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Credit: FDA

Gottlieb's Shock Resignation Leaves Ripples In The Industry

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US FDA Commissioner Scott Gottlieb, one of the most popular and visible commissioners in decades, will end his tenure as head of FDA in about a month, having moved the agency in new directions while also advancing high-profile policies.

Gottlieb amassed a legacy that includes new approaches to drug pricing and opioid policy, as well as record generic and novel drug approval output, despite running the agency less than two years.

Gottlieb cited his family in his decision to leave. In a note to staff, he said "there's perhaps nothing that could pull me away from this role other than the challenge of being apart from my family for these past two years and missing my wife and three young children."

THE PUBLIC COMMISSIONER

Gottlieb may be most remembered for his approach to communications. He often appeared on television and his daily Twitter posts complemented the numerous press releases announcing policy changes and other moves within the agency. Previous commissioners tended to avoid the limelight, as well as social media.

Nancy Myers, president of Catalyst Healthcare Consulting, said in an interview that Gottlieb was pro-patient, pro-industry and pro-safety at the same time, which is difficult. He also used the office in a "forward-leaning way" not seen often.

"He kind of drove the conversation through very good communication externally," Myers said. "He was able to use a lot of the ideas percolating in the agency, package them and get them moved forward."

Gottlieb pushed FDA to the forefront of the drug pricing debate, a position the agency had not sought in the past. In his first speech to staff after confirmation, he said that even though the agency cannot set drug prices, it can promote competition.

Gottlieb was vocal in chastising the brand industry for blocking generic competition, warning that Congress could make more drastic changes if it did not stop employing pay-for-delay and licensing tactics intended to prevent patent challenges. *(Also see "Gottlieb: Real Risk Of Congressional Action If Anti-Competitive Actions Continue" - Pink Sheet, 3 May, 2018.)*

He also publicly released a list of companies thought to be using the Risk Evaluation and Mitigation Strategy system to prevent generic companies from purchasing samples for testing, although it is not clear the move had much impact. *(Also see "REMS Abuse Website: Celgene, Actelion Top List Of Suspected 'Gamers'" - Pink Sheet, 18 May, 2018.)*

In addition, Gottlieb blasted the rebate system that he alleged was holding back biosimilar competition for expensive biologic drugs.

His emphasis on creating generic competition was partially successful. The agency set a record for generic drug approvals in fiscal years 2017 and 2018, although critics argued that not nearly as

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Skyrizi set to muscle in on competitive psoriasis market (p6)

Starry-Eyed Buy

Biogen moves beyond neurology with Nightstar deal (p12)

All-Time High

Cell and gene therapy investments sky rocket in 2018 (p13)

from the editor

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Gene and cell therapies experienced a major investment boost in 2018, as we report on p13-14 of this issue. With all the activity so far this year, the field could well attract even greater sums in 2019. At the same time as venture capital and public market funds have been rolling in, big pharma has also been investing, not least through acquisitions like Biogen's deal for Nightstar Therapeutics and Roche's for Spark Therapeutics (see p12 and p15).

But for a sector with nearly 1,000 companies in operation, there is still a large question mark over its commercial viability, since only a few therapies have made it to market, and those that have are generally sold at high cost in low volumes, with complicated manufacturing.

Elsewhere in the issue read about the concerns over conditions in Europe for innovation expressed by Bayer's executives – who have also declared the German company's desire to "be at the forefront of the activities in cell and gene therapy" (p21-23). Criticizing governments in Europe for supporting a car industry that has "basically been reduced to inventing batteries" while overlooking the value created by life sciences and creating a regulatory framework that is hostile to technologies like gene editing, they were equally scathing of the UK politicians who called the Brexit referendum, branding their behaviour "highly irresponsible."

The long shadows of Brexit certainly aren't making it any easier for European biopharma in its long-running attempts to cultivate a more fertile environment for early science to put down strong roots, flourish and mature on the continent where it was seeded.

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exclusive online content

Interview: ViroMed On Pricing, Manufacturing World's First Broadly Used Gene Therapy

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Despite ongoing debate over the sometimes staggeringly high cost of gene therapies, **ViroMed Co. Ltd.** does not appear too concerned about the likely pricing of its lead asset in this field, the non-viral therapy VM202.

While companies in the sector are considering various approaches, such as installment payments, to help facilitate market access to their pricey products, the South Korean biotech is looking at pricing the product at a more affordable level, especially given that it is targeting diseases with relatively large patient populations.

The firm is slated to announce later this year top-line results from the first Phase III study with VM202 in its most advanced indication, painful diabetic peripheral neuropathy (PDPN).

"The latest gene therapies are announcing prices of more than a million dollars and this is becoming a social issue. Our therapy targets at least a one million [patient] population in the US alone, so we have to find the right price level that is appropriate for the target disease and the patient populations," Jehee Suh, executive director of global business strategy at ViroMed, told *Scrip* in a recent exclusive interview in Seoul.

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many of those products were reaching the market. *(Also see "US FDA Sets Generic Approval Record, But Generic Sponsors Aren't Celebrating" - Pink Sheet, 12 Oct, 2018.)*

At the same time, the agency also approved a record number of novel drugs in 2018, which for the first time comprised mostly orphan products. *(Also see "Orphan Drugs Compose Majority Of Novel US Approvals For First Time Ever In 2018" - Pink Sheet, 3 Jan, 2019.)*

The Association for Accessible Medicines said in a statement that the generics and biosimilars industries "will miss this true champion of patient access."

"Dr. Gottlieb set a high bar for those who are working to bring relief to American patients from the burden of high drug costs," the trade organization said. "Gottlieb understood that approvals were not enough to spur competition, and his leadership extended to improving market conditions to ensure these generic and biosimilar medicines would not be blocked by 'shenanigans.'"

The Pharmaceutical Research and Manufacturers of America also praised Gottlieb's pricing mission, as well as his commitment to help new drugs reach the market.

"During his tenure, he focused on innovation in drug development and review, increased competition, and advanced the regulatory framework for approving novel technologies, including gene therapies," the brand drug trade group said. "His efforts have made a meaningful impact for patients in need of innovative medicines."

Gottlieb also oversaw several policy changes intent on fighting the opioid epidemic, most recently calling for new trials assessing long-term opioid efficacy and new prescribing guidelines. *(Also see "Long-Term Opioid Efficacy Studies Will Take Years, Gottlieb Says" - Pink Sheet, 28 Feb, 2019.)*

AN INDEPENDENT COMMISSIONER

During his tenure, Gottlieb was unafraid of bold pronouncements, whether about areas not under the purview of FDA (such as drug rebating) or public health areas where the agency has more of a role to play (two of his higher-profile statements in recent weeks have been support for raising the minimum age to purchase tobacco to 21 and suggesting the federal government could do more to mandate vaccinations).

Gottlieb's independence earned admiration, said former FDA Principal Deputy Commissioner Joshua Sharfstein.

Gottlieb "surprised many people by charting his own course at FDA, focusing on several important topics for public health," said Sharfstein, who now is vice dean for public health practice and community engagement at the Johns Hopkins Bloomberg School of Public Health. "These included the harms of nicotine and tobacco, the importance of lowering drug prices through generic competition, and the opioid epidemic."

