scrip, 19 Jun, 2018.)*

In all areas of medicine, personalizing therapy is essential to get to high levels of efficacy or cures, Sabry said.

Roche has done extensive research into which tumor types are susceptible to immunotherapy, and the company believes the neoantigen-directed therapies may work whether T-cells are present or not.

He noted that the cellular therapies are complementary to checkpoint inhibitors and believes that they will be used in combination, allowing the company to effectively treat a broader range of patients.

"If we are correct about our hypothesis, then the industry will follow us. I think we are leading the pack," Sabry said.

Published online 23 January 2019

The Netherlands

A Small Country With **BIG** Ideas

LIFE SCIENCES CLUSTERS

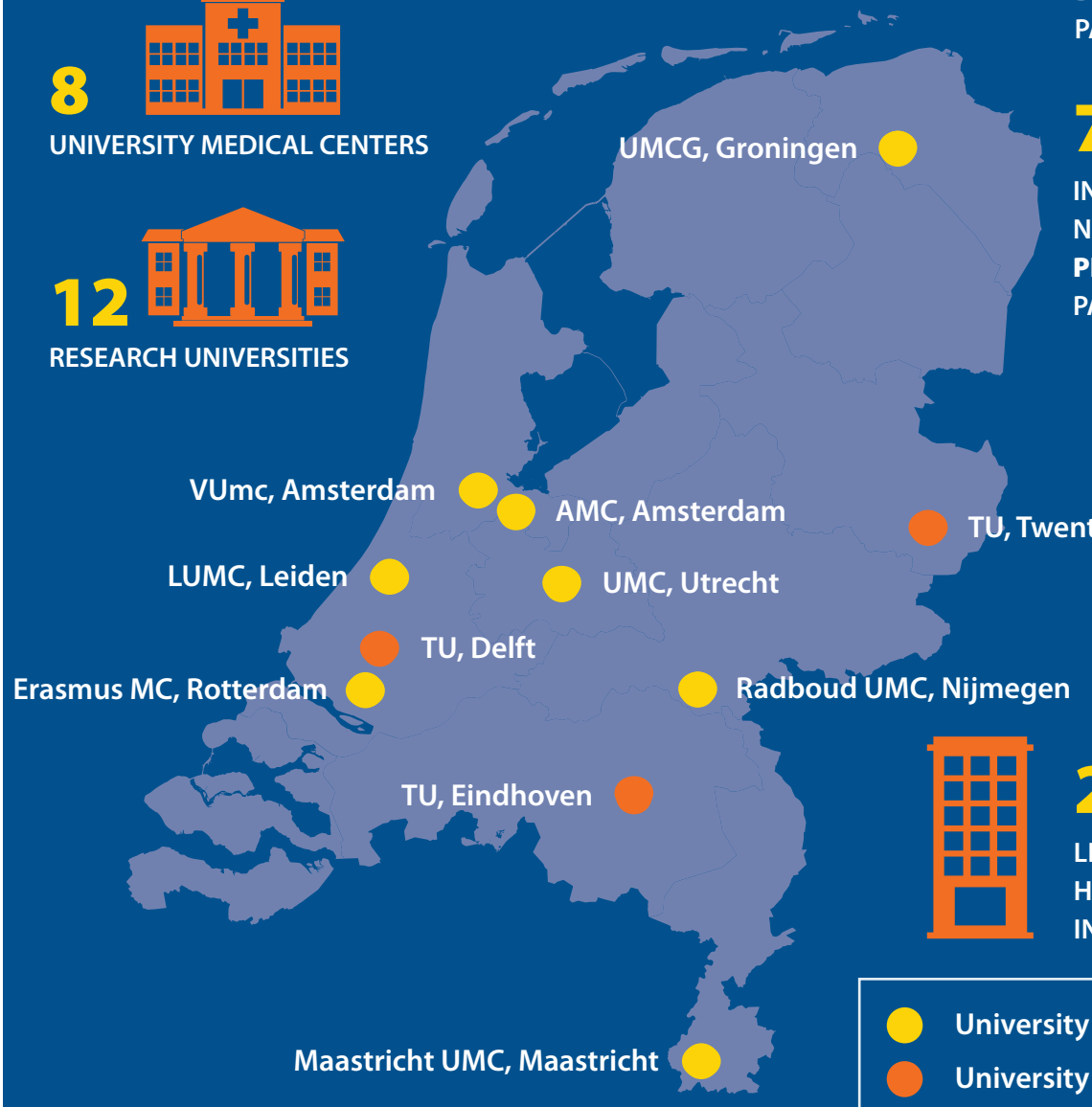
The country boasts the world's most concentrated life sciences and health clusters, based around the cities of Amsterdam, Rotterdam, Utrecht and Nijmegen.

8
UNIVERSITY MEDICAL CENTERS

12
RESEARCH UNIVERSITIES

3RD
IN THE WORLD FOR NUMBER OF **BIOTECHNOLOGY** PATENTS

7TH
IN THE WORLD FOR NUMBER OF **PHARMACEUTICAL** PATENTS



2,900
LIFE SCIENCES AND HEALTH COMPANIES IN A 200KM RADIUS

Sources: Netherlands Foreign Investment Agency, Health Holland

With the European Medicines Agency moving to Amsterdam in 2019, there is a buzz about the Netherlands and its role in the future of biopharma. With the hub of all European regulatory decisions soon to be positioned in the country, and with Brexit looming a short three months away, it is expected that more innovative companies will see the appeal of Amsterdam and the wider regions. Here is what the country can offer those that want to be where the action is.

GATEWAY TO EUROPE

Guido Rasi, the EMA's director general discussed the "excellent connectivity" of Amsterdam as a factor when deciding to relocate the EMA there.

