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# J.P. Morgan: No Big Deals, But Plenty Of Pipeline, Commercial Highlights

MANDY JACKSON JESSICA MERRILL ANDREW MCCONAGHIE

## NO BIG DEALS THIS YEAR?

The overarching theme so far at the J.P. Morgan Healthcare Conference this year is a big question: "Where are the deals?"

There were several partnerships announced as the meeting kicked off on 13 January, such as Biogen's agreement to license a neuroscience drug candidate from Pfizer Inc., but there were no big acquisitions revealed on day one of the conference.

That's in stark contrast to last year's J.P. Morgan meeting when Eli Lilly & Co. announced the $8bn acquisition of Loxo Oncology Inc., which came within days of Bristol-Myers Squibb Co.'s announcement that it would pay $74bn for Celgene Corp.

Bristol-Myers CEO Giovanni Caforio said on 13 January at this year's J.P. Morgan conference that the company remains committed to business development to expand its pipeline, even after digesting its Celgene acquisition. Those deals are likely to be smaller transactions and partnerships, however.

"We really believe in the importance of business development," Caforio said during the Q&A session following his presentation at the meeting, noting that the history of both Bristol and Celgene has been to complement internal innovation with external assets.

He said Bristol's business development focus primarily will be "small science deals" going forward, including opportunities reviewed during J.P. Morgan that may strengthen the company's early pipeline.

"When we believe there is great science that complements ours, we do have capacity to do those deals," Caforio said.

Merck & Co. Inc. opted for a fireside chat with CEO Ken Frazier and executive vice president/president of Merck Research Laboratories Roger Perlmutter instead of a 25-minute presentation by the CEO. When asked about business development, Frazier reminded the audience that the company doesn't see a lot of value in big M&A deals, but intended to continue with bolt-on acquisitions and smaller transactions.

"We think that business development will remain for us a very important element going forward," the CEO said. "What's the next great opportunity in science and how can we get a hold of it in a way that creates the most value for shareholders? As we think about bolt-on acquisitions, we are looking for those in a financially disciplined way."

He noted that Merck did more than 80 deals in 2019 and spent about $8bn, including the pending $2.7bn acquisition of ArQule Inc. that was announced in December.

Biogen CEO Michel Vounatsos left the door open for the company to enter into transactions of all sizes, noting that as of the end of 2019 it had about $16bn in financial capacity for deals, including $6bn on hand that could be leveraged with $10bn in debt.

Through 2024, the company expects to have $51bn in financial capacity for deals based on its current portfolio, but not including any sales from the Alzheimer's therapy aducanumab, which Biogen plans to submit for US Food and Drug Administration approval imminently, based largely

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## from the editor

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As I write, the J.P. Morgan Healthcare conference is getting under way in San Francisco and Twitter is abuzz with #JPM20 commentary. One talking point in particular stands out.

Jen Horonjeff is an arthritis patient who has set up a match-making service between patients and healthcare companies to improve health innovation based on what patients really need, and to compensate patients for their contributions. Her appearance on IDEA Pharma's UNHERD@JPM20 panel session to discuss the future of pharma could have been just another nod towards 'patient centricity', but instead she set the Twittersphere alight. This was because she took to the stage in a hospital gown.

Horonjeff's wardrobe statement was an eloquent call at a meeting that is all about the money in health to remember that it should be all about the patients. It spoke far louder than the discussion itself. There is a serious power imbalance between those who profess to provide health solutions and those on the receiving end of said solutions, and the hospital gown with its undignified back-fastening is a suitable emblem for that. As Horonjeff tweeted, "Patients are often stripped of agency and blamed when they don't 'comply'."

Horonjeff's rallying cry to #askpatients is one I'd urge biopharma executives large and small to keep front of mind. Bring real, actual patients into the conversation throughout the drug discovery, development and commercialization continuum, and you greatly improve your chances of doing good for society and making a success of your drug. In any case, it will be your rear end hanging out of a gown one day.

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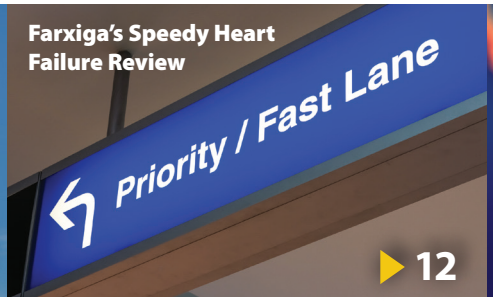



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## Novo Nordisk's New India Chief Steps Into Bustling Diabetes Arena

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Top-level executive changes continue in India, with Novo Nordisk AS bringing in experienced hand Vikrant Shrotriya to helm its operations in the country.

Shrotriya, whose career spans over two decades in the healthcare industry, was more recently vice-president for Novo Nordisk's GCC (Gulf Cooperation Council) business and corporate vice-president for Saudi Arabia. Novo Nordisk India long-timer and erstwhile managing director Melvin Oscar D'souza has moved to an "international role" within the Danish drug maker, the company told *Scrip*.

Shrotriya noted that India is an important market for Novo Nordisk, with its focus on enhancing healthcare through awareness and education. "We will continue to work towards improving access to quality care by working closely with the relevant stakeholders," the incoming managing director said.

Novo Nordisk joins a list of companies witnessing top-level changes in India in the recent past. Roche India managing director Lara Bezerra, Eisai Pharmaceuticals India Pvt. Ltd. head Sanjit Singh Lamba, Janssen India chief Sanjiv Navangul and Cipla Ltd.'s chief operating officer R Ananthanarayanan are among those who moved on last year.

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**To read the rest of this story go to: https://bit.ly/30i4g2G**

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on a Phase III program in which only one of two studies met the primary endpoint.

"The Biogen team is continuously screening opportunities from small to large size," Vounatsos said during the Q&A session following the company's presentation.

Gilead Sciences Inc. CEO Dan O'Day – in his first presentation at the company's helm from the J.P. Morgan podium – emphasized many times Gilead's investments in both internal and external innovation. O'Day said the company will pursue M&A "from a position of strength and with a sense of urgency," considering everything from early-stage collaborations to commercial-stage assets to expand Gilead's research and development pipeline as well as boost revenue growth. That said, both O'Day and chief financial officer Andrew Dickinson noted the unique nature of the company's partnership with Galapagos NV, which the companies expanded last year to give Gilead access to more of Galapagos's inflammation and fibrosis development programs.

"It is a really thoughtful partnership," Dickinson said. "We can't do a lot of those, but we would like to do at least one more." He noted that Gilead is most interested in small- to medium-sized bolt-on transactions, and it has a fiduciary obligation to look at larger transactions, but said the company doesn't see big M&A deals adding enough value over time.

## ZOLGENSMA REIMBURSEMENT: VBR IS IN, ANNUITIES OUT

Only one patient with spinal muscular atrophy (SMA) treated with Zolgensma in the US has not been reimbursed since the expensive gene therapy launched in mid-2019. Novartis AG's AveXis Inc. president David Lennon talked about the launch of Zolgensma and market access during an interview at the J.P. Morgan Healthcare conference on 13 January.

Even though Zolgensma has been widely reimbursed so far, some patients have had to go through several rounds of back-and-forth with payers to secure reimbursement. Those are generally not newly diagnosed patients, for which the turnaround time from initiation to treatment, particularly for newborns, has been typically less than two weeks, according to Lennon.

"There's another population, which skews to the older population that has been treating with Spinraza currently and often there is push-back on different elements," Lennon said. Some of the requirements payers have in place include formal assurance that patients are going to stop taking Biogen's Spinraza (nusinersen) or more information from physicians around the justification for initiating treatment.

Zolgensma launched in June with a $2.1m price tag as the first potential one-time gene therapy for SMA. Novartis offered payers a value-based reimbursement option and a five-year annuity payment model for those that might rather pay in installments as opposed to fronting the full cost.

Not a single payer has taken Novartis up on the extended payment plan, however. In Europe, where Zolgensma is not yet approved and where governments are looking at contracts for a group of patients at one time, the idea seems to have more traction, Lennon said.

"This isn't the use case for it," Lennon said of the annuity payments in the US. "I think you need something bigger or a more urgent bolus of patients." If Zolgensma eventually secures FDA approval for Type 2 SMA as Novartis hopes, that could represent a more relevant test case, he said. "Right now, we are talking about a few hundred patients, five to 10 patients per a big plan. It's just not a big enough number."

US payers, however, have been receptive to the value-based reimbursement plan, in which Novartis agrees to pay a rebate if the drug doesn't perform as expected. The outcome the rebate is tied to is death or permanent ventilation. Novartis has not yet had to pay a rebate linked to a disappointing outcome, Lennon pointed out.

Novartis did not disclose the latest revenue for Zolgensma, which will be provided later in January when fourth quarter financials are released. Zolgensma generated $160m in the third quarter, a strong launch.

## FOR SAREPTA, ANOTHER EXON-SKIPPING DRUG

Sarepta has initiated a rolling submission for a third exon-skipping drug, casimersen, with the US FDA, CEO Doug Ingram said during the company's 13 January presentation. The candidate, like Sarepta's other two exon-skipping drugs, would be targeted to a small subset of patients with Duchenne muscular dystrophy, this time for children who are exon 45 amenable.

"It is our goal to obtain that approval in 2020," Ingram said. If successful, he noted, "We will be among that very rare club of biotechs that have three or more internally developed and FDA approved therapies." Sarepta's exon-skipping drugs, including the first one Exondys (eteplirsen) and the second Vyondys (golodirsen), have not been without controversy, however, due to limited efficacy data. The three drugs together address about 30% of the DMD patient population.

The FDA approval of Vyondys in December was a bit of a surprise, as it represented a big reversal on the part of the agency, which had issued a complete response letter due to renal safety and then reversed its decision.

Presenting to the J.P. Morgan audience, Ingram thanked the FDA for working with the company to resolve their questions – and also restated that the company hadn't overstepped the mark or pressured the regulator to change its mind.

Sarepta already is gaining some commercial momentum. The company announced that Exondys generated more than $100m in the fourth quarter and around $381m in 2018.

Investors, however, are more interested in Sarepta's gene therapy SRP-9001. The therapy has produced positive nine-month functional data from the first four-patient cohort, significantly impacting biomarkers for the disease, including a 96% expression of micro-dystrophin measured by signal intensity, as well as encouraging improvements of the physical function of the first four boys in the trial.

Results from SRP-9001's first placebo-controlled trial will be ready in early 2021, with what Ingram, Sarepta and the Duchenne community hope will be a major step forward in halting the life-limiting disease.

"This is what the revolution looks like," Ingram said. The gene therapy initiative was also recently boosted by a new ex-US commercial deal with Roche.

Sarepta also announced at the J.P. Morgan meeting another coup – Gilead's ex-CEO John Martin joined its board. Ingram told *Scrip* that he had reached out to Martin to help advise the company, saying his experience in launching curative treatments in hepatitis C would be invaluable to Sarepta.

"He has been involved in so many transformative moments in medicine … but he has never joined any other company board before," Ingram said. "But if you are going to bet on any company, why wouldn't it be Sarepta?"

## BMS HAPPY WITH POST-MERGER PROGRESS

Bristol-Myers CEO Caforio's 2019 presentation at the J.P. Morgan Healthcare Conference in San Francisco occurred just days after the company announced that it would pay $74bn for Celgene and his 2020 presentation on 13 January came about two months after the companies closed their transaction.

And now that Celgene has been integrated into Bristol-Myers, Caforio told the audience, "I feel better about our opportunity at Bristol-Myers Squibb today than I felt one year ago when we announced the deal. The company truly is well positioned today and in the future."