"FDA staff respected him for his commitment to the agency's longstanding public health mission," Sharfstein added.

Peter Pitts, president of the Center for Medicine in the Public Interest and former FDA associate commissioner for external relations, said Gottlieb "did the right thing."

"He called it as he saw it," Pitts said. "And that's a rare commodity in Washington these days."

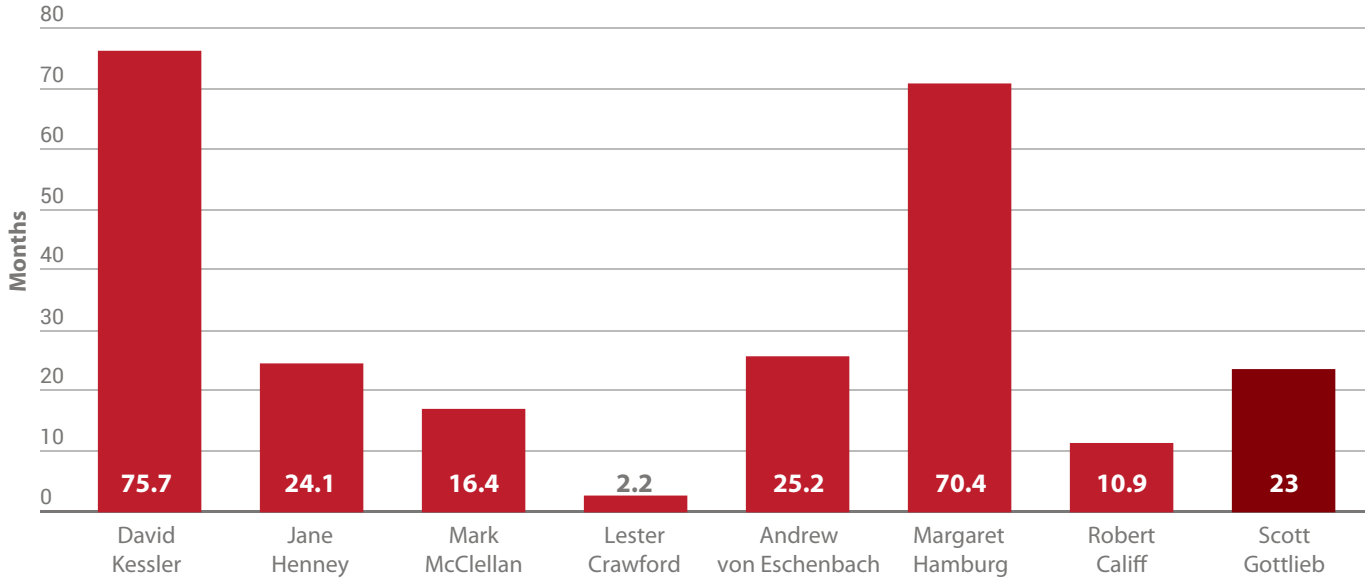
A WHITE HOUSE FAVORITE

Gottlieb also enjoyed unwavering public support from his boss, President Trump, another reason his departure was so surprising.

Trump tweeted that Gottlieb had done "an absolutely terrific job" as commissioner, adding that "his talents will be greatly missed."

Myers said that Gottlieb cultivated a good relationship not just with Trump and the White House, but also with lawmakers on Capitol Hill, "which gave him the cred-

Gottlieb's Tenure As Commissioner Relatively Short



Among recent US FDA commissioners, Gottlieb's approximately 23-month term will be the second-quickest voluntary departure, after Mark McClellan. The two commissioners with shorter tenures were involuntary departures: Robert Califf left at the end of the Obama administration, and Lester Crawford resigned due to ethics violations involving stock ownership.

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ibility in those circles that he was going to do the right thing."

Trump became especially enamored with Gottlieb during the 2018 World Economic Forum in Davos, Switzerland, calling him a "star." *(Also see "US FDA Commissioner A 'Star' At Davos: Hopefully Not A Bad Omen" - Pink Sheet, 29 Jan, 2018.)*

Unfortunately for Gottlieb, Trump also placed him in charge of the administration's efforts to pass right-to-try legislation, placing him in the awkward position of shepherding a bill that many agency officials and other stakeholders did not support.

Even as he worked to rein in what he saw as abusive brand tactics, Gottlieb also received criticism for his perceived deference to industry.

Sid Wolfe, founder and senior advisor of Public Citizen's Health Research Group, said Gottlieb brought a financial bias favoring the pharmaceutical industry to his role as commissioner.

Wolfe specifically criticized Gottlieb's handling of the opioid crisis, particularly the agency's decision to approve **AcelRx Pharmaceuticals Inc.**'s sublingual opioid *Dsuvia* (sufentanil). *(Also see "Dsuvia Approval May Be Followed By New Opioid Review Paradigm At FDA" - Pink Sheet, 2 Nov, 2018.)*

Wolfe and Raeford Brown, chairman of the Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC), also slammed the agency for not convening the full Drug Safety and Risk Management Advisory Committee as part of AADPAC's review of the controversial product. *(Also see "Public Citizen: US FDA Deliberately Excluded Risk Committee From Dsuvia Panel To Get Positive Vote" - Pink Sheet, 18 Oct, 2018.)*

IS ABERNETHY NEXT?

Until President Trump nominates a replacement, Principal Deputy Commissioner Amy Abernethy may be in line to head the agency on an acting basis.

Abernethy, who joined FDA about a month ago from **Roche** subsidiary **Flatiron Health Inc.**, has little experience inside the agency but has worked with FDA in other roles. She is an oncologist and has worked at Duke University, which employs former commissioners Mark McClellan and Robert Califf.

> "Gottlieb understood that approvals were not enough to spur competition, and his leadership extended to improving market conditions to ensure these generic and biosimilar medicines would not be blocked by 'shenanigans.'"

Former Commissioner Margaret Hamburg employed a similar strategy in hiring Califf as deputy commissioner for medical products and tobacco. Hamburg announced her departure a few weeks later and Califf soon was nominated for the permanent position. *(Also see "FDA Lands Califf As Top Deputy, Potential Next Commissioner" - Pink Sheet, 2 Feb, 2015.)*

Califf told the *Pink Sheet* that Gottlieb's departure "will be a big loss for the country. Scott had the skills and did a great job of meeting the mission of the FDA under difficult circumstances."

A QUICK EXIT

While Gottlieb's succession pattern may follow Hamburg's, his departure timing certainly doesn't. Hamburg, President Barack Obama's first FDA commissioner, stayed for most of his presidency.

Indeed, most recent commissioners have either left after a long tenure or due to a change in administration. Gottlieb would be the second-quickest voluntary departure in at least several decades. (*See chart opposite.*)

Gottlieb hinted last year that his time at the agency may end sooner than expected. He told a congressional committee in 2018 that he may to have less time as commissioner than initially thought. *(Also see "US FDA Commissioner Gottlieb Sees His Job As A Race Against The Clock" - Pink Sheet, 23 May, 2018.)*

And following the mid-term election, stakeholders began suggesting that Gottlieb may consider leaving the agency since it is a natural departure time. *(Also see "US FDA May Largely Avoid House Democrats' Investigation Agenda" - Pink Sheet, 7 Nov, 2018.)*

Former Commissioner Mark McClellan told the *Pink Sheet* that while it was clear Gottlieb cared about FDA and its mission, "it's an always-on and very demanding job, and especially hard with a young family elsewhere."