THE NETHERLANDS
42,500 km2
237 times smaller than the US

95%
OF EUROPE'S MAJOR MARKETS CAN BE REACHED WITHIN 24 HOURS

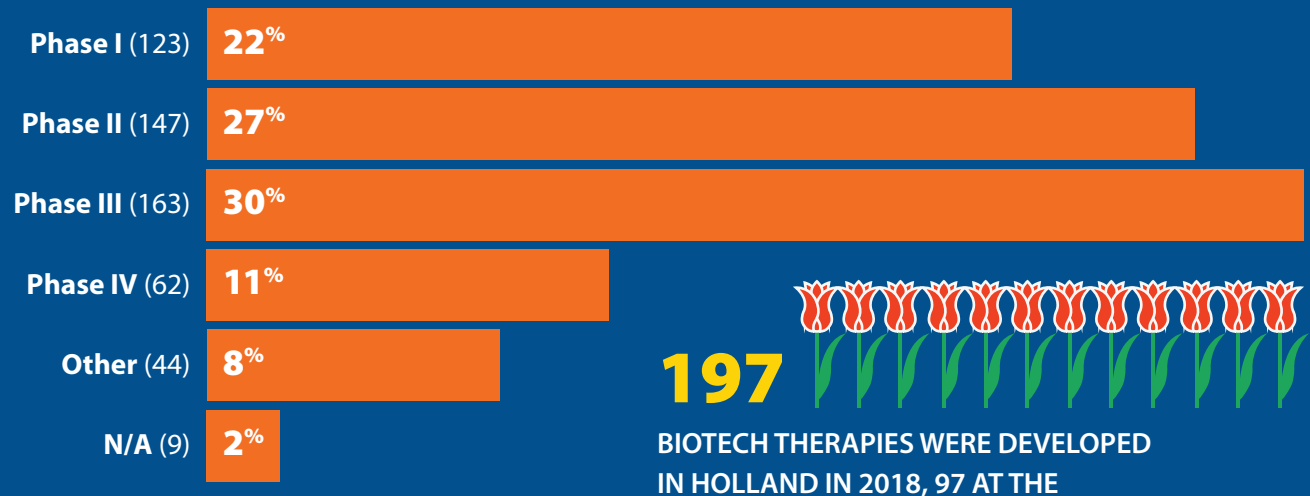
160m
CONSUMERS WHO CAN BE REACHED WITHIN A 300-MILE RADIUS

INVESTMENT AND OUTPUT

50
PUBLIC-PRIVATE-PARTNERSHIPS FUNDED BY Health~Holland
SHARED CHALLENGES, SMART SOLUTIONS

€33bn
ANNUAL TURNOVER OF DUTCH BIOPHARMA INDUSTRY, WITH A PRODUCTION VALUE OF MORE THAN €29BN.

Clinical Drugs Trials Based In The Netherlands, By Phase (2017)



197
BIOTECH THERAPIES WERE DEVELOPED IN HOLLAND IN 2018, 97 AT THE PRECLINICAL STAGE, AND 11 IN PHASE III.

Full Steam Ahead At Ferring To Unlock Microbiome Potential For Reproduction

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Having acquired **Rebiotix Inc.** in 2018 to advance its research into the human microbiome, **Ferring Pharmaceuticals AS** has unveiled a large clinical program involving 9,000 people to investigate its role in reproductive medicine and women's health, as well as gastroenterology.

The Swiss company and Swedish partner the Karolinska Institutet have announced a five-year extension of their collaboration signed back in January 2016, which led to the establishment of the Centre for Translational Microbiome Research (CTMR). The project includes six reproductive health clinical studies of approximately 6,000 women and babies and four gastroenterology trials of 3,000 adults and children and the aim of the studies is to examine the role of the microbiome in areas of high unmet need, including recurrent pregnancy loss, preterm birth and inflammatory bowel disease (IBD).

> RBX2660 has received US FDA fast track, breakthrough therapy and orphan drug designations, so it could be eligible for an expedited review.

Ferring upped its presence in the area last year with its purchase of the US late-stage clinical microbiome company Rebiotix and the latter's CEO Lee Jones said in a statement that the expanded partnership "presents an exciting research opportunity, bringing together unique capabilities of Ferring, Karolinska Institutet and Rebiotix across the clinical development continuum in the microbiome space."

Rebiotix has developed the Microbiota Restoration Therapy (MRT) platform for delivering live, human-derived microbes into a patient's intestinal tract to treat disease. MRT uses the microbes gathered from human stool material and uses Good Manufacturing Practices and quality control techniques to produce standardized, stabilized products that are ready-to-use in an easy-to-administer format.

Its most advanced investigational microbiome product – RBX2660 – comes in two formulations, a pre-packaged enema and a non-frozen lyophilized capsule, and both products are under investigation currently for preventing recurrent *Clostridium difficile* infection as well as other liver and gastrointestinal diseases. Ferring told *Scrip* that the products have a long shelf life and can be delivered to the patient on demand "with no special equipment or handling by the physician."

RBX2660 has received US FDA fast track, breakthrough therapy and orphan drug designations, so it could be eligible for an expedited review. If all goes well, it could be the first approved human microbiome product.

In terms of timelines for the Karolinska pact, Ferring pointed out that all of these early-stage population studies have now commenced and while some were initiated more recently, others began as far back as 2010. The company added that the first data are expected to be published during 2019 from both research areas, and Lars Engstrand, director of the CTMR said that "this innovative public-private partnership demonstrates our ongoing, shared commitment to investigating the human microbiome [and its] impact on important reproductive and gut health challenges."

Microbiome drug development is an area of huge interest for Ferring's new CEO Per Falk. Speaking to *Scrip* last year, he noted that there was "a tremendous opportunity to change healthcare, without a doubt it is a new frontier but that does not necessarily mean it will be faster or easier. In fact it will be more complicated than drug development is at present because these critters are alive and if they don't live, they don't work." *(Also see "Microbiome Clinical Studies Loom Large In 2018" - Scrip, 4 Jan, 2018.)*

The unmet need is certainly there. Up to 5% of couples have to cope with the impact of recurrent pregnancy loss and around 15 million babies are born preterm every year around the world - approximately one million children die each year due to related complications. As for gastroenterology, Ferring estimated that over 10 million people worldwide live with the pain and discomfort of IBD.

LICENSING DEALS

As well as advancing in innovative areas, Ferring has also recently added a couple of products to its fertility portfolio in the US.