Caforio outlined progress in Bristol's pipeline during the past year – including for the Celgene assets – and noted the eight launches that the company anticipates over the next 24 months. Among those are new indications for key products, including first-line lung cancer indications for the blockbuster combination of PD-1 inhibitor Opdivo (nivolumab) and CTLA4-inhibitor Yervoy (ipilimumab) based on the CheckMate-227 and CheckMate-9LA studies.

Celgene made progress on several late-stage assets prior to its merger into Bristol, such as a new drug application (NDA) resubmission to the US FDA for S1P receptor modulator ozanimod in multiple sclerosis.

Biologic license application (BLA)-supporting data for the CD19-targeting chimeric antigen receptor T-cell (CAR-T) therapy lisocabtagene maraleucel (JCAR017, liso-cel) in lymphoma were presented at the American Society for Hematology meeting in December – and Caforio emphasized Bristol's commitment to the cell therapy space in oncology at the J.P. Morgan meeting, noting that more products and new indications are coming in this space.

The company has filed its BLA for liso-cel and anticipates a BLA filing in the first half of 2020 for idecabtagene vicleucel (ide-cel, bb2121) against B-cell maturation antigen (BCMA) in multiple myeloma – a filing that must be expected sooner rather than later since executive vice president and president, hematology Nadim Ahmed said during the Q&A session following Caforio's presentation that Bristol will have two CAR-T therapies on the market by the end of this year.

The CAR-T programs have been high-profile assets under both Celgene and Bristol, but one asset that's flown somewhat under the radar is Reblozyl (luspatercept), which is partnered with Acceleron Pharma Inc. and was approved last year for transfusion-dependent beta-thalassemia.

An NDA is pending now at FDA for a much larger indication – the treatment of adults with very low to intermediate risk myelodysplastic syndromes (MDS)-associated anemia who have ring sideroblasts and require red blood cell transfusions.

Ahmed said anemia is one of the biggest problems associated with MDS, because patients become transfusion-dependent. He noted that Bristol will capitalize on its experience in MDS – through Celgene's long-term participation in that market with its drug Vidaza (azacitadine) – and its relationships with treating physicians in this area to maximize Reblozyl's potential beyond the "smaller niche indication" of transfusion-dependent beta-thalassemia.

## TEVA'S PROSPECTS FOR AN OPIOID LITIGATION SETTLEMENT

Teva Pharmaceutical Industries Ltd. CEO Kare Schultz said during the company's breakout session that he is cautiously optimistic the company could finalize a broad opioid litigation settlement ahead of a big state case in New York that is headed to trial in mid-March. "There is kind of a deadline coming up because it would be advantageous for everybody to get the actual settlement done before the next state trial," Schultz said.

The uncertain cost of the company's potential liability in ongoing opioid litigation has been a big overhang for Teva, even as the company has made some progress on its efforts to make a turnaround.

Last year, Teva proposed a national settlement framework that would allow the company to settle much of the ongoing litigation with some states' attorneys general. That proposal includes a $250m upfront payment and an offer to donate $23bn in supply of the opioid addiction treatment Suboxone (buprenorphine naloxone) tablets over 10 years.

"I think there's a lot of political momentum behind this because it's actually doing something really to try and improve the situation," Schultz added.

Teva did not update investors on the 2019 financials or outlook for 2020. The financial update is planned for 12 February. The company has said it hopes 2019 will be a trough year before it returns to growth in 2020, but there are a lot of elements of its business strategy that need to be in place to get there. One snag has been the slow launch of the CGRP drug Ajovy (fremanezumab) for migraine, which has struggled against Eli Lilly & Co.'s Emgality (galcanezumab) and Amgen Inc.'s Aimovig (erenumab), both of which are available in an auto-injector.

Teva is developing an auto-injector version of Ajovy that it thinks will help level the playing field, but it is pending at FDA. Pricing competition in the space has been stiffer than Teva had originally expected, Schultz said. The pricing set by Amgen when it launched Aimovig was lower than Teva had expected, and then rebates have been higher with three players in the market. "That means that the value per patient is probably maybe half of what we thought it would be net three/four years ago, but on the other hand, the volume is significantly higher."

## VERTEX'S LEIDEN PASSES THE BATON

In a fitting presentation for Vertex Pharmaceuticals Inc.'s big transition year, outgoing CEO Jeffrey Leiden and incoming CEO and current chief medical officer Reshma Kewalramani addressed J.P. Morgan attendees together. It was a symbolic changing of the guard as Leiden wraps up his seven-year tenure as Vertex CEO and Kewalramani begins her leadership reign. The leadership change comes at a broader period of transition for Vertex, which aims to move beyond its core therapeutic area of cystic fibrosis.

"I cannot underestimate, and I don't think anybody does, the challenge of going from one medicine to many, one disease area, to many," Kewalramani. But she said Vertex is well positioned to take on the challenge, having now built out the pipeline partly through internal R&D and partly through business development into areas like sickle cell disease, beta thalassemia, Duchenne muscular dystrophy and type 1 diabetes.

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# EQRx Aims To Upend Industry's Pricing Model, With Me-Too Drugs

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A start-up with ambitions to disrupt the industry's long-standing drug pricing model could be a new threat to big pharma. EQRx has $200m in financing, a big-name leadership team and a mission to develop me-too drugs that cost a fraction of the cost of first-to-market brands.

*EQRx hopes to disrupt industry's business as usual pricing model*

EQRx is the brainchild of venture capitalist and entrepreneur Alexis Borisy, formerly of Third Rock Ventures, who will be CEO. He has convinced some high-profile leaders to join him in his new venture, including Foundation Medicine Inc.'s former chief business officer Melanie Nallicheri, who is president; former Genentech Inc. chief medical officer Sandra Horning, who is co-founder and advisor; and Peter Bach, frequent industry antagonist and director of the Memorial Sloan Kettering Cancer Center for Health Policy and Outcomes, who is co-founder and advisor. Bach, in particular, is a notable addition to the team, given that he hasn't before tied himself to a drug maker.

The company came out of stealth mode with a bang, announcing the launch on the opening day of the J.P. Morgan Healthcare Conference on 13 January, and it plans to continue on a similar course.

## GO BIG OR GO HOME

"Our aim is to launch the first product in five years. We want to launch 10 within 10 years, with more than a dozen in late-stage development," Borisy said in an interview. He has a creative name for the products too – "equivelars." They'll be novel, patent-protected branded drugs, following three to five years after a first-to-market launch, though well ahead of a generic entry. EQRx will be focusing in oncology, immunology and inflammation, and rare genetic diseases.

The plan is ambitious and challenging, as he expects to deliver a healthy profit to investors and succeed in a way that hasn't so far worked in the industry. Late-to-market brand drugs usually struggle to catch up to their first-to-market rivals, unless they come to the market with some kind of impressive efficacy or safety benefit. Pfizer Inc.'s first-in-class CDK4/6 inhibitor Ibrance (palbociclib) is a perfect example, where it has largely held the market despite new rivals.

The drug distribution system is particularly complicated because it revolves around securing market access from payers and often, particularly in specialty therapeutic areas, comes down to high volumes and rebates, not price. The experience with some early biosimilars in the US has underscored that challenge. Even when later branded market entrants have tried to undercut on price, as was the case with the 2014 launch of GlaxoSmithKline PLC's GLP-1 product Tanzeum (albiglutide), the strategy hasn't delivered. GSK ultimately pulled Tanzeum from the market in 2017. But Borisy believes that because of the increasingly high cost of drugs and because EQRx will approach the entire drug development and commercialization process in a new way, using disruptive technologies, that it will triumph where others have not. Sometimes, it takes a big new disruptor to upend the system, he said.

## NOW IS THE TIME

"You could not have done this five years ago or 10 years ago because the technologies were not there to enable you to go and do it, and of course as the prices of drugs spiral ever higher that also creates more room in the disconnect," Borisy explained.

He said EQRx will do everything differently, engineering efficiencies into the process from R&D to commercialization, but he wouldn't provide a lot of details about how the company will do that.

"We are just approaching it in a disruptor business model of engineering at scale to say we can do this, where we are geared to efficiency and high productivity and high probabilities of success," he said. "In that rethinking, reimagining, reengineering the whole process of how you make a drug, prove it works and sell it, we can bring our unit costs down of making great new drugs, proving that they are great new drugs and selling those great new drugs."

As for how much cheaper EQRx might undercut its brand competition on price, Borisy only said he expects the company's products to cost "a fraction" of the price.

Borisy brings a certain amount of credibility to a scheme that might otherwise sound inspiring but outlandish. He has

spearheaded investments in more than 50 biotechs and been personally involved as a founder or CEO in 15, including Blueprint Medicines Corp., Foundation Medicine and Warp Drive Bio Inc.. He stepped away from Third Rock last year to work on this new project.

"Sometimes you have to believe, you have to look and assess what is possible, you have to begin to put the pieces together and if you know that your true north is strong, you have to just have your hand on the wheel and say we're going there because it has to be done," he said.

## CHANGE IS COMING

As a longtime biotech investor, Borisy said he certainly believes innovation should be rewarded, but that the current pattern of higher drug prices, well above the rate of inflation, against the back drop of patients worrying about how they are going to afford medicines or lose their life savings is simply unsustainable.

The name of the company, EQRx, was inspired by a lot of his thinking on those societal challenges around health care. It represents equitable medicine, equal access, equally as good quality at affordable prices. The name also stands for "emotional quotient," he said, "because our industry, which I'm so proud of, has had such high EQ, particularly in this golden age, but this is a company we want to have high EQ as well."

As for how the pharmaceutical industry might react to the start-up, Borisey said, "For those people that think 10 years from now we are going to be pricing in the way that we do today, I would say that they are sticking their head in the sand."

"Whether it's a company like EQRx or others that may follow in our business model, whether it is Chinese competition five to 10 years from now, whether it's the politicians, whether in this country or elsewhere, I think this is going to change radically," he added.

Borisy expects EQRx, which is based in Cambridge, MA, to be sizable, building quickly from its current 15 employees to more than 100 and growing next year.

The company's $200m series A financing included investors GV, ARCH Venture Partners, a 16z, Casdin Capital, Section 32, Nextech and Aboretum Ventures.

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# Lilly's Paying $1.1bn For Itch Advantage With Dermira's Lebrikizumab

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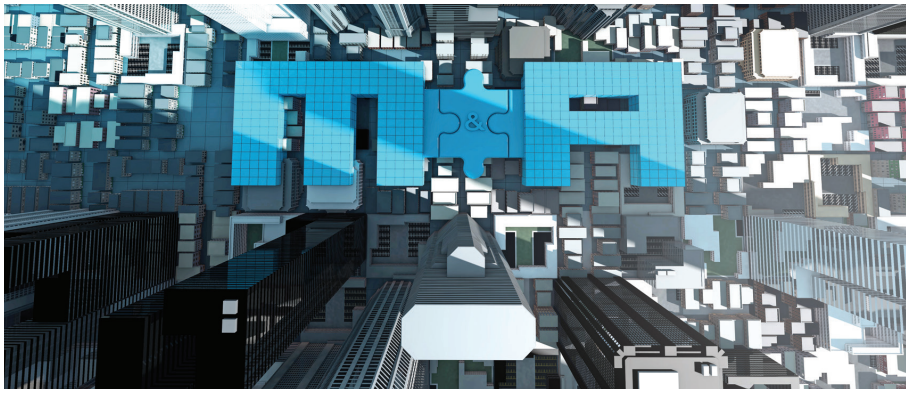

Not satisfied with the oral JAK inhibitor Olumiant (baricitinib) as its only potential competitor for Sanofi/Regeneron Pharmaceuticals Inc.'s atopic dermatitis blockbuster Dupixent (dupilumab), Eli Lilly & Co. agreed on 10 January to pay $1.1bn in cash for Dermira Inc. and its Phase III interleukin-13 inhibitor for that indication. Lilly expects to close its acquisition of the Menlo Park, CA-based dermatology drug developer by the end of the first quarter.