McClellan, whom Gottlieb served under during his first stint at the agency, may have set the template for a quick exit. McClellan was commissioner for less than 17 months, although he left for another post in the George W. Bush administration (CMS administrator) while Gottlieb hasn't announced any future plans.

Still, multiple stakeholders were shocked when the news broke March 5. Former FDA Chief Counsel Peter Barton Hutt, who now is senior counsel at Covington and Burling, said the departure was a huge loss and that Gottlieb was a brilliant commissioner.

"I wish he'd change his mind," Hutt told *Scrip*. "He reached out and took hold of every part of the agency."

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AbbVie's Skyrizi Poised To Enter Packed Psoriasis Market

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AbbVie Inc.'s bid to offset the impact of declining revenues in Europe from its off-patent mega blockbuster Humira has been boosted by a recommendation by the continent's regulators for one of the products seen as vital in lifting the US major's future fortunes, the psoriasis therapy Skyrizi.

The European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) has adopted a positive opinion for *Skyrizi* (risankizumab), an interleukin-23 inhibitor, for the treatment of moderate to severe plaque psoriasis in adults. The thumbs-up is based on a Phase III program evaluating more than 2,000 patients across four studies (ultIMMA-1, ultIMMa-2, IMMhance and IMMvent).

In all of the studies, all co-primary and ranked secondary endpoints were met, with the drug achieving a significantly higher response of clear or almost clear skin compared with placebo, **Johnson & Johnson**'s IL-12/IL-23 inhibitor *Stelara* (ustekinumab) and AbbVie's own *Humira* (adalimumab) at week 16 and up to week 52. The most frequently reported adverse reactions were upper respiratory infections, which occurred in 13 % of patients, but most of those were mild or moderate in severity.

AbbVie president Michael Severino, said in a statement that the firm was "excited that the CHMP has recognized risankizumab's potential to significantly reduce the signs and symptoms of psoriasis and provide an improved quality of life." In the aforementioned studies, it demonstrated consistently high rates of skin clearance with a favorable benefit/risk profile, he said, noting that at one year, "more than 50% of patients receiving risankizumab achieved completely clear skin. This is an important regulatory milestone."

It is indeed important. If the CHMP's positive opinion is, as widely expected, confirmed by the European Commission within the next two months, it could be Skyrizi's first approval worldwide. It may be a close run thing though, given that the FDA has an action of April 25 in the US for the drug which was licensed from **Boehringer Ingelheim GmbH**.

An AbbVie spokesperson told *Scrip* that the firm's intention was to launch across Europe "as soon as the reimbursement and pricing arrangements in each country allows." While the firm did not comment on individual commercial strategies, it said "we have been preparing for the expansion of our immunology portfolio and pipeline for some time. We firmly believe in risankizumab's potential to be a best-in-class therapy and we are positioning in accordance with the label approved by the CHMP as a therapy for treating all patients with moderate-severe psoriasis."

The clinical package behind Skyrizi is a strong one but the focus now is on whether the drug can make substantial inroads into the fiercely competitive psoriasis market. Two IL-23 inhibitors are available in the US – **Sun Pharmaceutical Industries Ltd.**'s recently-launched *Ilumya* (tildrakizumab) and J&J's *Tremfya* (guselkumab), both of which are selling well.

The latter, partnered with **MorphoSys AG**, is also benefiting from positive data from the Phase III ECLIPSE study with some endpoints showing that Tremfya bested **Novartis AG**'s big-selling IL-17A inhibitor *Cosentyx* (secukinumab). A spokesperson for the Swiss major, noting the CHMP positive opinion for Skyrizi, told *Scrip* that the firm "would like to reiterate that we strongly believe in Cosentyx to deliver exactly what physicians and patients need – clear skin and complete treatment of psoriatic disease."

The spokesperson added that the disease "is more than just skin plaques" and two thirds of biologic-eligible patients have psoriatic arthritis (PsA) and/or other persistent manifestations in nails, scalp and palmoplantar areas. "We therefore believe the approval and launch of another IL-23 inhibitor for the treatment of skin plaques will have limited clinical relevance," he said, noting that Cosentyx is supported by five-year "sustained efficacy and safety data across three indications" – psoriasis, PsA and ankylosing spondylitis (AS), with over 200,000 patients treated to date.

Other competitors to Skyrizi include **Eli Lilly & Co.**'s IL-17A inhibitor *Taltz* (ixekizumab), **Celgene Corp.**'s oral treatment *Otezla* (apremilast) and the anti-TNFs, with Humira still holding a dominant position in the market. This long list of rivals could significantly restrict the AbbVie drug's commercial potential at launch.

However, the company can take comfort from a recent survey of 74 dermatologists (30 in the US, 10 in each of the UK, Germany, Italy and Spain, as well as four from France) carried out by Informa's *Biomedtracker* team. The report showed that among the as-yet unapproved psoriasis drugs, Skyrizi was ranked the highest for expected uptake in five years' time when compared to Lilly's IL-23 inhibitor mirikizumab, **UCB Group**'s IL -17A and IL-17F inhibitor bimekizumab, **Pfizer Inc.**'s JAK inhibitor *Xeljanz* (tofacitinib) and **Bristol-Myers Squibb Co.**'s TYK2 inhibitor BMS-986165, as well as Cosentyx and Stelara.

Another advantage that Skyrizi seems to have, aside from showing a very high level of efficacy, durable effect and a strong safety profile, is that it offers the convenience of quarterly dosing. Where its place in the treatment paradigm will be remains to be seen although analysts at *Datamonitor Healthcare* believe the drug will be used in later lines of therapy, mainly targeting patients who have failed treatment with anti-TNFs and other IL inhibitors.

Analysts are putting a lot of pressure to succeed on Skyrizi which, along with the investigational oral JAK1 inhibitor upadacitinib for rheumatoid arthritis, is seen as critical for AbbVie once the ravages of biosimilar competition to Humira start to be felt. The company is being bullish about its prospects and has said that the drug could be launched in a number of indications; Phase III trials in Crohn's disease and PsA are ongoing, and the compound is also being investigated to treat ulcerative colitis, although a Phase II trial published last year showed that risankizumab is not effective in reducing the signs and symptoms of AS.

AbbVie's forecasts for Skyrizi and upadacitinib, which it hopes to launch in some seven indications (an FDA decision for RA is not expected much before the end of this year) certainly could not be described as conservative. Severino's presentation at JP Morgan in January this year included a slide stating that the two drugs could contribute over $10bn in incremental risk-adjusted sales by 2025, with $6.5bn of that expected to come from upadacitinib.

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Roche's Tecentriq Steals Lead In Triple-Negative Breast Cancer

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The US FDA's accelerated approval of **Roche**'s PD-L1 inhibitor *Tecentriq*, for use in combination with **Celgene Corp.**'s *Abraxane*,on March 8 gives Roche an opportunity to break into triple-negative breast cancer with an immunotherapy regimen ahead of competitors.