Last week, the firm inked a deal to acquire the US commercialization rights for a generic version of **Merck & Co. Inc.**'s *Orgalutran* (ganirelix acetate), a gonadotropin-releasing hormone antagonist which is used to prevent premature ovulation during controlled ovarian stimulation, from **Sun Pharmaceutical Industries Ltd.**. Paul Navarre, CEO of Ferring Pharmaceuticals in the US, said in a statement that with ganirelix, the firm had "added another proven treatment to what is already the most comprehensive reproductive health portfolio available."

That includes *Menopur* (menotropins for injection), *Novarel* (chorionic gonadotropin for injection) and *Endometein* (progesterone) vaginal insert. Sun got FDA approval for its version of ganirelix in November last year and noted that the branded product had sales of $67m in the US in the 12 months ended September 2018. No financial terms were disclosed.

In addition, Ferring also finalized a transaction with **INVO Bioscience Inc.** to bag exclusive US commercialization rights for INVOcell, an FDA-approved fertility system that uses a woman's own body as an incubator during fertilization and early embryo development.

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J&J Expects Persistent Pricing Pressure Into 2019

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Johnson & Johnson's net drug prices declined more than 6% in 2018 and similar pricing pressure is anticipated in 2019, the company outlined during a fourth quarter sales and earnings call Jan. 22. CEO Alex Gorsky highlighted the growing concern among the public over the cost of drugs in the US in his prepared remarks, pushing for industry to provide more pricing transparency and value-based health care approaches, while also underscoring the importance of investing in innovation.

"The cost of health care is one of the most pressing issues facing our country today," Gorsky said. "We share the administration's goals of reducing health care costs while improving the quality and efficiency of care."

He said J&J is working to be more transparent when it comes to pricing, highlighting the annual pricing transparency report the company releases outlining average list price increases across the pharma portfolio as well as net prices, including discounts and rebates. J&J is on track to disclose the 2018 price transparency report in a month or two, but the CEO confirmed that average net prices across the pharma portfolio declined 6%-8%. That's more than in 2017 when J&J reported that average list prices increased 8.1%, but average net prices declined 4.6%. *(Also see "Janssen Emphasizes Average Net Price Decline As Transparency Momentum Builds In States" - Pink Sheet, 12 Mar, 2018.) [Editor's note: this story was updated to reflect that net prices declined 4.6% in 2017, not 4.1% as originally reported).*

J&J and other drug makers that release these pricing reports averaging prices across the portfolio have also drawn criticism, however, because they don't show which drugs the companies are raising or lowering prices on. For example, J&J raised prices on two important and growing cancer drugs last year, *Darzalex* (daratumumab) and *Imbruvica* (ibrutinib), while net prices of *Remicade* (infliximab) declined significantly as J&J tried to fend off biosimilar competition; steep rebating helped them do so quite successfully. *(Also see "J&J Stays Within Price Pledge, But Average Doesn't Tell The Whole Story, Analyst Says " - Scrip, 27 Mar, 2018.)*

The company said Remicade continues to hold about a 93% share of the infliximab market despite the availability of two biosimilars on the market, though sales of the blockbuster drug fell 15.6% versus the prior-year quarter to $1.24bn in the fourth quarter as the company raised rebates to secure market access. That kind of brand retention for an off-patent product is something investors might applaud, but it sends another kind of message to the public about the brazen tactics industry can and does use to defend its brands against what are intended to be cheaper rivals.

Industry is under pressure to be more transparent about drug pricing in other ways too. By April 15, all Pharmaceutical Researchers and Manufacturers of America (PhRMA) members are expected to begin providing details about where the public can go to find pricing information in direct-to-consumer broadcast ads. The voluntary proposal was made in part to thwart HHS from releasing a similar mandatory policy proposal, which it did anyway. *(Also see "Industry Makes A Drug Price Transparency Push In DTC Ads, But Is It Too Little Too Late? " - Scrip, 15 Oct, 2018.)*

But while Gorsky said J&J is concerned about higher out-of-pocket costs for patients and is working with the administration to find solutions, he also pushed some of industry's most common talking points: that drugs represent just 14% of total health care costs in the US and that innovative medicines deliver a value to the broader health care sector.

Despite the ongoing US pricing headwinds, J&J's pharmaceuticals business was the biggest bright spot for the company in 2018. Worldwide pharmaceutical sales increased 12.4% for the full year to $40.7bn, driven by strong sales of *Stelara* (ustekinumab) for inflammatory diseases, *Zytiga* (abiraterone) for prostate cancer and the blood cancer drugs Darzalex and Imbruvica. The sales also included the impact of the Actelion acquisition in 2017, which contributed 3.4% to worldwide operational sales growth. Pharmaceutical sales in the fourth quarter increased 5.3% to $10.19bn.

Stelara outpaced Remicade as J&J's top revenue generator for the first time in the fourth quarter, as sales of Stelara grew 33% to $1.44bn in the quarter and sales of Remicade slipped further.

In contrast to the pharma business, J&J's consolidated growth was slower, just 1% to $20.4bn in the fourth quarter and 6.7% to $81.6bn for the year, held back by significantly slower growth in consumer health care and medical devices. The company guided investors to expect operational sales growth (excluding the impact of currency) of 1% or less in 2019 and a reported decline in revenues of 0.5% to 1.5% versus 2018 performance, with the pharma division facing more generic and biosimilar competition to Zytiga and Remicade, persistent US pricing pressure and a stronger US dollar.

The guidance came in below analyst consensus estimates and could set a watchful tone for the rest of the biopharma industry's fourth quarter financial readouts.

"Underlying 2019 revenue growth guidance of +0/0%-1.0% (reflective of -0.5%-1.5% overall growth; -1% at the midpoint) was below our +1.4% forecast (consensus +1.6%), which could be a negative indicator for the broader biopharma group given ongoing concerns over [foreign exchange] and drug pricing headwinds," Barclays analyst Geoff Meacham pointed out in a same-day research note.

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Innovation The Centerpiece In Mixed Japan 2019 Outlook

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A few weeks into 2019 and there has already been one global industry-shaking event emanating from Japan - the formal completion in early January of **Takeda Pharmaceutical Co. Ltd.**'s huge $62bn acquisition of **Shire PLC**.