The acquisition of Dermira makes two years in a row that Lilly announced a large acquisition around the start of the annual J.P. Morgan Healthcare Conference in San Francisco, which will run this year from 13-16 January. The pharma announced in early 2019 that it would pay $8bn to acquire Loxo Oncology Inc. and its tumor-agnostic approach to treating cancer; by the end of last year Lilly had decided to reorganize its cancer franchise around the Loxo pipeline and personnel. *(Also see "Lilly Taps Loxo Execs To Bring Back That Biotech Feeling" - Scrip, 5 Dec, 2019.)*

The Dermira deal is in keeping with Lilly's strategy to focus on diabetes, oncology, immunology, Alzheimer's disease and pain, said Lilly Bio-Medicines president Patrik Jonsson in an interview, but the transaction doesn't indicate that the Indianapolis pharma will look to make an M&A deal at this time each year going forward.

"Not necessarily at the time of J.P. Morgan, but augmenting our internal R&D efforts with external business development opportunities is something that we'll continue to do when the opportunity arises," the exec said.

Acquiring Dermira is motivated by the opportunity to pair a potential monthly injectable therapy for atopic dermatitis (AD) with its JAK1/2 inhibitor Olumiant as an oral therapy option for that patient base. Partnered with Incyte Corp., Lilly is running a Phase III program for Olumiant – already approved for rheumatoid arthritis – in AD and has reported out three positive Phase III trials in that indication. *(Also see "Lilly/Incyte's Olumiant Breezes Ahead of JAK Pack In Atopic Dermatitis " - Scrip, 5 Feb, 2019.)*

Dermira obtained lebrikizumab from Roche for $80m up front in 2017, with plans to test the antibody in AD after Roche decided the drug didn't offer the profile it hoped for in asthma. *(Also see "Dermira Takes Roche's Lebrikizumab With Best-In-Class Ambitions" - Scrip, 8 Aug, 2017.)* Last March, Dermira reported Phase IIb data showing lebrikizumab offered similar efficacy to Dupixent, an IL-4/IL-13 receptor antagonist, on a monthly dosing schedule.

Dupixent (dupilumab) is dosed twice-monthly, so less-frequent administration would offer one area of differentiation from the market leader, but Jonsson said Lilly thinks lebrikizumab will also offer an itch-relief advantage compared to Dupixent.

### UNMET NEED PERCEIVED FOR AD ITCH RELIEF

Jonsson said an estimated 18m Americans suffer from AD, also known as eczema, with about 10m having moderate-to-severe AD, the indication being sought for lebrikizumab. Lilly's market research indicates that both patients and doctors perceive an unmet medical need for itch relief in AD therapy, he added.

"We were encouraged by the Phase IIb data for lebrikizumab where we saw very good efficacy on skin but also the potential opportunity to differentiate positively on itching," Jonsson said. "We believe therefore that lebrikizumab has the potential to be a best-in-class and actually a best-in-this-space medicine for the treatment of AD."

The Indianapolis-based firm sees lebrikizumab and Olumiant as offering potential for a complementary franchise in AD, the exec said, with Olumiant providing an option for AD patients who don't want to start an injectable course of therapy. "We know that there is a big chunk of patients today hesitant to start an injectable treatment, so we see Olumiant and lebrikizumab as complementary to each other in this space," he said.

Olumiant, however, has presented some safety concerns with one patient experiencing a pulmonary embolism in the Phase III program. *(Also see "Lilly's Latest Olumiant Data Raise Question Of JAK Inhibitor Role In Atopic Dermatitis" - Scrip, 27 Aug, 2019.)*

Datamonitor Healthcare analyst Dominique Fontanilla told *Scrip* that recent data for both lebrikizumab and AstraZeneca PLC's competing tralokinumab suggest targeting IL-13 can offer similar benefits to the dual IL-4/IL-13 inhibitor approach of Dupixent.

Sanofi told investors in December that it forecasts €10bn in peak sales for Dupixent (about $11.1bn), after the product yielded €1.39bn during the first three quarters of 2019, and that it and Regeneron were planning to leave the JAK inhibitor class behind in AD. *(Also see "Sanofi's €10bn Dupixent Plan: 'We're Going To Put The JAKs Properly In Their Place'" - Scrip, 12 Dec, 2019.)*

"Without Phase III results for lebrikizumab and without quantitative Phase III results for tralokinumab, it's difficult to say whether IL-13 blockade translates to improved risk/benefit advantages over Dupixent, and numerical data will be vital to answering these questions," Fontanilla said. "This is especially the case with the monthly dosing schedule that is featured in lebrikizumab's Phase III maintenance program, since Dermira believes the drug will improve upon Dupixent's biweekly dosing schedule, but we have yet to see results from lebrikizumab administration on a monthly basis."

She sees some of the top unmet needs in the space as novel systemic products for patients refractory to current therapies, safe maintenance therapies and targeted therapies. "And despite the existence of [Pfizer's topical] Eucrisa (crisaborole) and Dupixent, the unmet need in AD is still high," the analyst continued, "especially for patients with severe or refractory disease."

While lebrikizumab also demonstrated solid efficacy in a biweekly dosing regimen, Lilly has no plans at this time to make any protocol changes, Jonsson said, and it expects the Phase III program to report data in late 2021, making a market launch of lebrikizumab in early 2023 feasible.

Dermira out-licensed European commercial rights to lebrikizumab last year to Almirall SA. Jonsson said Lilly anticipates a productive partnership with the Spanish pharma and will not seek to acquire the EU rights to the product. *(Also see "Almirall Extends Dermatology Reach With Dermira Lebrikizumab Deal" - Scrip, 12 Feb, 2019.)*

The deal terms specify that Lilly will pay $18.75 per share for Dermira, an 86% premium to the biotech's 60-day volume-weighted average trading price as of 9 January. Dermira would be eligible for a $40m termination fee if the deal falls through, but Jonsson said he sees no reason why it would. In addition to lebrikizumab, the transaction will give Lilly Qbrexza (glycopyrronium), a medicated cloth product for primary axillary hyperhidrosis.

Jonsson said this indication – uncontrolled excessive underarm sweating – is underdiagnosed and underserved and Lilly is impressed with how Dermira has developed physician and patient awareness so far. The exec said an estimated 10m Americans suffer from primary axillary hyperhidrosis, but only about 30% are diagnosed and far fewer treated. *(Also see "Dermira Leans On Patient Experience With Hyperhidrosis As It Readies For Qbrexza Launch" - Scrip, 5 Sep, 2018.)*.

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# Merck Joins KRAS Stampede In Deal With Otsuka Affiliates

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Amgen Inc.'s clinical success in targeting the KRAS oncogene for cancer therapy last year has led to large pharma companies entering the space, with Merck & Co. Inc. the most recent entrant via a collaboration with two biotechs operating under the umbrella of Japanese pharma Otsuka Pharmaceutical Co. Ltd. In a deal announced on 6 January, Taiho Pharmaceutical Co. Ltd. and Astex Pharmaceuticals Inc. will share a $50m upfront payment and could earn up to $2.5bn in milestones and other payouts by combining preclinical KRAS pipeline assets with Merck.

The goal is to develop small molecule KRAS (kirsten rat sarcoma virus) inhibitors, as well as cancer drugs addressing other unspecified targets, with Merck funding research and development and holding virtually all commercial rights to the candidates. Taiho will retain co-commercialization rights in Japan and an option to co-promote in unspecified southeast Asian markets.

Merck says the three firms will combine their knowledge and expertise in the target, including the New Jersey big pharma's experience in developing small molecule therapies and drugs that target cancer cell signaling. In addition to the $50m going to Taiho and Astex, Merck also will pay out preclinical, clinical, regulatory and sales milestones pegged to multiple potential commercial products resulting from the collaboration. The two biotechs can earn tiered sales royalties on products reaching market as well.

Noting that KRAS is one of the most commonly found oncogene mutations in

cancer, Merck said it is implicated in an estimated 90% of pancreatic cancers as well as 20% of non-small cell lung cancer cases, and is associated with poor outcomes.

But despite years of effort, the first real clinical success in targeting KRAS came at the American Society of Clinical Oncology conference last June, where Amgen presented Phase I data for AMG 510. The drug, which targets G12C (glycine-to-cysteine) mutations of KRAS, showed a 50% response rate with one complete response in 10 NSCLC patients. *(Also see "Amgen's KRAS Inhibitor AMG 510 Leans Toward Tumor-Dependent, Not Agnostic, Approach" - Scrip, 3 Jun, 2019.)* The highest dose of four tested in that study, 960mg daily, has advanced into further study.

In September, Amgen presented further data on AMG 510, indicating that while the agent had shown less efficacy in colorectal cancer than in lung cancer, it might still offer an improved therapeutic profile for CRC patients in combination with other drugs. *(Also see "Amgen KRAS Inhibitor Less Effective In Colorectal Cancer Than Lung" - Scrip, 28 Sep, 2019.)* Only one in 12 CRC patients (8%) in the study achieved a partial response, the company reported, but the drug did yield a 92% disease control rate, close to the 100% achieved in NSCLC patients. Amgen also updated the study's NSCLC data, saying seven of 13 patients (54%) had achieved a partial response.

In October, Mirati Therapeutics Inc. unveiled data showing that its KRAS G12C inhibitor MRTX849 might offer efficacy as good as that of AMG 510 in NSCLC and CRC patients. *(Also see "Mirati's First KRAS Data Look At Least As Good As Amgen's " - Scrip, 29 Oct, 2019.)* Those data made MRTX849 only the second drug to demonstrate a clinical trial effect in KRAS-mutated cancer, which before 2019 had been considered a possibly undruggable target.

Other agents are advancing, and the Merck deal isn't the only recent move into the KRAS space. In October, Novartis AG unveiled a multi-year research collaboration on novel KRAS inhibitors with Cancer Research UK, including exclusive options to license candidates discovered by the partnership. *(Also see "Novartis Snaps Up KRAS Inhibitor R&D" - Scrip, 24 Oct, 2019.)*

> "Building on the first clinical results for KRAS inhibitors released last year, the KRAS space continues to generate excitement." – Michael Ramirez

## COULD COLLABORATION MOVE KRAS SPACE BEYOND G12C MUTATIONS?

Datamonitor Healthcare oncology analyst Michael Ramirez said the field now anticipates development of KRAS inhibitors that target mutations other than G12C and said the Merck/Otsuka partnership may bring about such advances.

"Building on the first clinical results for KRAS inhibitors released last year, the KRAS space continues to generate excitement with the Merck/Taiho/Astex collaboration," Ramirez said. "Indeed, while the initial focus in this area has been on inhibitors for the KRAS-G12C mutation, we expect there may be an effort to expand the number of targetable mutations in the coming years."

"For example, Mirati Therapeutics is imminently expected to select a candidate inhibitor for KRAS-G12D, a different mutational variant that is frequently observed," he continued. "Going forward, we will be quite interested to see the kinds of compounds that result from the Merck/Taiho/Astex collaboration."

Also in 2019, Eli Lilly & Co. and Johnson & Johnson launched Phase I/II studies of their own KRAS inhibitors. Lilly has KRAS G12C inhibitor LY3499446, one of the candidates acquired in its purchase last year of Loxo Oncology Inc., in a nine-arm study of advanced lung cancer patients that will investigate both monotherapy and combination regimens. *(Also see "Lilly Taps Loxo Execs To Bring Back That Biotech Feeling" - Scrip, 5 Dec, 2019.)* Data are expected in late 2021.