On March 8, the agency granted accelerated approval for Roche/Genentech's Tecentriq (atezolizumab) used with Abraxane (nab-paclitaxel) to treat metastatic triple-negative breast cancer patients with tumors that have PD-L1 expression, as determined by an FDA-approved test.

It's the first use of an immune checkpoint inhibitor in breast cancer, but the breast cancer field is one where Roche has a wealth of experience – although it had a memorably difficult experience with accelerated approval of its VEGF inhibitor *Avastin* (bevacizumab) in breast cancer, which resulted in a contested withdrawal of the indication in 2008.

For Roche, the approval of Tecentriq in triple-negative breast cancer is a nice boost for the company's HER-2-positive breast cancer franchise. The company's flagship *Herceptin* (trastuzumab) is its top-selling pharmaceutical, bringing in CHF6.9bn ($6.8bn) in 2018 – but it will soon face biosimilar competition. Roche's *Perjeta* (pertuzumab) had sales of CHF2.7bn in 2018; the company did not break out its sales for the antibody drug conjugate *Kadcyla* (ado-trastuzumab emtansine) in its last annual report.

According to Roche, some 271,000 people in the US are diagnosed every year with breast cancer, of whom 15% have the tough to treat triple-negative form of the disease, meaning that the tumor lacks estrogen, progesterone and the HER-2/neu gene.

Tecentriq was first approved as a monotherapy for second-line treatment of locally advanced or metastatic urothelial cancer in May 2016. It went on to gain clearance as a monotherapy for second-line treatment of metastatic non-small cell lung cancer (NSCLC) in the same year. And at the end of 2018, the FDA approved Tecentriq in combination with Avastin and chemotherapy for first-line NSCLC. *(Also see "Roche's Tecentriq Becomes Second In PD-1/L1 Family To Gain First-Line Lung Cancer Approval" - Scrip, 6 Dec, 2018.)* On March 8, Tecentriq won approval in Europe for first-line NSCLC.

Approval in breast cancer was supported by the pivotal Phase III ImPassion 130 study, which compared Tecentriq with Abraxane vs. Abraxane and placebo in 902 women with locally advanced or metastatic breast cancer. The IO combination demonstrated a significant progression-free survival (PFS) benefit but overall survival (OS) results were immature when presented at the European Society of Medical Oncology meeting in the fall of 2018. The risk of progression of disease or death for those on the Tecentriq arm was significantly reduced by 40% (7.4 months vs. 4.8 months).

The trial results were well received, although some noted that it was mainly patients with cancer positive for the PD-L1 expression biomarker who benefited. *(Also see "Roche Remains Positive After Tecentriq Triple-Negative Breast Cancer Data" - Scrip, 22 Oct, 2018.)*

Safety was in line with reports from prior studies, with Grade 3-4 adverse events including neutropenia, peripheral neuropathy, fatigue, low potassium and increased liver enzymes.

At the 2017 American Society of Clinical Oncology meeting, Merck's Roger Perlmutter highlighted positive data for Keytruda in the signal-detecting Phase II ISPY-2 study of early breast cancer as his top pick among the company's data releases for the meeting.

Competitors have also been exploring the use of checkpoint inhibitors in triple-negative breast cancer, including **Merck & Co. Inc.**'s PD-1 inhibitor *Keytruda* (pembrolizumab), the market-leader for the PD-1/L1 class.

At the 2017 American Society of Clinical Oncology meeting, Merck's Roger Perlmutter highlighted positive data for Keytruda in the signal-detecting Phase II ISPY-2 study of early breast cancer as his top pick among the company's data releases for the meeting.

The KEYNOTE-355 trial is testing Keytruda in first-line locally recurrent inoperable or metastatic triple-negative breast cancer – this study is due to complete this year.

The Phase III KEYNOTE-522 study is evaluating Keytruda with chemotherapy against placebo in neoadjuvant and adjuvant treatment of triple-negative breast cancer. The estimated primary completion date for that trial is 2025.

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J&J Foresees Broad Insurance Coverage For Groundbreaking Spravato Nasal Spray

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Based on discussions with payers, **Johnson & Johnson** expects broad insurance coverage for its newly US FDA-approved treatment-resistant depression nasal spray drug *Spravato* (esketamine), which is set to become available in about two weeks at a list price of $590 or $885, depending on the dose, per treatment session.

The FDA announced approval of the drug/device combination for use with an oral antidepressant for patients with treatment-resistant depression late on March 5. J&J estimates that of the 16m people in the US with major depressive disorder (MDD), 5m have treatment-resistant depression (TRD), which is defined as a lack of response to at least two different antidepressants of adequate dose and duration during a current depressive episode.

Esketamine is the s-enantiomer of the NMDA receptor antagonist ketamine, which has been approved in the US since the 1970s for use as an anesthetic, but is also used on a generic basis off-label in major depression.

USE WILL BE TIGHTLY CONTROLLED

As only the second drug approved by the agency for treatment-resistant depression after **Eli Lilly & Co.**'s *Symbyax* (olanzapine and fluoxetine HCl), which was cleared for the acute treatment of TRD in 2009, Spravato is groundbreaking.

Approval was expected, following a strongly positive vote in favor of approval by the FDA's Psychopharmacologic Drugs Advisory Committee and the agency's Drug Safety and Risk Management Advisory Committee in February.

Spravato is associated with risks for sedation, dissociation, hallucinations, elevated blood pressure and abuse and, consequently, it was approved with a strict Risk Evaluation and Mitigation Strategy (REMS) to control distribution, as expected.

Spravato is a Schedule III drug, meaning it has moderate to low potential for physical and psychological dependence, and labeling has a boxed warning advising of risks for sedation, dissociation and abuse as well as suicidal ideation in younger patients.

Per the REMS, treatment must be administered in a certified treatment center, though patients may self-administer. Patients must be monitored for at least two hours by a health provider, need to make arrangements to get home safely after treatment and will be advised not to drive or use heavy machinery for the rest of the day, the agency noted in a March 5 statement about the approval.

OPTIMISTIC ABOUT PROSPECTS WITH PAYERS

The product will be made available for purchase by certified treatment centers during the week of March 18, and J&J subsidiary Janssen said that it is "working quickly to educate and certify sites in accordance with the REMS."

Hundreds of centers are expected to become certified in 2019; those with large behavioral health clinics will most likely be able to start up and get established fairly quickly, Courtney Billington, president of Janssen Neuroscience, said in an interview.

The company expects the drug will be covered in a similar manner as other specialty pharmaceuticals for serious mental illness, the exec added.

Prior to approval, the company spent a "good amount of time" with payers explaining the benefits of the treatment and provided a range of pricing they could expect. These early discussions suggest Spravato should be broadly covered, Billington said.

As with most novel medications, it will take time to get Spravato through the approval systems and pharmacy and therapeutics (P&T) committees, but the company believes that the insurance companies understand the high unmet need and will allow broad access, Billington said.

LIST PRICE VARIES DEPENDING ON DOSING REGIMEN

The cost of therapy varies based on the dose used per session and how many sessions take place, both of which can differ from patient to patient, Janssen said.

Each nasal spray device includes 28 mg of esketamine. Spravato's labeling advises that two devices may be used to deliver a 56 mg dose and three for an 84 mg dose, with a five-minute rest between each administration. The wholesale acquisition cost (WAC) for a treatment session is $590 for the 56 mg dose and $885 for 84 mg.