In the Asian 12-year zodiac cycle, 2019 is the year of the pig (or boar in Japan), which traditionally is characterized by diligence, honesty, positivity and compassion. These traits might come in useful as managers start implementing the deal in practical terms over the next few months.

Takeda CEO Christophe Weber has already said he is aware that speedy and decisive execution will be the key to success. While a 200-strong core leadership team has been decided and the near-term future already mapped out, as one Takeda employee told *Scrip*, "the hard work starts now".

So what can we expect? Divestments for sure, to align with Takeda's strategic therapeutic focus and to raise cash to pay down deal-related debt. The size and shape of these is not yet clear, but Weber has said selected sell-offs will certainly happen.

One likely candidate is Shire's eye care portfolio, given that ophthalmology is not among the core focus areas of the combined entity. Takeda's large Japanese OTC/consumer health business seems less likely, given the company's view that this already has the requisite critical mass.

Some reports have also surfaced recently that selected emerging market portfolios acquired along with **Nycomed SPA** in 2011 may be on the block, although this has yet to be confirmed.

It also seems highly likely that some level of job cuts – possibly in the US sales force – will be used to help achieve the minimum of $1.4bn in combined annual cost savings anticipated by Takeda from three years after the deal.

Further major R&D restructuring appears unnecessary, however, given this has already been underway at Takeda over the past few years.

MORE M&A DEALS LIKELY?

The size and scope of the Takeda-Shire deal has inevitably given rise to speculation that

What's On The Cards In Japan In 2019?

it will prompt other Japanese companies to consider a major strategic alliance, or even full-fledged M&A, to remain competitive in a challenging global marketplace.

Globally, experts seem to be of the view that - despite other planned deals emerging in early 2019, such as **Bristol-Myers Squibb Co.**'s $74bn bid for **Celgene Corp.** and **Eli Lilly & Co.**'s $8bn buy of **Loxo Oncology Inc.** - technology- and product-focused bolt-on moves to fill specific gaps are most likely.

But in a Jan. 8 report, Morgan Stanley analysts looked at the effect on Japanese peers of the doubling of Takeda's market capitalization to JPY6.4tn ($58.4bn), predicting there would be "substantial negative impact on Astellas" in particular, given a possible shift in investor funds back to post-Shire Takeda.

While M&A activity is hard to predict, it's always interesting to speculate about possible combinations. In the Japan Pharma Outlook 2027 report issued around the middle of last year, Datamonitor Healthcare modeled a couple of a theoretical deals that, on the surface, appear to have just as strong a rationale as Takeda/Shire.

For example, a merger of **Astellas Pharma Inc.** with **Daiichi Sankyo Co. Ltd.** would create an entity with significantly enhanced strength in the US and in oncology, with only a 38% current portfolio overlap.

The combination would also provide a substantial boost to scale in Japan, where companies are facing the need to raise innovation to benefit from changes to the reimbursement pricing system, and older drugs are coming under substantial pressure from both price revision policies and generics. Meanwhile, the report surmised that a potential combination of **Otsuka Pharmaceutical Co. Ltd.** with **Eisai Co. Ltd.** would provide a strategic enhancement in CNS and oncology, with a relatively low exposure to generics on both sides, and again much improved scale and strength in both the US and Japan.

While the portfolio overlap is around 66%, overlap in primary indications is only around 20%.

Eisai has already said it sees "strategic partnerships" as a key pillar of its current mid-term business plan in a period of transformation, but we'll have to see if this translates into major deal-seeking activity.

LOSSES OF EXCLUSIVITY, JOBS

In these hypothetical cases, a potential catalyst is that all the companies are facing past or upcoming fallout from major patent expiries - Otsuka for atypical antipsychotic *Abilify* (aripiprazole), Daiichi for its olmesartan family of antihypertensives including *Benicar*, and Eisai for Alzheimer's drug *Aricept* (donepezil).

Astellas meanwhile is facing a sizeable patent cliff in the US this year for its big-selling overactive bladder therapy *Vesicare* (solifenacin).

Meanwhile, older products in Japan are being squeezed both by increased generic penetration and reforms that more aggressively cut the prices of such products.

Datamonitor is forecasting a combined $4.8bn worth of patent expiry and other impact on revenues in Japan's 10 major companies in the 2017-27 period, with Daiichi alone seen losing $802m over the period.

Astellas has already unveiled plans for early retirement for up to 600 employees in Japan, while Daiichi has already shed several thousand positions over the past few years, including 1,200 mainly sales positions in the US in 2015.

Eisai this March will implement the first in a planned three annual rounds of early retirement, under which it has had 300 applicants (three times more than initially planned), and will pay out related additional costs of around JPY6.6bn.

Even so, Morgan Stanley sees Eisai and Daiichi Sankyo individually as growth stocks with "substantial upside potential", deriving mainly from pipeline drugs for dementia and cancer respectively.

What is clear in all this is that major Japanese firms' strategic shift to oncology and innovation will continue pretty much across the board, against the background of the exclusivity losses in other areas and the increased pricing pressure on older drugs.

YEAR OF CELL AND REGENERATIVE THERAPIES?

Looking ahead to some significant likely product approvals in Japan, 2019 seems set to be the year when regenerative medicines and cell therapies truly become more mainstream.

Nipro Corp.'s *Stemirac*, the world's first stem cell therapy for spinal cord injury, set the stage with a approval in late December (it is still awaiting price listing and launch), and others look set to follow.

Nine cell/regenerative therapies have already been granted "sakigake" (pioneering therapy) designation by the national drugs regulator, the PMDA, enabling speedier, conditional reviews and approvals, and illustrating the growing pipeline.

Among foreign firms, **Novartis AG** is poised to be an important player, given that approval of its gene therapy for spinal muscular atrophy, AVXS-101 (which came as part of its $8.7bn acquisition of **AveXis Inc.**), could come in the first half.

The Swiss firm's *Kymriah* (tisagenlecleucel) also appears on course to become the first CAR-T therapy to be approved in Japan, for acute lymphocytic leukemia and diffuse large B-cell lymphoma, following an April 2018 submission.