J&J, meanwhile, began a two-part Phase I study this past July testing KRAS G12C inhibitor JNJ-74699157 in patients with advanced solid tumors with that mutation. It is expected to yield data in 2023. The compound was discovered at the Janssen Labs incubator in San Diego.

Taiho and Astex both have some experience in the cancer space. Taiho reached the US market in 2015 with the approval of Lonsurf, a combination chemotherapeutic for metastatic CRC consisting of trifluridine and tipiracil, which to date has not made much commercial impact. *(Also see "First US product approval for Taiho Oncology" - Scrip, 23 Sep, 2015.)* On 12 November, the company reported 2019 sales through three quarters of Lonsurf totaling ¥24,565m (about $227,000), up 8%.

Astex has two Phase III candidates for cancer, including ASTX727 (cetazuridine and decitabine), which has produced successful Phase III data in in adults with intermediate or high risk, treated or untreated myelodysplastic syndromes (MDS) or chronic myelomonocytic leukemia (CMML). *(Also see "Astex Eyes First Filing For Oral Decitabine On Positive Combo Results " - Scrip, 10 Jun, 2019.)*.

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# Silence Signs Takeda Deal And Sets Sights On US

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Despite the surprise departure of CEO David Horn Solomon at the end of 2019, Silence Therapeutics PLC of the UK says it is in good shape and has unveiled a deal with Takeda Pharmaceutical Co. Ltd. as well as plans to set up a US subsidiary.

The pact with Takeda, worth "single-digit million dollars of research funding," will see the Japanese major use the London-based gene silencing specialist's platform to generate siRNA molecules against a novel, undisclosed target. Should the initial evaluation study prove successful in terms of proof of concept, Silence and Takeda will negotiate a licence agreement.

The agreement with Takeda "represents further validation of our technology and capabilities," said chairman Iain Ross, who took over day to day control of the business following the exit of Solomon on 17 December last year. His departure came after it was revealed that Solomon was subject to a private creditor action in Denmark arising as a result of his time as managing partner of healthcare investment fund Sund Capital from 2016 to 2018.

The company announced at the time that while "this is a personal matter entirely unrelated to Silence, a bankruptcy motion has been filed against David in Denmark which is due to be heard by the courts in the next few days." Solomon stepped down and Silence commenced a search to find a suitable successor.

Ross said he hoped to be able to give an update on the search later in the first quarter, saying "we've had a fantastic response already." He also praised the efforts of Solomon in creating a strong management team in the 17 months he was at the helm; during 2019, several high-profile appointments were made, including Rob Quinn as chief financial officer and new R&D chief Giles Campion.

While it was a blow to lose such a high-profile CEO, Ross insisted that it was "business as usual" and the company had made "substantive progress in 2019, cementing its reputation as a leading participant in the burgeoning field of RNAi therapeutics." He cited a deal inked in July with Mallinckrodt PLC which is worth $20m up front and a further $100m in milestones and centers around a preclinical asset called SLN500 that targets a specific protein in the C3 complement pathway.

Ross, claiming that "we are in our most robust health now, both financially and operationally," noted that Silence ended 2019 with £33.5m in cash which should be sufficient to fund operations under the current business plan into the second half of 2021. A sizeable chunk of that will go on moving SLN124, the company's lead candidate, towards the clinic.

> "It has always been our intention to focus on the US." – Iain Ross

Patients are currently being screened for a Phase Ib study, with six sites already open in the UK, Bulgaria and Turkey, to test SLN124 for the treatment of non-transfusion dependent beta-thalassemia and myelodysplastic syndrome. Interim results are expected in the second half of 2020 for SLN124, which has already been granted orphan drug designation by the European Medicines Agency.

Further back in the pipeline is SLN360, which silences a component of lipoprotein (a), elevated levels of which have been associated with increased risk of cardiovascular disease. A pre-investigational new drug meeting was held with the US Food and Drug Administration in December 2019, with a submission to start trials touted for the second half of 2020.

## US SUBSIDIARY IN 2020

Ross also announced plans to create a US subsidiary in the coming year "to improve the company's visibility and capture value for shareholders by more actively participating in the rapidly expanding field and the world's most significant healthcare market." He added that "it has always been our intention to focus on the US," but when asked about a possible listing on the NASDAQ, he said the timing had yet to be determined.

Silence said it was encouraged by the growing prominence of RNAi technology, as evidenced by the recent approval of Alnylam Pharmaceuticals Inc.'s Givlaari (givosiran) for acute hepatic porphyria. *(Also see "Alnylam Wins FDA Approval For Givlaari, Its Second RNAi Drug" - Scrip, 20 Nov, 2019.)*

The company also cited "a number of significant partnerships and transactions in the RNAi space," including agreements between Dicerna Pharmaceuticals Inc. and Novo Nordisk AS and the just-closed $9.7bn acquisition of The Medicines Company by Novartis AG. *(Also see "Dicerna Ready To Challenge Alnylam's RNAi Dominance In 2020" - Scrip, 6 Jan, 2020.)* *(Also see "It Has Been A Long Farewell To The Medicines Company" - Scrip, 26 Nov, 2019.)*

In addition, Ross noted that "we will continue to explore multiple opportunities to create shareholder value through significant partnerships that leverage the company's proprietary GalNAc-siRNA platform." However he stressed that Silence had no plans to license SLN124 or SLN360, adding that to get the most out of the assets, the company is currently in discussion "with several world-leading scientists" to form a scientific advisory board to be led by Sir Gordon Duff, former chair of the UK's Medicines and Healthcare products Regulatory Agency.

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# New Cash Moves NorthSea Up In NASH

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NorthSea Therapeutics BV (NST) has raised €36m which the Netherlands-based firm hopes will propel its non-alcoholic steatohepatitis (NASH) candidate icosabutate ahead of numerous rivals in this fiercely competitive field.

The Dutch biotech has closed a series B financing which brought on board new US investors venBio Partners, which led the round, and Sofinnova Investments. Existing investors Forbion, Novo Seeds, New Science Ventures and BioGeneration Ventures, which backed NST's €25m series A funding in December 2017, also participated.

Sander Slootweg, NST's chairman, said the company was particularly pleased to add venBio and Sofinnova to its shareholder's base, stating that "as both parties only selectively invest in Europe, we see this as a true testimony to the excitement of our most advanced drug candidate icosabutate."

NTS licensed icosabutate and other structurally engineered fatty acid (SEFA) candidates from Pronova BioPharma ASA, the developer of the now-generic cardiovascular blockbuster Omacor (omega-3 ethyl esters capsules). The Norwegian company, acquired by BASF SE in 2013, demonstrated that icosabutate was safe and effective in two Phase II studies for the treatment of hypertriglyceridemia and dyslipidemia but development in those two indications was stopped after Pronova failed to find a partner.

The compound was subsequently snapped up by NTS for NASH, the leading cause of liver disease affecting an estimated 15-30 million patients in the US, western Europe and Japan. Icosabutate has been specifically designed to regulate pivotal pathways involved in hepatic lipids, inflammation and fibrosis, NTS said, and in September last year, the first patient was dosed in the Phase IIb ICONA study; around 30 clinical trial sites have been initiated in the US.

## MULTIPLE APPROACHES

Richard Gaster, principal at venBio who has joined the NTS board, noted that NASH was an area of large unmet medical need "where we are confident there is room for multiple successful approaches with the right cardiometabolic profile." He added that the financing would enable the firm, which has sites in the UK and Norway as well as the Netherlands, to complete the Phase IIb trial of icosabutate "before the vast majority of NASH assets currently in clinical development."

There are still no approved therapies for NASH. Intercept Pharmaceuticals Inc.'s obeticholic acid is nearing the end of its review at the US Food and Drug Administration and the agency has scheduled an advisory committee for 22 April, nearly a month after its scheduled action date of 26 March.

If approved, the Intercept drug will have a healthy lead over competitors such as Gilead Sciences Inc. which suffered a setback at the end of 2019 when its Phase II ATLAS trial investigating monotherapy and combinations of three different drug candidates for NASH failed to meet statistical significance. France's Genfit SA remains Intercept's closest pursuer, with its dual PPAR agonist elafibranor slated to read out Phase III data soon.

Intercept is hoping to get approval of obeticholic acid for NASH patients with advanced fibrosis. Icosabutate is not a direct anti-fibrosis product but NST is confident that the anti-inflammatory and metabolic benefits seen in previous trials of the drug will differentiate it from other NASH treatments down the line.

As well as advancing icosabutate, NST will use some of the cash from the series B financing to develop two additional programs. SEFA-1024 is being evaluated for dyslipidaemia and the company aims to initiate a Phase I study in the second half of 2020.

The third SEFA program is SEFA-6179 for parenteral nutrition-associated liver disease (PNALD), an orphan disorder that affects patients with intestinal failure who are dependent on nutrition administered via alternative routes to the mouth or alimentary canal. NTS noted that there are no approved treatments available and it aims to initiate a Phase I study in the first half of 2021.

Slootweg concluded by saying that with the proceeds of the series B round, "we expect to show both the breadth and strength of our technology in patients and establish SEFAs as a new and exciting therapeutic modality."

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# Blueprint Medicine Gains US Approval For First Drug, Precision Medicine Ayvakit

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Blueprint Medicines Corp. has gained its first ever drug approval, the US Food and Drug Administration giving the green light to Ayvakit (avapritinib).

The US regulator is continuing in 2020 as it ended 2019, turning around approvals on new drugs far ahead of its own PDUFA deadlines - producing a decision on Ayvakit a full five weeks earlier than scheduled.

The small molecule kinase inhibitor drug is a 'precision medicine', treating a sub-population of patients with a metastatic gastrointestinal stromal tumor (GIST) who carry a very rare mutation.

This is called a platelet-derived growth factor receptor alpha (PDGFRA) exon 18 mutation, including PDGFRA D842V mutations, which is present in just 6% of

patients with GIST. This makes it the first drug approved to treat a genomically defined population of patients with GIST. Blueprint has announced the list price as $32,000 for a month's supply, or $384,000 for a year's treatment.

The approval is also notable because of the very early stage data on which the FDA based its decision: the regulator has granted full approval to Ayvakit based only on results from the company's Phase I NAVIGATOR trial, as well as combined safety results from other studies.

The FDA had granted the drug Breakthrough Therapy Designation and then fast-tracked its appraisal because patients with PDGFRA exon 18 mutations have very few existing options.

The most common PDGFRA exon 18 mutation is the D842V mutation, which is resistant to all other approved therapies.

A retrospective study showed that when these patients were treated with standard therapy Gleevec [imatinib] they had an ORR of 0%.

The FDA approval was based on the clinical trial results from 43 patients with GIST harboring a PDGFRA exon 18 mutation, including 38 patients with PDGFRA D842V mutation.

The trial's primary endpoint was overall response rate - and found high rates in patients with these mutations: for those with a PDGFRA exon 18 mutation, the overall response rate was 84%, with 7% having a complete response and 77% having a partial response.

For the subgroup of patients with PDGFRA D842V mutations, the overall response rate was 89%, with 8% having a complete response and 82% having a partial response. The median duration of response was not reached, but 61% of the responding patients with exon 18 mutations had a response lasting six months or longer (31% of patients with an ongoing response were followed for less than six months).

In patients with PDGFRA exon 18 mutant GIST, the drug had an overall response rate (ORR) of 84% and a median duration of response (DOR) was not reached.

The most common adverse reactions (≥20%) include edema, nausea, fatigue/asthenia, cognitive impairment, vomiting, decreased appetite, diarrhea, hair color changes, increased lacrimation and abdominal pain.

Blueprint Medicines plans to make Ayvakit available in the US within a week.