"During the induction phase of therapy, which lasts for one month, patients are treated twice a week with either 56 mg or 84 mg, so the WAC for the one-month induction phase ranges from $4,720-$6,785. Patients who have responded to therapy in the induction phase move on to the maintenance phase. During the maintenance phase, patients are treated with either the 56 mg dose or 84 mg dose either weekly or every two weeks, so the WAC for a month of maintenance therapy will range from $2,360 –$3,540," the company explained.

These costs don't include other costs associated with administration or monitoring of patients and Billington declined to speculate what the total tab will be.

The WAC is in line with list prices for other specialty mental health drugs, including long-acting injectables for schizophrenia, the company said.

Esketamine and other drugs for depression are slated to be reviewed this year by the third-party Institute for Clinical and Economic Review (ICER), which is influential for reimbursement policies. *(Also see "ICER's 2019 Agenda Includes CAR-T Therapy, Drugs For Depression, Arthritis, AMD" - Pink Sheet, 14 Aug, 2018.)*

COMPETING WITH KETAMINE

Spravato will be competing with generic ketamine, which is typically administered intravenously, but ketamine is not approved for depression and it is administered in pricey private clinics that charge

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hundreds of dollars per infusion, with an overall course of therapy involving six to eight sessions.

Billington noted that in contrast with ketamine, Spravato has undergone testing in clinical trials that informed the FDA approval and that Janssen has invested more than nine years in R&D to develop the product.

Furthermore, he added that ketamine is not broadly reimbursed for off-label use in treatment-resistant depression.

Spravato was evaluated in three short-term trials and one longer-term maintenance-of-effect study. The drug demonstrated significantly improved efficacy in one of the short-term studies and in the longer-term trial.

Datamonitor analyst Stephanie Yip commented that the mixed efficacy data is partially a reflection of the hard-to-treat patient population and added that real-world off-label experience with intravenous ketamine in depression favors Spravato.

The analyst also noted that key opinion leaders are enthusiastic about the extremely rapid onset of action, which suggests Spravato will carve out a place for itself in the market.

Datamonitor forecasts sales of close to $2bn in 2026 in the US, Japan and five major European markets (France, Germany, Italy, Spain and UK).

During the FDA advisory committee review in February, Walter Dunn, a psychiatrist at the West Los Angeles Veterans Administration Medical Center, described the rapid response in treatment-resistant depression as "unprecedented" and said esketamine is a "game changer."

Following the drug's approval, Theresa Nguyen, vice president of policy and programs at the Mental Health America, also cited potential for immediate response as appealing for patients with treatment-resistant depression.

Depression is one of the hardest mental illnesses to treat – patients may not feel relief until 30 to 60 days on treatment and many give up rather than stay the course, she said in an interview with *Scrip*. Esketamine "changes all of that," she said.

Some analysts expected that esketamine's success would bode well for other new antidepressants, with potential to widen the market. *(Also see "J&J Seeks A Priority Review For Depression Drug Esketamine" - Scrip, 4 Sep, 2018.)*

However, on March 6, **Allergan PLC** announced that its NMDA receptor partial antagonist rapastinel failed as an adjunctive treatment for major depressive disorder in three Phase III studies, missing primary as well as secondary endpoints.

In February, the FDA issued a complete response letter for a filing of **Alkermes PLC**' major depressive disorder drug ALKS 5461, a combination of the opioid buprenorphine and the μ-opioid receptor antagonist samidorphan.

Previously, in November, the FDA extended the user fee date for the review of a filing for **Sage Therapeutics Inc.**'s *Zulresso* (brexanolone) in post-partum depression by three months after the company submitted a proposed REMS. *(Also see "Sage Gets More Time For Zulresso Launch Preparations With Delay Of US FDA Approval" - Scrip, 20 Nov, 2018.)*

Published online 7 March 2019

Scrip Awards Winner 2018

Syneos Health's Best New Drug Award

This year the Award was jointly given to Novartis and Kite Pharma Inc./Gilead Sciences Inc. for their pioneering CAR-T therapies, Kymriah (tisagenlecleucel) and Yescarta (axicabtagene ciloleucel), respectively. These first two chimeric antigen receptor T-cell therapies are at the forefront of immunocellular therapy in which a patient's own T-cells are engineered to seek and destroy cancer cells, and which has been touted as the new frontier of cancer therapy.

Sponsored by Syneos Health

Winner: Novartis's Kymriah and Kite Pharma/Gilead Sciences' Yescarta

"These are outstanding clinical results revolutionizing treatment and were the first FDA-approved therapies to have a gene therapy step."

Scrip Awards Judges

Scrip Awards
Pharma intelligence | informa

Same Drug, Two Versions And Prices, This Time For Lilly's Humalog

JESSICA MERRILL Jessica.merrill@informa.com

Eli Lilly & Co. is the latest company to join the new trend of offering the same drug in two different versions to get around obstacles in the health care system that keep some patients from benefiting from rebates. The company announced March 4 that it will launch an authorized generic version of its short-acting insulin *Humalog* in the US at a 50% discount to the list price of the brand.

The authorized generic will be called Insulin Lispro – the generic name for the molecule – and will be available in vial and pen options. The list price of a single vial will be $137.35, while the list price of a five-pack of *KwikPens* will be $265.20. The authorized generic has already been manufactured and Lilly said it is working with supply chain partners to make it available to patients as quickly as possible.

> "We don't want anyone to ration or skip doses of insulin due to affordability. And no one should pay the full Humalog retail price," CEO David Ricks said in a post explaining the decision on the company's website.

Branded Humalog remains available for patients who receive the drug through their insurance plans. That would generally be those patients who are already seeing lower out-of-pocket expenditures because of rebates Lilly has provided payers in exchange for formulary access.

"We don't want anyone to ration or skip doses of insulin due to affordability. And no one should pay the full Humalog retail price," CEO David Ricks said in a post explaining the decision on the company's website.

"Insulin affordability is a great example of the breakdown in the US health care system and why patients need a fairer pricing system," he said. One issue that seems lost in the debate over insulins and rebates is the lack of biosimilar competition. Humalog generated $2.99bn in 2018, growth of 5%, a solid performance for a product that has lost patent protection in major markets. Branded insulins, which have been regulated in the US as complex small molecules but are transitioning to be classified as biologics, have benefited from the delay of biosimilars in the US.

Sanofi launched the first follow-on version of Humalog in April under the brand *Admelog,* at $90 for a 3mL pen and $233 for a 10mL vial. Under Sanofi's patient access program, uninsured patients pay $99 per vial or $149 for a pack of five pens. But uptake of the product has been limited in the US, where it generated $86m in 2018.

A TREND THAT HIGHLIGHTS COMPLEX SYSTEM

Lilly is one of several drug manufacturers that have opted to launch the same drug in two versions with two different list prices, highlighting just how convoluted the US health care system can be when it comes to reimbursing drugs.

Amgen Inc., for example, launched a version of its cholesterol-lowering medicine *Repatha* (evolocumab) under a new Medicare Part D national drug code (NDC) at a list price 60% lower than the wholesale acquisition cost (WAC) of *Repatha*. The higher-priced product is still available to health plans and pharmacy benefit managers that have negotiated discounts and rebates. And **Gilead Sciences Inc.** introduced authorized generics for its hepatitis C drugs.