Other nods in the gene therapy sector may come for Otsuka and **Takara Bio Inc.**'s TBI-1301 for synovial sarcoma, which uses NY-ESO-1 antigen-specific, TCR gene-transduced autologous lymphocytes, while **AnGes Inc.**'s HGF therapy *Collategene* (beperminogene perplasmid) may finally be cleared following a resubmission around a year ago for critical limb ischemia after a checkered development history.

PRICING CHALLENGES

On the pricing, policy and regulatory side, a hike in Japan's general value added tax, from 8% to 10%, is due in October, and the indications so far are that an extraordinary drug price revision will be implemented at the same time.

This would come on top of the revision in April 2018 that saw reimbursement levels cut by an average of 7.5%, and ahead of the planned start of more frequent annual (rather than biennial) price revisions from 2021.

One given in 2019 is that the research-based industry will continue to express its concerns over the changes last year to the pricing of new therapies, which raised the hurdle for innovation and the price premiums that come along with this status.

In a nutshell, only those first few best-in-class or first-in-class products will be eligible for higher starting prices and exempt from regular price cuts, rather than all new products as under the old system.

In the meantime, companies will come under increasing pressure to demonstrate cost effectiveness under Japan's planned gradual introduction of a formal Health Technology Assessment scheme.

The system saw a number of assessments in 2018 and will be steadily be applied to more new products, creating a growing need for the industry to demonstrate clear outcomes and economic benefits as part of the development process.

Given the past experience with some of the more expensive new immuno-oncology therapies, which have had substantial price cuts as sales grew, eyes will also be on how the new wave of potentially curative cell, gene and regenerative therapies will be priced, amid ongoing debate over how Japan can continue to effectively fund innovation amid a rapidly ageing population.

The R&D industry will certainly continue to argue for the creation of a virtuous cycle, whereby improved pricing to reward innovation will encourage this, in turn bringing down overall health costs and freeing up further funds to support innovation.

At the other end of the innovation spectrum, continued volume growth for generics is likely, ahead of the official goal of an 80% volume share of the substitutable market by the end of September 2020, which has been reached ahead of time.

In the wider healthcare environment, there have been predictions that the planned spread of a community-based, regional integrated healthcare provision scheme in Japan will lead to more specialized facilities, better coordinated care, and improved tracking of outcomes and cost effectiveness. This in turn may encourage uptake of products that can demonstrate utility, regardless of price.

DIGITAL HEALTH, AI MOVES

Extrapolating from moves in 2018, developments in digital Health and artificial intelligence (AI) are likely to continue apace this year, at least at the more progressive companies.

One of these has emerged as **Chugai Pharmaceutical Co. Ltd.**, which has already unveiled early this year a new automated medical information ChatBot system, *MI chat*, which provides AI-driven automated responses to product information enquiries via computer or smartphone.

Initially designed for handling medical professional questions on flu drug *Tamiflu* (oseltamivir), the 24-hour service will improve response times and reduce staff workload for the roughly 12,000 such questions on the product annually.

The human department fields 60,000 questions in total, and the plan is to extend MI chat to all Chugai products by the end of 2021.

The application of AI in drug discovery is also gaining further ground in Japan, which ventures such as **Interprotein Corp.** making use of it to better predict druggable protein-protein interactions.

Elsewhere, the increasing reliance by physicians on online information systems rather than physical interactions with medical reps may be another factor behind further sales force reductions as part of wider corporate restructuring.

And then of course there are a multitude of global macro-economic factors set to play on Japan Pharma, including China's cooling economic growth and uncertainty in Europe over the timing and form of the UK's planned Brexit from the EU.

Against this background, for research-based companies there is a clear imperative to innovate across all aspects of what they do, but also to demonstrate the true value of that innovation to healthcare systems.

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From the editors of PharmAsia News.

Bone Therapeutics Cracks On With Allogeneic Cells For Spinal Fusion, Broken Bones

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The results from an ongoing Phase IIa clinical trial with an allogeneic bone cell therapy, *ALLOB*, are keenly awaited by Gosselies, Belgium-based biotech **Bone Therapeutics SA**, which may eventually have to look at further financing options to progress its cell therapy platform.

Top-line Phase IIa results are expected in mid-2019 with the "off-the-shelf" bone cell therapy, ALLOB, in 32 patients undergoing spinal fusion procedures, Bone Therapeutics said on Jan. 22. These results should be followed, in the second half of 2019, with a submission to EU regulators to start a clinical study of ALLOB, produced using an optimized manufacturing process, in patients with delayed-union bone fractures, the company added.

Last September, Bone Therapeutics reported the final readout from an initial Phase I/IIa clinical study of ALLOB in the treatment of delayed union bone fractures, which was positive. All 21 patients in the study met the primary endpoint six months after cell administration, showing an increase of at least two points on the radiological Tomographic Union Score, or an improvement of at least 25% on the clinical Global Disease Evaluation (GDE) score versus baseline.

Bone Therapeutics is almost alone in evaluating potential therapies in this therapeutic sector.

ALLOB is derived from the *ex vivo* culture of undifferentiated stems cells from the bone marrow of healthy adult volunteer donors, converting them into bone-forming human osteoblastic cells. The company is also developing a way of implanting these cells directly into bone defects using a needle or trephine (a surgical instrument which bores holes in tissue). In the second half of 2019, Bone Therapeutics also expects to start Phase III studies with a potential viscosupplement preparation, JTA-004, in patients with knee osteoarthritis.

Euronext-quoted Bone Therapeutics says it will have sufficient cash until the fourth quarter of 2019, a rapidly approaching timepoint. "Bone Therapeutics is continually reviewing financing options to strengthen its cash position," a company spokesperson told *Scrip*. At the end of 2018, the company had net cash of €8.2m, boosted in January 2019 with a milestone payment of €1m from licensee **Asahi Kasei Corp.**

OSTEONECROSIS DISCONTINUED

Bone Therapeutics was previously developing a potential autologous bone cell therapy, *PREOB*, but in November 2018 decided to stop a Phase III study in hip osteonecrosis because an independent data and safety monitoring board recommended discontinuation for futility – PREOB was well tolerated but the efficacy endpoint was unlikely to be achieved, the board concluded. Bone Therapeutics and its licensee, Asahi Kasei, are reviewing their options with regards to the future of the PREOB licensing agreement, the Belgian biotech noted.