Jeff Albers, CEO at Blueprint Medicines said: "Aykavit is the first of what we hope will be many approved medicines enabled by our research platform. Now, as we begin to deliver Ayvakit to patients and their healthcare providers, we aim to fortify our leadership in the field of precision medicine and build a foundation for our broader portfolio by pairing our strong research and development capabilities with an equally talented commercial organization focused on addressing patient needs, accelerating diagnostic testing and enabling access."

Analysts say the approval is just the start for Blueprint. Avapritinib is being studied in a number of other settings, including systemic mastocytosis (SM), for which the FDA has also granted a Breakthrough Therapy Designation. The disease involves the accumulation of mast cells in internal tissues and organs, and also has limited existing treatment options, with early data from avapritinib encouraging.

A direct competitor to Aykavit is waiting in the wings, however. Deciphera's KIT and PDGFR inhibitor ripretinib recently produced positive Phase III results tin heavily pre-treated GIST patients, extending progression-free survival to six months compared to one month for patients taking a placebo.

Cambridge, MA-headquartered Blueprint has also produced compelling results from its BLU-667 in patients with RET-driven tumors, including lung cancer and thyroid cancer, and is expected to complete its submission to the FDA for this drug in the first quarter.

A rival in the RET mutation drug field is Lilly, which filed its own drug selpercatinib at the end of 2019.

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# AZ's Farxiga Gets FDA Priority Review For Heart Failure

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Having ended 2019 with two new approvals from the US Food and Drug Administration, AstraZeneca PLC is getting a speedy evaluation by the agency for a label expansion on Farxiga which will boost its leadership over other SGLT2 inhibitor diabetes drugs in the treatment of heart failure (HF).

The FDA has granted a priority review for Farxiga (dapagliflozin) to reduce the risk of cardiovascular death or the worsening of HF in adults with reduced ejection fraction (HFrEF) with and without type 2 diabetes. The Prescription Drug User Fee Act date for the supplementary new drug application is scheduled for the second quarter of 2020.

The sNDA was based on results from the landmark Phase III DAPA-HF trial presented at the European Society of Cardiology Congress in Paris, France, in September 2019. They showed that the drug reduced the composite endpoint of cardiovascular death or worsening HF by 26% when given on top of standard of care and the benefits were seen in both diabetic and non-diabetic patients.

The FDA appears to like the look of the cardiovascular data that AstraZeneca has been generating from Farxiga of late. A fortnight after the DAPA-HF results were presented at the ESC, the agency granted fast track designation for Farxiga in HF and in October it approved the drug to reduce the risk of hospitalization for HF in patients with type 2 diabetes and established cardiovascular disease or multiple risk factors, based on results from the DECLARE-TIMI 58 cardiovascular outcomes trial.

At the American Heart Association meeting in Philadelphia in November, AstraZeneca presented additional analyses of DAPA-HF which revealed that Farxiga cut the risk of cardiovascular events by 27% compared with placebo in patients without diabetes, while the risk reduction for those with the disease was 25%. Farxiga cut the risk of cardiovascular death by 21% in patients with diabetes and by 15% in those without, with patients with and without diabetes seeing a 23% and 38% cut to the risk of HF incidents, respectively.

An approval in HFrEF would represent a significant market opportunity for Farxiga, which has become a growth driver at AstraZeneca. Third-quarter 2019 sales reached $398m, up 12% on the like, year-earlier period.

Mene Pangalos, head of biopharmaceuticals R&D, said that if approved, Farxiga would be the first medicine of its kind indicated to treat patients with HF, which affects 64 million people worldwide, at least half of which have a reduced ejection fraction. AstraZeneca noted that HF remains as fatal as some of the most common cancers in both men (prostate and bladder) and women (breast) and is the leading cause of hospitalization for those over the age of 65.

If all goes well with the FDA review, the drug will have a considerable lead over rival SGLT2 inhibitors, Eli Lilly & Co./Boehringer Ingelheim International GmbH's Jardiance (empagliflozin) and Johnson & Johnson's Invokana (canagliflozin) for the indication.

Before the bells rang to herald the end of 2019, AstraZeneca bagged two key approvals from the FDA. The first was a widely expected green light for the PARP inhibitor Lynparza (olaparib) in a new indication, namely the first-line maintenance treatment of BRCA-mutated metastatic pancreatic cancer, while the second one, earlier than expected given it had a PDUFA date of April 2020, was for Enhertu (trastuzumab deruxtecan,) partnered with Daiichi Sankyo Co. Ltd. for metastatic breast cancer.

### LOKELMA OK IN CHINA

AstraZeneca also announced that Lokelma (sodium zirconium cyclosilicate) has been approved by China's National Medical Products Administration (NMPA) for adults with hyperkalemia.

The approval was based on positive results from the drug's extensive clinical trial program (it is already on the market in the US, Canada and Europe) and a pharmacodynamic study in China which showed that patients receiving Lokelma experienced a significant, rapid and sustained reduction of potassium in the blood. Last year, the NMPA included the therapy on the accelerated approval list of "overseas new drugs in clinical urgent needs for China," AstraZeneca noted.

Pangalos, who has just been awarded a knighthood in the Queen's New Year Honours List, said, "This approval marks an important milestone for more than two million patients in China who suffer from hyperkalemia. Lokelma will offer the opportunity for patients and physicians to achieve long-term disease control and potentially reduce the risk of acute episodes, which can have serious, even life-threatening consequences.

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# Alnylam Interview: RNAi Leader Expands Into NASH, CNS And Eye Diseases

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Alnylam enjoyed a very successful year in 2019, gaining US approval for its second RNA interference (RNAi) therapy, Givlaari (givosiran), with two more of its drug progressing towards regulatory filing.

The firm was the originator of inclisiran, developed by The Medicines Company, which has just been acquired by Novartis, and the Swiss major hopes to turn the cholesterol-lowering RNAi drug into a blockbuster. Meanwhile, lumisiran, Alnylam's next in-house molecule, produced pivotal data in primary hyperoxaluria type 1 (PH1), and both drugs are on track for early 2020 filing and approval later this year.

*Akshay Vaishnaw*

These will be core to growth, alongside a planned expansion of its first-launched drug, Onpattro (patisiran, approved for hATTR amyloidosis) into transthyretin amyloidosis with cardiomyopathy which will help it combat competition from Pfizer's Vyndaquel (tafadamis) and Ionis's Tegsedi (inotersen).

Alnylam's second-generation follow-up vutrisiran (ALN-TTRSCO2) is already in Phase III and could give it the upper hand in this hATTR market. But Alnylam knows that drugs with bigger commercial potential are needed if it is to break through into being a major biopharma company.

Founded 17 years ago, Alnylam Pharmaceuticals Inc. exemplifies the biotech

business case for vision, great science and long-term investment that is required to develop novel therapeutics. The company is still making an annual loss, but hopes to repay investor patience by reaching profit within the next few years.

Key to that is the next generation of RNAi therapies in the company's pipeline, being overseen by Alnylam's president of R&D, Akshay Vaishnaw. Akshay has been at the company since 2006, and has served in his current role for the last eight years, working closely with CEO John Maraganore to make the company a trailblazer in RNAi therapeutics.

Once only rivalled by Ionis's oligonucleotide antisense platform, lots of competitors are now entering the RNAi field, but Alnylam's head start is expected to pay off handsomely in the next five years.

Analysts at Jefferies forecast the company's revenues will ramp up from 2019 levels of around $227m to $3.7bn within five years, and then $4.69bn by 2030.

But much of those forecast earnings depend on the R&D investments the company is making in 2020.

## NEW TARGETS AND REGENERON PARTNERSHIP

Two significant developments which occurred last year will help to accelerate Alnylam's progress beyond a rare disease specialist in the next decade.

These are an $800m R&D alliance with Regeneron and the development of next generation RNAi platform.

The companies say their work will be a broad multi-product alliance across CNS, ocular and select liver targets, with a 50/50 structure in CNS and certain liver programs.

The partnership arrives just as Alnylam is developing its next-generation RNAi drug delivery platform. It has now produced proof-of-concept data for this "extrahepatic delivery" of its RNAi molecules, demonstrating early safely and efficacy in the central nervous system and eye. In November, in a dedicated R&D day, it showcased a number of early-stage advances, which included: a bis-RNAi – a single chemical entity silencing two targets; Reversir, which allows the rapid reversal of target silencing; plus an oral delivery mechanism.

It has also developed a next-generation proprietary platform, called a glycol nucleic acid modification (GNA) with ESC+ technology, which helps reduced the off-target effects seen in its existing platform.

Vaishnaw says it "profoundly attenuates" the raised liver function test (LFT) scores in its first generation drugs.

The Regeneron partnership represents a likely doubling of Alnylam's pipeline output: adding one to two new INDs per year in CNS or ocular targets, on top of previously planned one to two new INDs in the liver every year.

Vaishnaw says this "opens up a whole new vistas of targets" associated with a number of significant areas of unmet need, such as Alzheimer's, Huntington's, Parkinson's and ALS.

"These and more are all now available to us with the conjugate technologies for those two compartments. That's been triggered by the landmark deal with Regeneron in the spring [of 2019] with $800 million up front, from Regeneron," said Akshay.

"So that helps us fuel the next chapter in the growth of the Alnylam pipeline, which is a liver-focused pipeline currently, and now we include the CNS and the eye as well."

The companies are not disclosing targets in ophthalmology as yet, but the potential is broad. Akshay says they hope to develop new glaucoma treatments which would involve just one injection every six or 12 months to replace a daily regime of eye drops in glaucoma. Equally, a once or twice yearly RNAi treatment to replace wet AMD treatments such as Eylea and Lucentis, which must be given more frequently is something that Vaishnaw says could "dramatically changes the landscape" in those diseases.

In CNS, Alnylam is having to play catch up with its rival Ionis. It has enjoyed great

**RNAi/antisense drug milestones 2020-2021**

| MOLECULE | COMPANY | CATALYST | TIMING | INDICATION |
|---|---|---|---|---|
| Inclisiran | Novartis/Medicines Co. | Filing | Q1 2020 | Atherosclerotic cardiovascular disease (ASCVD) |
| Lumasiran | Alnylam | Filing | Q1 2020 | Primary hyperoxaluria type 1 (PH1) |
| Akcea-Apo(a)-LRx (TQJ230) | Akcea/Ionis | Phase II data | Q1 2020 | CVD + elevated lipoprotein (a) |
| IONIS-HTTRx (RG6042) | Roche/Ionis | Phase II data | H1 2020 | Huntington's Disease |
| Fitusiran | Sanofi | Phase III data | 2020 (delayed from 2019) | Hemophilia A and B |
| DCR-PHXC | Dicerna | Phase III data | H1 2020 | Primary hyperoxaluria type 1 and 2 |
| Tofersen | Ionis/Biogen | Phase III data | 2021 | Amyotrophic lateral schlerosis (ALS) |
| Vutrisiran | Alnylam | Phase III data | 2021 | ATTR amyloidosis (next gen) |
| JNJ3989 | Janssen/Arrowhead | Phase IIb data | Q1 2021 | Chronic hepatitis B |
| Cemdisiran | Alnylam/Regeneron | Phase II | Q4 2021 | Atypical Hemolytic-Uremic Syndrome (aHUS) |
| Patisiran | Alnylam | Phase III data | Q4 2021 | ATTR Amyloidosis With Cardiomyopathy |

success with its antisense oligonucleotide platform, most notably in blockbuster SMA therapy Spinraza (nusinersen), licensed to Biogen.

Ionis could be on the cusp of a breakthrough in Huntington's disease, with its IONIS-HTTRx (RG6042) candidate, being co-developed with Roche. Phase II data is expected shortly, and encouraging results could persuade regulators to accept the data for filing later this year.

Alnylam is betting on its RNAi platform being superior in hitting these CNS targets, but is undoubtedly lagging behind Ionis in this field.