The new trend underscores the ongoing debate in the industry around the rebate drug companies make to payers off the list price of a drug that often result in a substantially lower net price for the drug. Those rebates go to lower insurance premiums, according to payers, and are not given to patients at point of sale, which disproportionately impacts uninsured patients or those paying out-of-pocket with a high deductible.

Industry increasingly favors doing away with the rebate system so that list and net prices are better aligned and so patients who pay out of pocket don't feel the disproportionate impact of the hit.

There are some obvious problems, too, with industry's new path to get around the rebate problem and address the patient affordability issue – notably, why should patients whose insurance does cover a particular drug be getting a higher priced product? And how will manufacturers in these cases make sure patients know about the different options?

Rebates were a big focus of the recent Senate Finance Committee hearing on drug pricing, where seven top pharmaceutical executives testified that they support changing the rebate system. Interestingly, Lilly was not one of the companies invited to testify before the committee Feb. 26, despite the increasing public concern over the high cost of insulin.

HHS recently released a proposed rule that would eliminate the safe harbor that allows drug companies to negotiate rebates with payers, unless those rebates are shared with the patients at the point of sale. Ricks said Lilly supports the HHS proposal as an opportunity to change the system.

"Lilly's Insulin Lispro can serve as a bridge that address gaps in the current system until we have a more sustainable model," Ricks said. "Those not well served by the current system will have a more affordable option – which can also count toward their deductible."

"While this change is a step in the right direction, all of us in the health care community must do more to fix the problem of high out-of-pocket costs for Americans living with chronic conditions," he added.

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Roche's EU Accelerated Assessment Bid For Tumor Agnostic Entrectinib Backfires

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Roche has failed to secure an accelerated assessment from the European Medicines Agency for its tumor agnostic anticancer agent, entrectinib, putting it further behind its rival, **Bayer AG**/Loxo's *Vitrakvi* (larotrectinib) in that market.

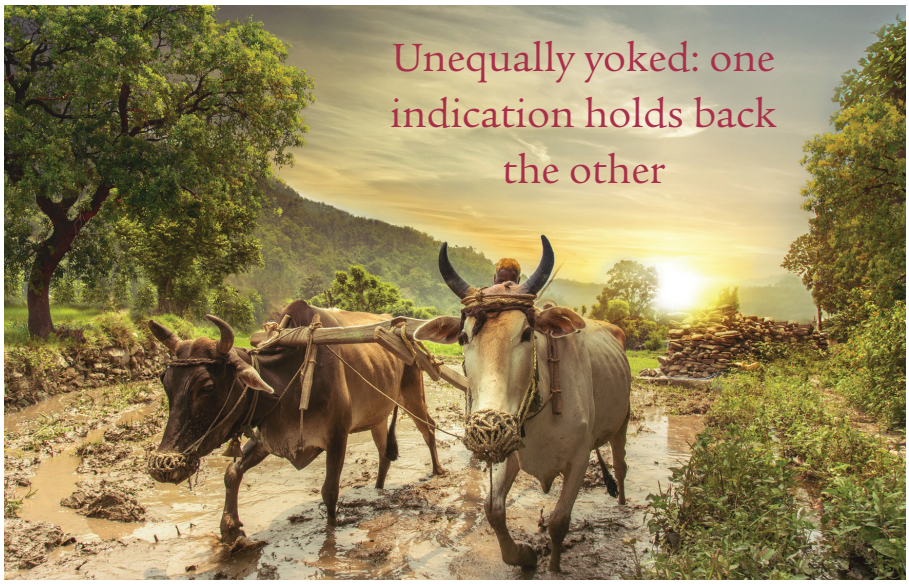
In what could prove a lesson to other companies, the Swiss firm came unstuck by its decision to request an accelerated assessment for the drug in both its potential indications: the tumor agnostic NTRK gene fusion indication and its NSCLC-specific indication in ROS1-positive metastatic disease. Unlike larotrectinib, entrectinib inhibits not just NTRK but is also an inhibitor of ROS1 kinase, a protein predominantly found in lung cancer.

As reported by *Scrip*'s sister publication *Pink Sheet*, the EMA was prepared to fast-track entrectinib for the NTRK gene fusion indication but not for use in the ROS1 NSCLC setting. Under the EMA's rules, an accelerated assessment can only concern the entire scope of a single MAA. If a single initial MAA covers two indications, both indications need to be deemed worthy of an accelerated assessment by the agency for it to be granted.

This means that the marketing authorization application (MAA) for entrectinib, once filed and accepted, will be given a standard 210 day review (not including clock stops) rather than the accelerated 150 day review (again not including clock stops).

By yoking the two indications together, Roche has lost out on a speedier EMA review for the NTRK indication that is being enjoyed by Bayer for larotrectinib, the leading tumor-agnostic product to market.

The EMA encourages companies to request an accelerated assessment two to three months ahead of filing their MAAs. Bayer received an accelerated assessment for larotrectinib in July last year, and filed the product in the EU in late August. The EMA began its assessment in September.



Vitrakvi was launched in its first market, the US, late last year following a US approval in November and Bayer has guided that its peak sales should reach €750m. *(Also see "FDA Nod For Loxo/Bayer Tissue Agnostic Drug Marks Paradigm Shift In Cancer" - Scrip, 27 Nov, 2018.)*

Roche said it was disappointed not to get the accelerated review for ROS1 "especially with the high unmet need in patients [with NSCLC] who progress with [central nervous system] metastases."

The company did have the option to remove the second indication from the request before the EMA made a final decision on accelerated assessment but decided against doing so. "The decision to file jointly was based on our desire to ensure that patients with both ROS1 and NTRK gene fusions receive the treatment in a timely manner," the company told *Pink Sheet*. *(Also see "EU Accelerated Assessment Tracker 2018: Rejection Rates Remain High" - Pink Sheet, 28 Feb, 2019.)*

In the EU, entrectinib benefited from inclusion in the EMA's PRIME (priority medicines) scheme, but only the NTRK gene fusion indication is covered.

The regulatory disappointment for Roche comes in the wake of its pivotal data for the product in the tumor-agnostic setting presented at the ESMO meeting in Munich last October being compared unfavorably by analysts with that for larotrectinib, although others pointed to its promising effects in patients with brain metastases, which also seems to set the product apart in the ROS1 NSCLC setting. *(Also see "Roche's Entrectinib Differentiates Itself From NSCLC Competitors With CNS Data" - Scrip, 24 Sep, 2018.)*

Given that the NTRK mutation is rare, finding suitable patients is a real challenge for both companies, and here Roche's diagnostic expertise could come to the fore and give its product a boost.

US FDA DIFFERED

In the US, both entrectinib indications will undergo priority review, which is similar to the EU accelerated assessment mechanism. Also, in the US, both indications have breakthrough therapy designation.

Meanwhile, entrectinib also been filed in Japan, by Chugai, but seemingly only for NTRK not for ROS1. It is included in the "Sakigake" scheme for breakthrough therapies, which enables priority review and early approval.