Bone Therapeutics noted at the time of the discontinuation that the science of cellular therapies has advanced; ALLOB cells have shown stronger osteogenic properties than PREOB cells, and 100 million allogeneic cells can be administered in a single local injection, five time more than possible with PREOB. ALLOB has further advantages with regard to logistics and dosing. "The discontinuation of PREOB does not affect development of ALLOB in other promising indications which have different pathophysiologies," the company added.

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Editas Seeks New CEO, CFO Ahead of CRISPR Specialist's New Clinical Era

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With **Editas Medicine Inc.** poised to enter experimental gene-editing tests in humans, backed by a $25m payment from partner **Allergan PLC** for hitting that milestone, the announced departure of the CEO who led the CRISPR specialist to that juncture could be seen as just practical timing.

But that's not how investors saw it when the news broke on Jan. 22.

INVESTOR REACTION

They instead rushed to sell shares in the NASDAQ-listed biotech, sending its value down more than 20% after the gene editing group said Katrine Bosley was stepping down on March 1, becoming the CRISPR specialist's second top executive set to exit on that date. No explanation or reason was given for Bosley's decision to step down.

Editas said board member Cynthia Collins had been appointed to the position on an interim basis.

Bosley briefly discussed her move on Twitter, but offered no details on why she is departing or what her next plans might be.

News of her leaving comes less than a month after Editas' CFO Andrew Hack said he would be exiting the gene-editing company on March 1 to take a position as a managing director at investment group Bain Capital.

Katrine Bosley

PROBABLY OVERDONE

But the initial reaction by investors might prove to have been overly negative in light of where Editas is now and where it is going - and what type of management skills it will need to successfully navigate that.

Bosley's career has been almost exclusively in the biotech industry. She started with the then start-up **Alkermes PLC** in 1991. From there she went on to roles in venture capital and business development in **Biogen Inc.** and **Adnexus Therapeutics Inc.** She has been steering Editas as its CEO for nearly five years.

But moving Editas' lead asset, EDIT-101 - an experimental CRISPR genome editing medicine being investigated for the treatment of Leber Congenital Amaurosis type 10 (LCA10) - into clinical trials could demand different skills.

"We expect the new CEO to be clinically oriented with a focus on transitioning Editas toward a robust product portfolio," Morgan Stanley said in a brief but relatively sanguine reaction sent to investors under the headline: "CEO Transition For Next Phase Of Growth."

> "We do not believe there is any read through or impact to the initial clinical program (EDIT-101) in terms of safety or start of the clinical studies." – Morgan Stanley.

"Importantly, we do not believe there is any read through or impact to the initial clinical program (EDIT-101) in terms of safety or start of the clinical studies," they added.

Morgan Stanley said its projections for Editas remained unchanged despite the announced executive changes, and incorporate US and EU sales from the biotech's gene editing therapy targeting LCA10, which it expects to be earning sales revenue by 2024, as well as additional product revenues starting in 2025 derived from CAR-T therapies, non-malignant hematology, Duchenne muscular dystrophy and cystic fibrosis.

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GSK Looks For New Chair To Lead It Through Fresh Strategic Direction

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Sir Philip Hampton is to stand down as chairman of **GlaxoSmithKline PLC**'s Board, a month after the UK pharma giant announced its decision to split the company into two, combining its consumer business with **Pfizer Inc.**, and leaving it more freedom to invest in its R&D pipeline.

It is thought the separation of GSK's new $9.8bn consumer business with Pfizer (which will eventually become a separately listed company) and its pharma business will take up to five years to complete. A new chairman could see the split through to the end. *(Also see "Pfizer Consumer Combo Deal Frees Capital For GSK Pharma Investment" - Scrip, 19 Dec, 2018.)*

Sir Philip said: "Following the announcement of our deal with Pfizer and the intended separation of the new consumer business, I believe this is the right moment to step down and allow a new chair to oversee this process through to its conclusion over the next few years and to lead the Board into this next phase for GSK."

Sir Philip, 65, was appointed to the board in January 2015, and was made chairman in May 2015. His chairmanship began when the company was embroiled in a Chinese bribery scandal, as well as a major restructuring of the previously announced asset swap with Novartis, and increasing generic competition to its leading products.

Sir Philip was used to guiding companies through difficult times, though. He joined GSK from Royal Bank of Scotland (RBS), chairing the bank at the time of the 2009 banking and financial crisis. Prior to his time at RBS he was CFO at the UK supermarket J. Sainsbury's and previously an investment banker at Lazard.

CONTINUED ON PAGE 23

Juggling Gene Therapies: Sarepta's Focus Grows, With Many Balls In The Air

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Sarepta Therapeutics Inc.'s micro-dystrophin gene therapy program for Duchenne muscular dystrophy (DMD) is getting a lot of attention from investors as a near-term potential cure for the progressive and fatal disease. But while Sarepta is hyper-focused on executing on that program as quickly as possible, the company also is branching out in new directions with the aim of being a leading gene therapy specialist.

In 2018, Sarepta signed multiple partnerships that gave the company access to new gene therapy technologies, broadened its manufacturing footprint, and established a new gene therapy business unit led by Louise Rodino-Klapac, a gene therapy pioneer who previously led gene therapy research for muscular dystrophies at Nationwide Children's Hospital. The company more than doubled in size in terms of employees, now with around 500.

It was a big year for Sarepta as the company started to expand beyond the exon skipping portfolio, including its first marketed drug *Exondys 51* (eteplirsen), which was granted accelerated approval by FDA in 2016, with limited efficacy data. The European Medicines Agency went on to decline marketing authorization, citing concerns about the size of the study used to support the application and duration of follow up. *(Also see "Not The End For Exondys In EU, Says Sarepta " - Pink Sheet, 21 Sep, 2018.)*

Now, in 2019, Sarepta will need to deliver on the plan it has set in motion, showing investors it can balance multiple clinical priorities at the same time while driving toward a big catalyst of getting its first gene therapy onto the market at the end of 2020.