Vaishnaw comments: "We think we can do better because our drugs are more potent and are more durable, with less frequent intrathecal administration than the Ionis drugs – maybe once every six months or 12 months versus monthly or bi-monthly for them."

## BREAKING INTO NASH

One of the 'next big thing' therapy areas in recent years has been fatty liver disease non-alcoholic steatohepatitis (NASH), with companies crowding in drug development with the hope of producing a blockbuster.

But expectations were dashed in 2019 by a series of late-stage failures and disappointments, and even with a potential first approval for Intercept later this year, the field looks open for new contenders. *(Also see "Gilead Moves On From Selonsertib, Looks To ATLAS To Map Its NASH Future" - Scrip, 11 Nov, 2019.)*

Regeneron and Alnylam hope to succeed where others have failed in NASH, thanks to identifying two genetically validated targets. The companies are collaborating on producing RNAi therapies to target HSD17B13, an enzyme upregulated in NASH sufferers and the PNPLA3 enzyme, arising from a mutation closely linked to NASH, liver fibrosis and cirrhosis.

"Some of the pitfalls that we've seen in the global NASH pipeline is from people going after targets that look promising but may not necessarily have genetic validation against them," said Akshay.

"In the case of both targets, we know that there are strong genetics that support going after those targets and reducing the [enzyme] levels, and that should alter the course of NASH."

Regeneron research established that knocking out the *HSD17B13* gene in mice helped protect patients from NASH and other liver diseases, giving a strong genetic validation for a therapy to mimic this process.

"That gives us hope that addressing that target will lead to better outcomes than we've seen with some of these small molecules that have failed. Similarly, with PNPLA3, we know that there's a mutation that leads to rapid acceleration and worsening of NASH." Vaishnaw says Alnylam will stay disciplined and only pursue genetically validated targets. "We're going to stick to our knitting, and these genetic validated target approaches in NASH. We'll go to the clinic and let's see what happens. But as illustrated by Onpattro and Givlaari, it's been a good approach for us so far."

## HITTING TARGETS GENE THERAPY CANNOT REACH

In terms of new modalities, causing even greater excitement than RNAi therapeutics are, of course, gene therapies.

Spark has pioneered gene therapy for inherited retinal disease with Luxturna (voretigene neparvovec) while BioMarin is set to gain approval this year for the first ever gene therapy for hemophilia A.

Gene therapies hold out the unique promise of delivering a functional cure for many diseases, via a single treatment. So what can Alnylam's RNAi platform offer that gene therapies cannot?

Vaishnaw points out that Alnylam's therapies can target "gain of function" mutations ie, diseases where previously inactive genes are turned on. This is in contrast to the "loss of function" disorders which can be treated by inserting the missing gene in cells.

"There's a long list of possibilities there in terms of gain of function, toxic mutations that should be knocked down to help patients with a variety of eye diseases," he said.

"Many of those diseases cannot be helped by gene therapy because they typically augment or increase the expression of missing gene, and that's a very different area from what we're trying to do with RNAi in the eye."

That's not to say RNAi therapeutics won't go head-to-head with gene therapies; the Alnylam-discovered fitusiran is being developed by Sanofi for hemophilia A, and has produced early data which shows it could rival Roche's blockbuster Hemlibra (emicizumab).

Speaking at the company's R&D day in November, Vaishnaw highlighted the company's higher than average hit rate so farHe says Alnylam's success rate for the 12 programs it has put into clinical trials (including the four approved or nearing filing) averages out as 54.6%.

He says that is a "massive expansion in terms of productivity and probability of success" on the industry average, and asserts that Alnylam is determined to continue the strategy of only pursuing genetically validated targets.

This could be a key factor in Alnylam's future growth, as it enters broader and more competitive therapy areas, and also faces challenges from a range of rivals within RNAi and other novel modalities.

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# Dicerna Ready To Challenge Alnylam's RNAi Dominance In 2020

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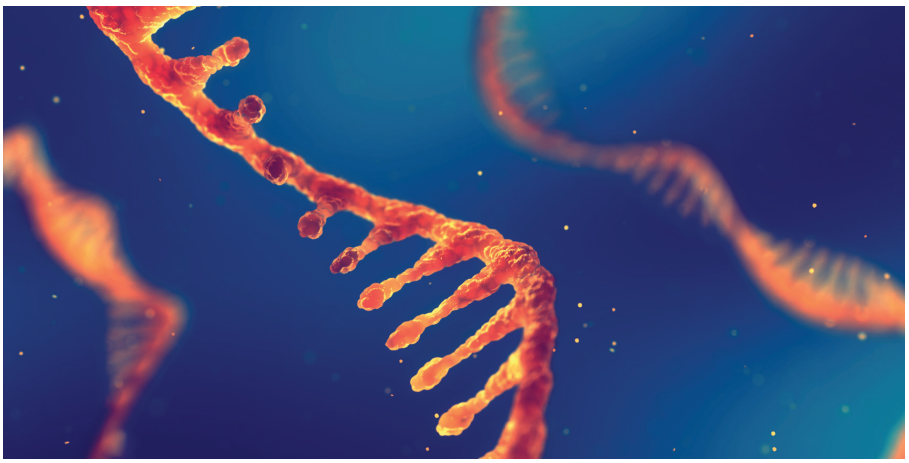

Drugs in the RNA interference (RNAi) class will truly become a force to be reckoned with in 2020, but trailblazer Alnylam Pharmaceuticals Inc. will also see its lead challenged by rivals.

Alnylam's perseverance in the field paid off with the approval of the first ever RNAi-based drug Onpattro in 2018 and then with Givlaari in November. *(Also see "Alnylam Wins FDA Approval For Givlaari, Its Second RNAi Drug " - Scrip, 20 Nov, 2019.)*

These two orphan drug approvals are just the start for Alnylam, which plans to expand its reach significantly in 2020. This will include the expected approval of primary hyperoxaluria 1 (PH1) candidate lumasiran in the latter part of the year, plus the expected approval of the Medicines Company/Novartis candidate inclisiran, which was discovered by Alnylam.

But Alnylam will not have the field to itself for much longer – and most notable among its challengers in RNAi therapeutics is Dicerna Pharmaceuticals Inc..

Headquartered in Lexington, MA, just down the turnpike from Alnylam in Cambridge, Dicerna has gained considerable momentum in late 2019, after having spent years in the shadow of RNAi frontrunner Alnylam, including a skirmish over intellectual property.

Dicerna has just announced the closing of one of its deals (with Novo Nordisk), kicking off what will be a pivotal year for the company.

In October, Dicerna also signed a major deal with Roche to develop novel therapies for the treatment of chronic hepatitis B virus (HBV) infection, focused on its lead candidate DCR-HBVS, currently in Phase I.

The following month, the agreement with Novo Nordisk to discover and develop novel therapies for the treatment of liver-related cardio-metabolic diseases, including chronic liver disease, non-alcoholic steatohepatitis (NASH), type 2 diabetes, obesity and rare diseases.

These plus an expanded collaboration with Alexion and an existing Lilly partnership, have given Dicerna more than $500m in upfront payments to help fuel its development pipeline, which will reach some crucial milestones in 2020.

## HEAD-TO-HEAD WITH ALNYLAM

However Dicerna's lead candidate is one that it has retained full rights to itself. DCR-PHXC, an RNAi therapy for ultra-rare kidney disease primary hyperoxaluria (PH).

There is no doubting that Alnylam has a commanding lead in PH, however. It took a major step toward securing a first-to-market place for its candidate lumasiran in December. Its Phase III study of 30 patients with PH1 showed the product's benefit by significantly lowering urinary excretion levels of a metabolite called oxalate, a biomarker validated last year by the Food and Drug Administration. Full results from its ILLUMINATE-A study will be presented at the OxalEurope International Congress in Amsterdam on 31 March.

Alnylam will now proceed to file lumasiran for approval in the first half of this year, but Dicerna hopes to mount a challenge, as its candidate treats all subtypes

### Alnylam versus Dicerna

| COMPANY | CANDIDATE | STAGE | TRIAL | INDICATION | RESULTS | TIMELINE |
|---|---|---|---|---|---|---|
| Alnylam | lumasiran | Phase III | ILLUMINATE-A | Primary hyperoxaluria type 1 | Achieved primary endpoint with as-yet undisclosed % change from baseline in 24-hour urinary oxalate excretion compared to placebo. Also hit 6 secondary endpoints | Filing in early 2020 |
| Dicerna | DCR-PHXC | Phase I | PHYOX1 | Primary hyperoxaluria type 1 and 2 | Four PH1 patients achieved mean maximal reduction in urinary oxalate of 48%. Three PH2 patients achieved 42% mean maximal reduction | Pivotal PHYOX2 trial enrolling |

of PH – types 1, 2 and 3, compared with only PH1 covered by its rival. But analysts at SVB Leerlink say they believe DCR-PHXC can establish itself as a new standard of care in PH types 2 and 3, and split the market with Alnylam in PH type 1. With Alnylam leading the way in treating PH with an RNAi, Dicerna will be able to follow on rapidly, but it still has to achieve its own clinical readout milestone first.

This year will see a number of pivotal trial readouts and milestones across the RNAi field. For Dicerna in particular, the year could see its proprietary GalXC platform prove its value in producing RNAi molecules to rival Alnylam's.

Dicerna's first read out this year will be of multi-dose data from PHYOX3, open-label clinical trial of DCR-PHXC, which is due in the first half of 2020.

Proof-of-concept data from its Phase I clinical trial of hepatitis B candidate DCR-HBVS are also expected in mid-2020.

Compounds generated using GalXC target the liver, and enable subcutaneous delivery of RNAi therapies designed to bind specifically to receptors on liver cells.

Like Alnylam, the company hopes that its platform can produce RNAi therapeutics across multiple therapeutic areas, including both liver and non-liver indications.

Alnylam announced progress on developing RNAi drug delivery platforms for the central nervous system (CNS) and the eye last year, including proof-of-concept data for its Ga1NAc-conjugated small interfering RNAs (siRNAs), which would provide a convenient oral route of administration.

Leerlink analysts say positive results from trials this year will transform Dicerna into a commercial rare disease company in what it terms an "attractive duopoly market" alongside Alnylam, while potentially claiming a best-in-class breadth of label.

Alongside these, the Roche partnership in HBV is also seen as having major revenue potential, and could provide Dicerna with significant milestone payments and long-term royalty streams.

However Dicerna has a rival of its own in this field, where another RNAi-specialist company, Arrowhead Pharmaceuticals, is working on a therapy in collaboration with Janssen.

This illustrates the proliferation in RNA-targeting therapies, including antisense drugs from Ionis and its subsidiary Akcea. The latter is also expanding out of rare disease into research into cardiovascular and metabolic diseases, including a new alliance with Pfizer.

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# AMR Crisis Experts See Hopeful Signs For 2020

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Efforts in the US and elsewhere to battle the threat of antimicrobial resistance did not get very far in 2019, and the lack of viable commercial models caused some biotechs to go to the wall.

Still, some experts tell *Scrip* they see reasons for optimism in 2020, despite fears the US presidential elections could keep the AMR issue on the back burner there.

They point to recent promises of action from entities like the Centers for Medicare and Medicare Services (CMS) and the Biomedical Advanced Research Development Authority, or BARDA.

Other promising signs include legislation signed in late December by Congress to fund the US government through September 2020 and which provides a $50m increase in funding to NIAID (the National Institute of Allergy and Infectious Diseases) for antimicrobial resistance.

But these initiatives all take time, something that AMR experts say the US and the world are running out of as the cupboard of novel antibiotics empties.

Meanwhile, deteriorating market conditions are making life perilous for innovative antibiotics makers, many of whom face financial disaster if solutions are not soon found and applied.