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Biogen Targets Ophthalmology As Emerging Growth Area With Nightstar Buy

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Biogen Inc. will move beyond neurological, rare and autoimmune diseases and into ophthalmology with its planned acquisition of UK-based **Nightstar Therapeutics PLC**, thereby getting two potentially first-in-class mid- to late-stage clinical assets as well as preclinical programs.

CASH OFFER

Biogen on March 4 said it was buying the gene therapy biotech for about $877m in cash, and that the offer price of $25.50 per share represented a premium of 68% to Nightstar's previous closing price of $15.16. Biogen put the transaction's total value at around $800m on a fully diluted basis, after taking into account expected transaction expenses and anticipated cash at closing.

Ophthalmology is viewed as a key pipeline area by Biogen, as retinal diseases are part of the central nervous system and retinal degenerative diseases have similar characteristics to degenerative CNS diseases.

"Nightstar would accelerate our entry into ophthalmology by contributing two mid- to late-stage gene therapy assets, with the potential to create long-term shareholder value," Biogen's CEO Michel Vounatsos told an analyst call when outlining the planned acquisition.

The tie-up is the latest gene-therapy driven in the field of ophthalmology.

Analysts at Deutsche Bank said that the deal hedged Roche's efforts in hemophilia, allowing it to grow Hemlibra "and be part of the next big thing that could be around the corner in this fast-paced environment." The acquisition "may add extra concern on the long-term dynamics of the market for Hemlibra, but at the same time reassures that Roche could be part of this change," they added. *(Also see "Hemophilia Seen As Good Testing Ground For Commercializing Gene Therapy" - Scrip, 8 Oct, 2018.)*

Roche last month said it was buying gene therapy specialist **Spark Therapeutics Inc.** for $4.8bn to obtain the target's Luxturna therapy for inherited blindness, and a pipeline containing potential hemophilia A treatments.

'SENSIBLE', ANALYSTS SAY

Analysts said the price Biogen was paying for Nightstar was more reasonable than that Roche has agreed to pay for Spark.

"Compared to Spark's $4.8bn sticker price paid by Roche, we think Biogen's acquisition of Nightstar represents a much more sensible valuation," analysts at BTIG said in a reaction note.

BMO Capital Markets agreed: "Biogen is getting Nightstar at a good price considering the stock was trading at the acquisition price at the end of September."

> "Compared to Spark's $4.8bn sticker price paid by Roche, we think Biogen's acquisition of Nightstar represents a much more sensible valuation." - BTIG

FOR NIGHTSTAR PIPELINE

Nightstar's lead asset NSR-REP1 is in Phase III development for choroideremia (CHM), a rare degenerative disorder that leads to blindness and has no approved treatment options.

A second asset is NSR-RPGR for the rare eye disorder known as X-linked retinitis pigmentosa (XLRP). Both REP1 and RPGR have shown positive proof-of-concept in their respective indications and Phase III REP1 data in choroideremia are expected in the second half of 2020.

Nightstar also has an early preclinical stage pipeline of other programs including Stargardt's disease and Best disease.

The indications chosen by Biogen in targeting Nightstar are not surprising given its prior, ill-fated collaboration with gene therapy-focused **Applied Genetic Technologies Corp.** (AGTC) which was for similar indications but which was ended in late December last year by Biogen after interim data on one of AGTC's investigational therapies showed it was ineffective at treating a rare eye disorder known as X-linked retinoschisis (XLRS). *(Also see "Deal Watch: Millendo Completes Merger With OvaScience, With $85m In Bank For Two Mid-Stage Programs" - Scrip, 13 Dec, 2018.)*

Nightstar's NSR-REP1 is comprised of an AAV2 vector containing recombinant human complementary DNA, or cDNA, which is designed to produce REP1 inside the eye. NSR-REP1 is administered surgically by injection into the sub-retinal space, which is between the outer layers of the retina.

NSR-RPGR is being evaluated in a dose-ranging Phase I/II clinical trial for the treatment of XLRP in patients with the RPGR mutation, known as the XIRIUS trial. Biogen and Nightstar believe NSR-RPGR has the ability to slow or stop retinal degeneration of photoreceptors and to restore or maintain vision in patients affected by these mutations.

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Gene Therapy Investment At All Time High, Commercialization Challenges Noted

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2018 saw a huge uptick in investment in gene therapy companies, but the path to efficient manufacture and commercial success for these products is still far from clear, new research from the Alliance for Regenerative Medicine suggests.

2019 has so far continued the trend, kicking off with some big investments in gene therapy companies. **Biogen Inc.**'s $877m **Nightstar Therapeutics PLC** buy, which gives it access to the gene therapy developer's expertise in retinal diseases, is the latest deal in big pharma's quest to establish strongholds in this emerging area by investing heavily in companies and products that have disease-modifying potential.

Just last week, on Feb 25. **Roche** marked its territory by agreeing to pay almost $5bn for **Spark Therapeutics Inc.** to get hold of inherited blindness drug *Luxturna* (marketed in Europe by **Novartis AG** and in the US by Spark), and a few hemophilia A candidates.

This follows on from 2018's stellar investment year in cell and gene therapy companies according to figures released by the Alliance for Regenerative Medicine (ARM) from its *Annual Regenerative Medicine Data Report.*

Globally, companies active in gene and cell therapies and other regenerative medicines raised more than $13.3bn in 2018, a 73% increase over 2017. This financing surpassed figures from 2015, which according to ARM's CEO Janet Lambert, was a "watershed year" in terms of investment in the sector when it attracted over $10bn in financing.

By sector in 2018, gene and gene-modified cell therapy companies raised $9.7bn in 2018 financing, cell therapy companies raised $7.6bn, and tissue engineering companies raised $936.9m, a 258% year-on-year increase from 2017.

It was also a standout year for IPOs, to name a few: **Allogene Therapeutics Inc.** floated for $372.6m, **Rubius Therapeutics Inc.** for $277.3m and **Orchard Therapeutics Ltd.** for $225.5m. Secondary financing also found a responsive investment community ready and willing to invest with **bluebird bio Inc.**, **AveXis Inc.**, **Iovance Biotherapeutics Inc.** and **Sangamo Therapeutics Inc.** all raising hundreds of millions to develop their regenerative medicine pipelines.

"Several of these [cell and gene] therapies have made it to market in the US and Europe, and both public and private payers have

Scrip Awards Winner 2018

Licensing Deal of the Year

This deal worth up to $8.5bn aims to maximize the potential of two anticancers, AZ's PARP inhibitor Lynparza and Merck's MEK inhibitor selumetinib, by exploring the growing scientific evidence that combining of each these two drugs with other drugs could offer even greater benefits to patients in multiple indications. The strategic collaboration is expected to further increase the number of treatment options available for patients.

Sponsored by WORLDWIDE CLINICAL TRIALS

Winner: AstraZeneca and Merck & Co (MSD) for Lynparza and selumetinib

"This deal was novel in the partnership of two big pharma sharing resources and access to technology to deliver unique combinations. An unusual aspect is the focus on enabling a combination with each party's own checkpoint inhibitor. Very beneficial for both parties and shows that two big pharmas can work together."