A VERY DIFFERENT COMPANY

"As we track into 2019, in part because we have really significantly increased our vision and our ambition, the amount of inflection points and milestones and activities that we are doing in 2019 is enormous," CEO Doug Ingram said in an interview. "I think if we execute brilliantly we will be a very different company at the end of 2019."

Ingram talked to *Scrip* at the J.P. Morgan Healthcare Conference in January about the development plan for micro-dystrophin, which got a lot of attention at the meeting, but also about the broader strategy for Sarepta to build out the pipeline and branch into new therapeutic areas beyond its heritage in DMD.

The company has 10 gene therapy programs in development, much of it built through business development last year, and Ingram believes the company is poised to be a leader in the field.

Beyond micro-dystrophin, the company is focused on gene therapies for various forms of Limb-girdle muscular dystrophies (LGMD), which are being developed in partnership with **Myonexus Therapeutics Inc.** and were developed by Rodino-Klapac. It also has a gene therapy candidate for the lysosomal storage disorder mucopolysaccharidosis type IIIA (MPS IIIA) from **Lysogene**, and a gene therapy for Pompe disease from **Lacerta Therapeutics Inc.** Sarepta acquired an option to buy Myonexus last year for $60m up front, and in-licensed the MPS IIIA candidate from Lysogene for $17.5m upfront, along with other business development transactions. The in-licensing deal with Lacerta involved a $30m equity investment in exchange for rights to up to three new CNS-targeted gene therapies.

Doug Ingram

"One of the things that we have to be careful about as we expand into other areas is ensuring that we are staying educated and becoming experts in the new areas that we are in."

Micro-dystrophin, meanwhile, has been front and center in the minds of investors after Sarepta presented data on the gene therapy last year showing functional improvements and positive biopsy data on gene expression and biomarkers in a handful of boys. *(Also see "Sarepta Commits To Rapid, Thorough Pivotal Study For DMD Gene Therapy Based On Functional Improvements" - Scrip, 4 Oct, 2018.)*

Sarepta laid out the development plan for moving the therapy forward, based on discussions with the FDA, at the J.P. Morgan meeting, which seemed to confuse some investors. In-

gram said the company has initiated a 24-patient trial focused on functional benefits, but will need to run a confirmatory trial using commercial supply. Nonetheless, he insisted in a follow up interview that the timeline for getting micro-dystrophin approved has not changed and remains late 2020. *(Also see "J.P. Morgan Notebook Day 1: Pfizer, Gilead, Alnylam, Novartis, Sarepta, Deal Trends And Cell Therapy Challenges" - Pink Sheet, 8 Jan, 2019.)*

FROM DMD TO LGMD

But there is another catalyst investors are waiting on, the first biopsy data from the initial LGMD program, MYO-101 targeting LGMD2e. Those data are anticipated shortly; some investors thought it might be available at J.P. Morgan. If the results are positive, they would set the stage for a big development initiative.

MYO-101 uses the same AAVrh.74 vector system as the one used in the micro-dystrophin program and it is designed to transfect a gene that codes for and restores beta-sarcoglycan protein with the goal of restoring the dystroglyan complex. Myonexus also is developing gene therapies for four other forms of LGMD: 2d, 2c, 2b and 2l.

"We are going to look at the data for the 2e program, and if it looks good, we are going to meet with the agency and talk through what the pathway forward for that program is," Ingram said.

The LGMD programs combined could represent a big commercial opportunity, about the same size as micro-dystrophin in DMD.

"While those individual programs are smaller, for instance, in the number of patients than Duchenne muscular dystrophy, Limb-girdle as an umbrella is about the same size as DMD and the five that we have are likely the majority of the Limb-girdle population," Ingram said. "There is an enormous amount of opportunity within Limb-girdle and it is also a devastating disease."

Ingram said the potential for faster, smaller clinical trials when it comes to gene therapies – coupled with the severe nature of the diseases Sarepta is targeting – makes the company's whole strategy possible.

"The idea of building out an enormous pipeline of programs might very well be a fool's errand," he said. "But with gene therapy we think we can build constructs or in-license constructs that have high probabilities of success and the timelines can be greatly contracted because of the unique features of gene therapy, and therefore we can build this pipeline."

One of the big questions that remains if gene therapies successfully reach the market, however, is how expensive one-time cures that could cost millions of dollars will be reimbursed. Alternative payment models for gene therapies were a big discussion topic at J.P. Morgan. *(Also see "The Gene Therapies Are Coming – And So Are New Ways To Pay For Them " - Scrip, 15 Jan, 2019.)*

Sarepta's strategy is also forward looking. As Ingram pointed out, the very nature of working in an area like gene therapy that could deliver one-time cures also requires a broad portfolio to sustain the company long-term. If Sarepta is building the manufacturing footprint and talent to develop and sell micro-dystrophin, and it is successful, than it also needs to think about how it will put those resources to work after the initial bolus of patients are treated.

"Let's think about what is going to happen. We are going to have this enormous period of growth where we are benefiting the patients and treating patients as we get through the prevalent population and then at some point, we will be through the prevalent population and we'll have built up this enormous capacity and this enormous talent and it only makes sense to start thinking now about ways to deploy that talent and capacity to continue to benefit patients."

EXPANDING THROUGH ADJACENCIES

The company is trying to be thoughtful as it looks to expand into new therapeutic areas beyond DMD, where it has a long heritage and has built a patient advocacy network.

"One of the things that we have to be careful about as we expand into other areas is ensuring that we are staying educated and becoming experts in the new areas that we are in," Ingram said. "One of the ways we do that is that we are moving through adjacencies."

LGMD was a natural extension because of the expertise Sarepta has built in neuromuscular rare disease from its background in DMD. The company also has a gene therapy for Pompe disease in early development, which will bring Sarepta into the central nervous system arena.

"Pompe is an interesting one because it is a serious rare disease, and it is a neuromuscular disease in one sense, but it has a significant CNS component, so that starts to bring us into the next adjacency of CNS, and that's where we start thinking about things like MPS as well," Ingram said.