That was the key message heard at the two-day World AMR Congress held in Washington DC in November which brought together scientists, government officials, doctors, and economists from 40 countries to discuss one topic – antibiotic resistance.

"The key message we hear regularly is that the market challenges of AMR are not getting better. They are getting worse," said Greg Frank, who heads up the Working to Fight AMR coalition and who was a panellist at the congress.

"Every single talk, every single discussion focused on what's going to happen if more of these biotechs go bankrupt," he said in an interview.

One company, Melinta Therapeutics Inc. used the forum to give public guidance that they would be folded up by the end of the year. Melinta did just that, declaring bankruptcy on 27 December, be-

coming the latest casualty of a relentless cash burn in the antibiotic industry which lacks a viable business model.

"What's troubling about Melinta is that they don't just have one novel antibiotic, they have four! So this was a far larger company than Achaogen Inc., which went bankrupt in April," Frank said.

"Not surprisingly there's a lot of concern about what impact that's going to have. And there are other companies that alluded to similar financial problems more nebulously to the congress."

Another speaker at the AMR Congress, Marc Lemonnier, the CEO of Fance-based Antabio SAS and a board member of the BEAM alliance, the EU AMR innovation hub, echoed Frank's comments.

"This is a typical example of a broken business model. We are seeing bankruptcies and we will see more of that," Lemonnier told *Scrip*.

And he did not see an early end to the problem. "We'll need to have more pain before we stop suffering and find solutions. Those solutions need to fix the broken market. More push incentives, more subsidies, more grants will not be enough," Lemonnier said.

Unfortunately, attendees did not think the congress's urgent message for needed action was taken in by those most needing to hear it.

"The AMR Congress is attended by the true believers, so probably the people who we need to take action on this topic weren't in the room," Frank told *Scrip*.

"It's very hard to get anything done in Washington DC today, given all that's going on regarding drug pricing, the impeachment battle, and other dramas which are taking all the air out of Congress and the Trump Administration," Frank observed.

Still, there were some positive messages heard at the AMR Congress, conveyed by officials from the CMS and from BARDA.

"Both CMS and BARDA led off their presentations to the AMR congress with outlines on how they plan to do something to address this urgent need for reimbursement initiatives for antimicrobial products," Frank said.

Just before the Congress kicked off, the CMS announced that they are going to lead what they called an "overhaul" of reimbursement for antimicrobial products.

"CMS effectively put a flag in the ground to say they want to do something substantive in the future, and I see the future as being 2020," Frank commented.

"So BARDA and CMS have said they are looking into doing an effort to help strengthen the commercial market. We don't know what that might look like. Hopefully we'll see some concrete action from the US government in 2020 to help us start to address these challenges."

If CMS were able to implement reimbursement reform in the next year, then that could be a lifeline to companies on the market engaged in making novel antibiotics.

"A lot of private investors are waiting to see what the US government is going to do and until that becomes clearer, they are not willing to inject any more money into these companies," Frank said.

> "We'll need to have more pain before we stop suffering and find solutions." – Marc Lemonnier

He noted that BARDA has authority to buy and stockpile medicines for crisis preparedness.

"The potential exists for BARDA to negotiate to buy some of the antimicrobial products from companies. This doesn't solve the problem, but it would buy time and keep the companies going while efforts continue to find a more durable solution."

For companies like Melinta and like Achaogen Inc. that development would come too late.

"The battlefield is shifting now to focus on the next crop of companies that are struggling. I hate to say that, but it's unfortunately the truth," Frank said.

## PROJECTED RISE IN AMR INFECTIONS

Another big takeaway from the AMR Congress in November was that the Centers for Disease Control and Prevention (CDC) made available an updated report and forecast on antibiotic resistance, its first in depth report on AMR in six years and showed a big rise on projected AMR infections occurring in the US. According to the report, more than 2.8 million antibiotic-resistant infections now occur in the US each year, with more than 35,000 people dying as a result.

"It's previous report in 2013 had underestimated AMR; it's actually two-fold higher," Frank said, Even so, the updated report is still behind times, he believes.

"CDC's latest report is significantly underestimating the amount of expected AMR infections because it's very difficult to track using hospital medical records as those records don't say whether someone dies of resistance infection. They die of something else. We hope CDC will continue to improve their data. That said, we also heard some very promising comments from the US government in early 2019 and not much happened," Frank said.

As bad as this antimicrobial resistance crisis has become in the US, Frank said it is even worse in the developing world. Globally, superbugs are already on track to kill 10 million people per year by 2050, outpacing cancer deaths, he said.

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# Merck & Co's Keytruda Disappoints In Small-Cell Lung Cancer

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Merck & Co. Inc.'s release of somewhat disappointing top-line final Phase III data from the KEYNOTE-604 study of Keytruda (pembrolizumab) in extensive-stage small-cell lung cancer (SCLC) has drawn attention to what may be one of the remaining major untapped markets for the anti-PD-1 immunotherapy.

> Although there are numerous agents in Phase II for SCLC, there are only a handful in Phase III.

In KEYNOTE-604, Keytruda was found to significantly improve progression-free survival (PFS) but not overall survival (OS) when combined with chemotherapy for the first-line treatment of SCLC.

"For Merck, front-line SCLC represented one of the largest metastatic market opportunities remaining for Keytruda to penetrate," noted analysts at SVBLeerink, who pointed to the forthcoming readout of KEYNOTE-355 in first-line triple-negative breast cancer as now becoming an increasingly important event for the anti-cancer agent.

Other potential topline Phase III readouts for Keytruda in 2020, according to Informa Pharma's pipeline database, Biomedtracker, include: KEYNOTE-204 in Hodgkin's lymphoma; KEYNOTE-361, involving first-line use in bladder cancer; KEYNOTE-177 in patients with microsatellite instability-high colorectal cancer; and KEYNOTE-122, second-line use in nasopharyngeal cancer.

Other immunotherapies have fared better in SCLC therapy; Roche's PD-L1 inhibitor, Tecentriq (atezolizumab), was approved in the EU in September 2019, and in the US in March 2019, for use with chemotherapy for the initial treatment of extensive-stage SCLC, based on the IMpower133 study which showed it improved OS and PFS. However, the UK HTA NICE has more recently questioned its long-term effectiveness.

And AstraZeneca PLCs anti-PD-L1 MAb, Imfinzi (durvalumab), was granted priority review in the US in November 2019 for first-line extensive-stage SCLC use, based on the results of the CASPIAN study, with action expected in the first quarter of 2020.

"The Keytruda miss lends credence to the argument that targeting the PD-L1 side of the PD-1/PD-L1 axis is more effective in settings characterized by low PD-L1 expression and poor patient fitness (like SCLC)," commented the SVBLeerink analysts.

Bristol-Myers Squibb Co.'s PD-1 inhibitor Opdivo (nivolumab) was approved in the US in 2018 as a third-line therapy in patients with metastatic SCLC.

Keytruda is already approved in five lung cancer indications, including being granted an accelerated US approval in June 2019 as a later-line monotherapy for patients with metastatic SCLC. But the keenly awaited results from KEYNOTE-064 appear to compare poorly at first-sight with other immunotherapies.

## FIRST-LINE USE IN SCLC

On the positive side, in KEYNOTE-064, pembrolizumab added to chemotherapy (etoposide plus cisplatin or carboplatin) resulted in a significant improvement in PFS compared with chemotherapy alone (HR=0.75; 95% CI, 0.61-0.91), Merck announced on 6 January.

However, for the second co-primary endpoint, OS, an improvement was seen when pembrolizumab was added to chemotherapy, but this did not achieve significance when compared with chemotherapy alone (HR=0.80; 95% CI, 0.64-0.98).

The study enrolled 453 patients with newly diagnosed extensive-stage SCLC, and secondary endpoints include objective response rate and duration of response.

SCLC is a fast-growing cancer with early metastases, and has usually spread to both sides of the lung at the time of diagnosis. It is therefore classified as extensive-stage disease, notes Datamonitor Healthcare's October 2019 Market Spotlight report on the condition. SCLC accounts for about 10% to 15% of all lung cancer cases, and the five-year survival rate for patients diagnosed in the US with any stage of SCLC is 6%.

Although there are numerous investigational agents in Phase II for SCLC, there are only a handful in Phase III SCLC studies, including AstraZeneca's Imfinzi (durvalumab), PharmaMar SA's Zepsyre (lurbinectedin), and United Therapeutics Corp.'s dinutuximab. In December 2019, PharmaMar announced it had filed a US NDA for accelerated approval of lurbinectedin in relapsed SCLC, on the basis of the results of a Phase II clinical trial, and United Therapeutics has also previously indicated that its Phase II/III DISTINCT study of dinutuximab in SCLC is fully enrolled.

Merck says it is continuing to evaluate pembrolizumab across 20 company-sponsored clinical trials in lung cancer, involving various clinical settings and stages of disease. *Published online 7 Jan 2020*

# Novartis Touts Ligelizumab As Xolair Successor In CSU

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Novartis AG is highlighting the advantages of its new chronic spontaneous urticaria (CSU) treatment ligelizumab over the current standard of care Xolair which the firm markets with Roche for the distressing condition that causes red, itchy and sometimes painful hives on the skin.

Like Xolair (omalizumab), ligelizumab is an immunoglobulin E inhibitor but Novartis has pointed to new mechanistic data published in the journal *Nature* which show that the two drugs recognize and bind differently to IgE. The results show that ligelizumab can bind to IgE with an 88-fold higher affinity than Xolair, "resulting in a significantly enhanced blockade" of IgE pathway signalling.

Speaking at an R&D day in London last month, Novartis's development head for immunology, hepatology and dermatology, Eric Hughes, said that before Xolair was approved in the US and Europe for CSU in 2014 (it got the green light for severe allergic asthma associated with IgE in 2003) "there was really nothing going on in the field for people who had failed on antihistamines and we really changed their treatment." While ligelizumab "is another IgE, its mechanism actually is almost completely different. It binds a different epitope of the IgE molecule, creates a different conformation and actually hits receptors that are important in the disease process," he added.

Hughes went on to say that despite the advances, "there's a lot of people who are underserved." There are about 3.4 million people with CSU and "while we can treat about 2.1 million of those people with high doses of histamines, there's still 1.3 million people who don't respond and we're only treating 15% of those today with Xolair."

He referred to the Phase IIb study of ligelizumab published last October which showed that at 12 weeks, "we're essentially doubling the amount of clear skin over Xolair. We're very confident about its activity and the excitement around the drug was affirmed by the fact that it was published in the *New England Journal of Medicine* … it's been very well received by the community."

*Novartis hopes ligelizumab will be top dog for CSU*

Novartis is now running the largest and longest CSU Phase III studies ever undertaken – PEARL 1 and PEARL 2 – that are recruiting more than 2,000 patients across 48 countries and comparing ligelizumab with Xolair and placebo. Hughes noted that the trials, which have been going on for a year, are about 60% enrolled and "we're going to learn a lot about how long we should treat people. We will re-randomize them afterwards to see how they respond off drug and see if we're having any disease modifying activity…this dataset will be by far the best ever seen in CSU."

Enrolment is expected to be completed in the third quarter of this year and Novartis said that first results and filings are scheduled before the end of 2021.

## FOOD ALLERGY POTENTIAL

Hughes noted that ligelizumab has potential beyond CSU, with the drug being studied in chronic inducible urticaria and food allergy.

He said that globally up to 520 million people may suffer from food allergy, including 4-6% of children which represents a huge burden for patients and families due to anxiety, social stigma and fear of death from anaphylaxis. Hughes added that ligelizumab will be delivered through an auto-injector allowing for easy use through self-administration at home.