"We might look out in five to seven years and be very far from where we are today in the rare diseases that we are focused on, but it will be natural adjacencies that moved us in that direction," he added.

At the same time, Sarepta expects to continue generating revenues from Exondys 51 and potentially new exon skipping drugs. Exondys 51, which is available only for children who are exon 51 amenable – about 13% of the DMD market – generated $301m in 2017, the company reported at J.P. Morgan.

HUNTING FOR NEW ASSETS

Sarepta already has submitted a second product, golodirsen, for children who are exon 53 amenable, and could get FDA approval in 2019. A third RNA therapy, casimersen, for children who are exon 45 amenable, could follow, pending the result of biopsy data in the first quarter. The three drugs together could represent about 30% of the DMD patient population.

Ingram said Sarepta will continue looking for new assets to bring in while bringing forward gene therapies internally from its 85,000-sq. ft. gene therapy center of excellence in Columbus, Ohio.

"We will bolster our program internally and then we are going to continue to do what we've been doing, which is look for smart opportunities to partner with the best and brightest, in-license programs that fit our pipeline and bolster ourselves there as well," Ingram said.

With more than $1.1bn in cash as of Dec. 31, Sarepta is well positioned to fund its ambitious plan. Investors and patients will be watching closely.

Published online 25 January 2019

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, 18–24 JANUARY 2019

Event Stage	Lead Company/Partner	Drug Name	Indication	Comments	Change To LOA (%)	LOA (%)
Phase III Published Results	Acorda Therapeutics, Inc.	Inbrija (levodopa) Inhalation	Parkinson's Disease	SPAN-PD; The Lancet Neurology, Feb. 2019	0	100
Phase III Published Results	Eli Lilly & Company	Cyramza (ramucirumab)	Hepatocellular Cancer	REACH, REACH-2; The Lancet Oncology, Jan. 18, 2019	0	92
Phase III Published Results	ElsaLys Biotech SAS	Leukotac (inolimomab)	Graft vs. Host Disease	INO-0107; Blood Advances, Jan. 22, 2019	0	0
Phase III Published Results	Proteon Therapeutics, Inc	vonapanitase	Chronic Kidney Disease	PATENCY-1; Journal of Vascular Surgery, Jan. 22, 2019	0	62
Phase III Suspension	AbbVie/Johnson & Johnson	Imbruvica (ibrutinib)	Pancreatic Cancer, Metastatic	RESOLVE; Missed Primary PFS And OS Endpoints	-35	0
Phase III Updated Results	Vifor Pharma	Venofer (iron sucrose)	Anemia Due to Chronic Renal Failure, Dialysis-Dependent	PIVOTAL (CV Outcomes); Achieved Endpoints On Re-Analysis	0	100
Phase III Top-Line Results	Eli Lilly	Lartruvo (olaratumab)	Sarcoma, Advanced	ANNOUNCE (w/doxorubicin); Missed OS Primary Endpoint	0	100
Phase III Top-Line Results	Clearside Biomedical, Inc.	Xipere (triamcinolone acetonide)	Macular Edema Due to Non-Infectious Uveitis	MAGNOLIA; Durable Responses	0	86

Source: Biomedtracker | Informa, 2019

CONTINUED FROM PAGE 19

Hampton receives a £700,000 salary for his role at GSK.

Since Emma Walmsley took up the CEO position at GSK, several high-profile positions have changed hands across all elements of the business. In November 2017 Hal Barron was appointed CSO and president of R&D. Luke Miels joined from **AstraZeneca PLC** to head up GSK's pharmaceutical operations in September 2017, and in April 2018, the company recruited a new head of worldwide business development for pharmaceuticals R&D, Kevin Sin, previously global head of oncology business development at **Genentech Inc.**. The latest change came when long-standing CFO Simon Dingemans announced his retirement, making way for HSBC's group finance director Iain Mackay.

GSK has not confirmed when Sir Philip will be leaving the board, but it has started to look for a replacement. Its share price was largely unchanged by the news. Vindi Banga, GSK's senior independent director, said: "The Group has a clear strategy, is delivering improved operating performance and has a clear pathway forward, this is a good time to start the process to find Philip's successor."

Sir Philip Hampton

Sir Philip also chairs the UK government's Hampton-Alexander review of women on company boards, which aims to improve gender balance in FTSE companies.

Published online 22 January 2019

APPOINTMENTS

Executive	To Company	New Role	From Company	Previous Role	Effective Date
Andrew Oxtoby	Aimmune Therapeutics	Chief Commercial Officer	Eli Lilly & Co	Vice President, US Diabetes Connected Care	22-Jan-19
Paul Streck	Alder Biopharmaceuticals Inc	Chief Medical Officer	Insmed Inc	Chief Medical Officer	21-Jan-19
Jay Venkatesan	Angion Biomedica Corp	Chief Executive Officer and President	Alpine Immune Sciences	President	4-Jan-19
John F. Neylan	Angion Biomedica Corp	Chief Medical Officer and Senior Vice President	Keryx	Chief Medical Officer	4-Jan-19
Eric Sandberg	AxoGen Inc	Chief Commercial Officer	Visura Technologies	Chief Executive Officer	21-Jan-19
Israel Gutierrez	Geron Corp	Vice President, Pharmacovigilance and Drug Safety	Clindatum LLC	President, Innovation	Mid-2019
Johan Luthman	H. Lundbeck AS	Executive Vice President and Head, Research and Development	Eisai	Senior Vice President, Head, Clinical Development	1-Mar-19
Lewis Warrington	Ironshore Pharmaceuticals Inc	Vice President and Head, Medical Affairs	Merck	Lead, Medical Affairs	14-Jan-19
Fatih Uckun	Oncotelic Inc	Chief Medical Officer	Ares Pharmaceuticals	Head, Immuno-Oncology	22-Jan-19
Susanne Dorn	Pharnext	Chief Regulatory Officer	Sanofi Genzyme	Head, Regulatory Affairs, Immunology and Neurology	14-Jan-19
Samantha Paston	Scancell Ltd	Head, Research	Immunocore	Head, T Cell Cloning	15-Jan-19

Click here for all appointments: https://bit.ly/2oHWRYn

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