Sales of Xolair are split between Roche and Novartis and the two companies reported revenues of $1.49bn (in the US) and $870m respectively from the drug in the first nine months of 2019. If the Phase III trials go as planned, one of Novartis's challenge will be to switch patients from Xolair to ligelizumab in the hope that it could eventually absorb the blockbuster drug's sales.

Another challenge is the fact that Xolair lost primary patent protection in the US and Europe in 2017. No biosimilars are close to the market but there are a number in development, notably Glenmark Pharmaceuticals Ltd.'s GBR310 (Phase II) and Celltrion Inc.'s CT-P39 (Phase I). Dutch/Australian biotechnology company Biosana initiated a Phase I trial of its Xolair biosimilar BP001 early last year, while STI-004 from Sorrento Therapeutics Inc. and Mabtech AB has been in late-stage studies in China.

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# NICE Rejects Akcea's High-Cost Waylivra

The UK's cost effectiveness body NICE has rejected Akcea's rare disease treatment Waylivra (volanesorsen), citing high cost and uncertain long-term benefits to patients.

Waylivra was granted conditional marketing approval in Europe in May 2019 to treat familial chylomicronaemia syndrome (FCS), a group of rare genetic conditions that cause very high levels of triglycerides in the blood, and which is currently managed by a very strict low-fat diet.

The condition is ultra-rare, and is thought to affect between 55 and 110 people in England. Waylivra's annual list price cost is more than £340,000 and was discounted confidentially, but has nevertheless proved to be too high for NICE.

Its draft decision is a setback for Akcea (a subsidiary of Ionis Pharmaceuticals Inc.), which is relying on key European markets to generate revenues from the drug.

That is because the FDA rejected the drug in August 2018 owing to concerns about sudden drops in platelet counts as well as Akcea's decision to alter the dosing regimen and platelet monitoring system. This is required as the treatment is very commonly associated with reductions in platelet count in FCS patients, which may result in thrombocytopenia.

Waylivra was reviewed via NICE's Highly Specialised Technologies (HST) route, designed to give rare disease treatments more flexibility on cost effectiveness measures – even so NICE's committee said cost-effectiveness estimates were "much higher than what NICE considers acceptable for highly specialised technologies".

The drug has a UK list price of £11,384 per injection, which is given weekly for three months, and then every two weeks after that. Despite the confidential discount on the £341,520 list price offered via the now routine 'patient access scheme, NICE still found Wayliva too costly. It also questioned the company's data submission. In a statement issued after the draft judgement on Friday (3 January), the cost effectiveness watchdog said there was a lack of evidence to show whether the drug's benefit were maintained in the longer term.

It also highlighted uncertainty because Akcea's pivotal clinical trials used a different dose to the dose described in the marketing authorisation for the drug.

The draft guidance is open for public consultation until 24 January 2020, and recommends that Akcea provides further clarification and analyses on its methods used for health related quality of life experienced by patients, and it also recommends that the company carry out a further scenario analysis to explore the impact of the condition on the health-related quality of life of carers.

Andy Caldwell, UK and Ireland country manager at Akcea Therapeutics said the company was disappointed at the decision, but would continue to work with NICE.

A small number of patients were given access to the drug via the UK's Early Access to Medicines Scheme from March 2018, and these patients will be unaffected by the draft ruling.

Akcea already has experience of NICE's HST process – in April 2019 it gained approval for another ultra-rare disease treatment Tegsedi (inotersen, for hereditary transthyretin-related amyloidosis or hATTR) after the company offered an improved commercial arrangement.

*Published online 6 January 2020*

# AbbVie Updates Exec Team, Creates A Separate Aesthetics Business Unit

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AbbVie Inc. will keep Allergan PLC's market-leading medical aesthetics business in the hands of Allergan employees who know how to develop and market products in this unique biopharmaceutical and medical device category after the big pharma closes its $63bn acquisition of the specialty firm in the first quarter of 2020.

Allergan senior vice president of US medical aesthetics Carrie Strom will become a senior vice president at AbbVie and president of the new business unit Allergan Aesthetics; Strom also will be the only executive from Allergan to be added to AbbVie's executive leadership team when the companies' merger is completed.

Allergan also markets the dry eye drug Restasis (cyclosporine ophthalmic emulsion), which generated $1.26bn in 2018 sales, but is poised to face generics this year, and Lumigan (bimatoprost ophthalmic solution) to reduce eye intraocular pressure in glaucoma. *(Also see "Going Generic: Big Brands Poised To Lose Marketing Exclusivity In The US In 2019 " - Scrip, 15 Mar, 2019.)* Allergan also sells Linzess (linaclotide) for irritable bowel syndrome under a partnership with Ironwood Pharmaceuticals Inc., and some women's health products, like the birth control pill Lo Loestrin.

The transaction is on track to close in early 2020, as AbbVie intended when it announced its big purchase in June 2019, despite increased scrutiny of biopharma mega-mergers by the US Federal Trade Commission (FTC) that has delayed the closing of other deals. *(Also see "When It Comes To FTC M&A Review, The Times May Be A Changin' " - Scrip, 8 Jul, 2019.)*

AbbVie said on 8 January that it will create Allergan Aesthetics to house medical aesthetics brands, including Botox Cosmetic (onabotulinumtoxinA), the Juvederm and Voluma lines of dermal fillers, the Coolsculpting body sculpting device and breast implants. The new business unit will have its own dedicated research and development group; Allergan has 32 aesthetics R&D

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, 3–9 JANUARY 2020

| Event Type | Lead Company/Partner | Drug Name | Indication | Comments | Change To LOA (%) | LOA (%) |
|---|---|---|---|---|---|---|
| Phase III Updated Results | Scynexis, Inc. | ibrexafungerp | Refractory Fungal Infections | FURI; Encouraging Results | 0 | 63 |
| Phase III Top-Line Results | Orphazyme A/S | arimoclomol | Niemann-Pick Disease | Extension Study; Sustained Effect | 2 | 65 |
| Phase III Top-Line Results | Pharnext | PXT3003 (baclofen/naltrexone/sorbitol) | Charcot-Marie-Tooth Disease | PLEO-CMT-FU; Encouraging Data | 2 | 60 |
| Phase III Top-Line Results | Apellis Pharmaceuticals, Inc. | pegcetacoplan (APL-2) | Paroxysmal Nocturnal Hemoglobinuria | PEGASUS; Achieved Efficacy Endpoint | 2 | 66 |
| Phase III Top-Line Results | VBI Vaccines Inc. | Sci-B-Vac | Hepatitis B Prevention | CONSTANT; Met Endpoints | 0 | 67 |
| Phase III Trial Initiation | SELLAS Life Sciences Group, Inc. | Zeltherva (galinpepimut-S) | Acute Myeloid Leukemia | REGAL; Peptide Vaccine | 25 | 37 |
| Phase III Trial Initiation | QED Therapeutics/BridgeBio | infigratinib | Advanced Cholangiocarcinoma | PROOF; As First-Line Therapy | | |
| Phase II/III Trial Initiation | Amo Pharma Limited | tideglusib (AMO-02) | Congenital Myotonic Dystrophy | A Pivotal Study | 0 | 24 |

**Source: Biomedtracker | Informa, 2020**

programs under way, including new indications for Botox and new Juvederm and Voluma products.

Allergan's eye care and other specialty businesses – including Botox Therapeutic and the company's central nervous system, women's health and gastrointestinal disease franchises – will be integrated into AbbVie's broader R&D and commercial organizations. The company noted, however, that several business leaders from Allergan across these different specialties will join AbbVie.

Botox Cosmetic is by far the top-selling botulinum toxin in the wrinkle-reducing market globally, despite competing products from Merz Pharmaceuticals GMBH and Galderma SA/Ipsen. Strom told *Scrip* in an overview of the medical aesthetics market published in 2018 that Allergan saw a lot of untapped potential worth investing in. *(Also see "Medical Aesthetics: A Rising Tide Lifts All Ships In A Booming Market With Room For Growth" - Scrip, 11 Sep, 2018.)*

However, new competitors are emerging for Allergan's aesthetics empire, particularly for Botox Cosmetic, such as Evolus Inc.'s Jeuveau (prabotulinumtoxinA), which launched last year. *(Also see "With Jeuveau Approval, Evolus Will Focus On The Beauty Business To Gain Market Share" - Scrip, 5 Feb, 2019.)* Also, Revance Therapeutics Inc. submitted a biologic license application to the US Food and Drug Administration in November for RT002 (daxibotulinumtoxinA), which the company hopes to market as a longer-lasting toxin. *(Also see "Another Botox Competitor: Revance Prepares Longer-Lasting RT002 For BLA Submission" - Scrip, 22 Feb, 2019.)*

Allergan's investments in aesthetics R&D include a fast-acting, shorter duration toxin that it acquired in 2018 with the purchase of Bonti Inc. for $195m up front. The company has also studied longer-term response rates for Botox Cosmetic to show that the drug's efficacy can be maintained for up to six months in some patients. *(Also see "Allergan Buys Bonti, Releases New Data In Defense Of 'Iconic' Botox Brand" - Scrip, 14 Sep, 2018.)*

AbbVie is holding Botox Therapeutic, which provides a greater share of overall Botox revenue, closer to its core business. Sales of the drug for chronic migraine prevention, spasticity, overactive bladder, hyperhidrosis, cervical dystonia and other therapeutic indications totaled $525.5m in the third quarter versus $403.2m for Botox Cosmetic. *(Also see "Allergan's Botox Gains Continue, Pipeline Progresses Ahead Of AbbVie Merger" - Scrip, 5 Nov, 2019.)*

While AbbVie and Allergan operate in some of the same therapeutic areas, there is relatively little overlap in the indications where they market and develop products, which probably is why it does not appear that FTC scrutiny has delayed the merger. *(Also see "AbbVie Will Use Allergan Revenue To Fund Combined Firm's Large R&D Pipeline" - Scrip, 27 Jun, 2019.)*

Also, AbbVie notified the FTC last year that it would sell off two Allergan assets to thwart any anti-competitive concerns – the interleukin-23 inhibitor brazikumab in Phase II/III for Crohn's disease and Phase II for ulcerative colitis, and Zenpep (pancrelipase), which is approved to treat exocrine pancreatic insufficiency due to cystic fibrosis. *(Also see "Skyrizi Launch Skyrockets, Boosting AbbVie Hopes For Humira Successors" - Scrip, 1 Nov, 2019.)*

*Published online 9 January 2020*

## APPOINTMENTS

| Executive | To Company | New Role | From Company | Previous Role | Effective Date |
|---|---|---|---|---|---|
| Erick J. Lucera | Aveo Oncology | Chief Financial Officer | Valeritas Inc | Chief Financial Officer and Executive Vice President | 6-Jan-20 |
| M. B. Chinappa | Biocon Biologics India Ltd | Chief Financial Officer | Syngene International Ltd | President (Finance) and Chief Financial Officer | 6-Jan-20 |
| Enrique Conterno | FibroGen Inc | Chief Executive Officer and Director | Eli Lilly & Co | President, Lilly USA | 6-Jan-20 |
| Venkat Reddy | Macrophage Pharma | Chief Scientific Officer | Glenmark Pharmaceuticals Limited | Senior Vice President and Global Head, Translational Sciences | 9-Jan-20 |
| Steve Arkinstall | Revitope Oncology Inc | Chief Executive Officer | Elstar Therapeutics | Chief Executive Officer | 8-Jan-20 |
| Rami Levin | Saniona | Chief Executive Officer and President | Sobi Inc | President | 7-Jan-20 |
| Saryah Azmat | Turnstone Biologics Inc | Senior Vice President, Business Development and Corporate Strategy | Bristol-Myers Squibb | Global Lead, Oncology Search and Evaluation | 8-Jan-20 |

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

**Source: Medtrack | Informa, 2020**

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