Scrip Awards Judges

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shown at least some willingness to engage in innovative financing and reimbursement approaches," Janet Lambert, CEO of ARM told *Scrip* in an interview. "These strides give investors the confidence that scientifically, these technologies are promising and in some cases, proven; clinically, these products have and will continue to provide significant improvement over current palliative approaches, and in some cases, provide a viable, durable treatment option where perhaps there was none."

INVESTOR RETURNS

While investor enthusiasm is evidently surging, the industry needs to now deliver on its promises and address some of the concerns investors have about return on investment. "We don't have a lot of commercial success stories in this space yet," Janet Lambert told *Scrip*. "There will be a time when investors will want to see that, to see that these products can come to market; that patients can access them and that all of that can create a good business opportunity for them as investors. I think right now there's still confidence that all that will get worked out, but there's still things that need to be worked out."

Whether this level of investment will continue, Lambert said that ARM anticipated "sustained investor commitment to this space, especially as more product candidates enter the clinic, and those already there progress towards commercialization".

There are now 906 regenerative medicines companies globally, with north America home to 484 of them.

Speaking specifically about Europe, which hosts 241 regenerative medicine companies, Lambert thinks the region's companies have been at the forefront of addressing the main investor commercialization concern, manufacturing.

"We saw Novartis as one of the first movers in CAR-T therapy. It's tackling some of the manufacturing challenges in that space and part of its solution to that was to acquire its French CDMO partner, CellforCure," she said, which is "evidence that some of the best thinking and most advanced work around manufacturing is going on in Europe".

THE PATH LESS TRODDEN

Three approved products have created a buzz over the last 18 months; Novartis's *Kymriah* (tisagenlecleucel), Spark's *Luxturna* (voretigene neparvovec) and Gilead's *Yescarta* (axicabtagene ciloleucel). Products expected to come to the European market this year include bluebird bio's *LentiGlobin* for beta thalassemia and **Kiadis Pharma Netherlands BV**'s leukemia drug ATIR101 which are both expected by the middle of 2019.

Expected by the end of 2019 is Novartis/AveXis' therapy *Zolgensma* for spinal muscular atrophy type 1. It is anticipated that Orchard Therapeutics will file a marketing authorization application (MAA) in Europe for its gene therapies in ADA deficiency and metachromatic leukodystrophy in 2020.

There were 1,028 clinical trials underway in 2018 that utilized specific regenerative medicine or advanced therapy technology. Gene therapy trials numbered 362, while cell therapy came to 263, with tissue engineering clinical trials amounting to 41.

"We've had a period of incredible scientific innovation. Now we need commercial innovation for this sector," Lambert told *Scrip*. "That is like figuring out how to scale up manufacturing; how to have a distribution network that's both personalized but also efficient."

She added that from a reimbursement and market access standing, the industry needed to still figure out how it can work with public and private payers to "effectively integrate these kinds of products into the healthcare system as we know it, and to do so in a way that is financially sustainable and delivers real access to patients."

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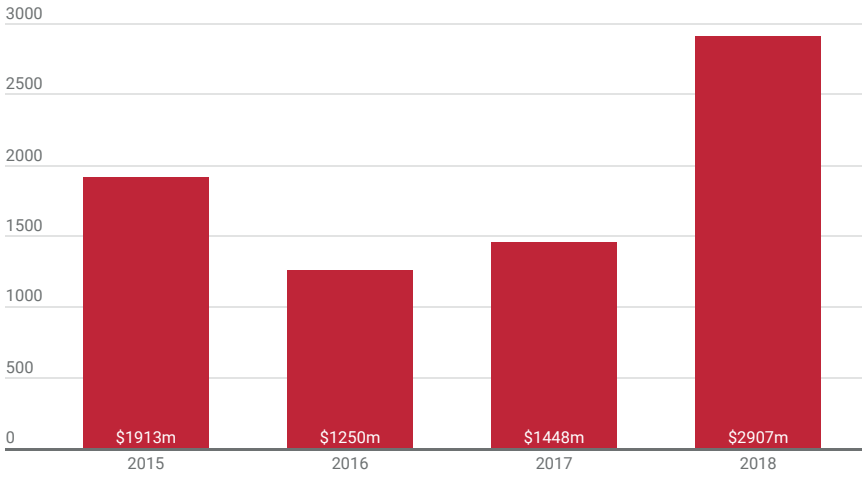
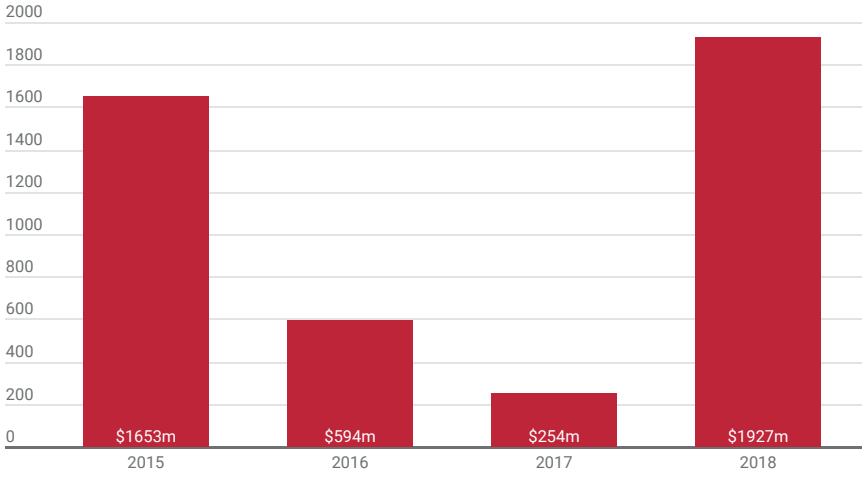
Venture Capital Investment In Regenerative Medicine Companies 2015-2018



IPO Financing 2015-2018



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How Roche Won The Bidding Battle For Spark

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Details have emerged about the process that saw **Roche** beat off competition for its proposed $4.8bn acquisition of **Spark Therapeutics Inc.** by outbidding three rivals, although the Swiss major had to up its first offer by over 60% to get hold of the gene therapy specialist.

A filing by Spark to the US Securities and Exchange Commission also highlights the considerable negotiating skills of the company's CEO Jeff Marrazzo and his team. Having got FDA approval in Dec. 2017 for *Luxturna* (voretigene neparvovec), its one-time gene therapy licensed to **Novartis AG** for the rare eye disease biallelic RPE65 mutation-associated retinal dystrophy, last May Spark "began actively considering ways in which the company could optimize the global success of its hemophilia A gene therapies," the SEC filing notes, and identified three candidates "reasonably likely to have a strategic interest" in a hemophilia A collaboration – Roche and "two other global biotechnology and pharmaceutical companies" referred to as Party A and Party B.

NEXT BIG THING

However, rather than collaborating, Roche was more interested in an acquisition and CEO Severin Schwan met with Marrazzo in New Jersey on Dec. 11 to tell him that an offer was going to be made and three days later, the Swiss major submitted an unsolicited, non-binding proposal on Dec. 14 to buy Spark at $70 per share. Marrazzo informed Schwan that the bid did not provide a sufficient basis to allow Roche to proceed to due diligence and that Spark would be discontinuing discussions regarding a hemophilia collaboration as well.

Schwan called back saying Roche was still keen and the companies met again at the J.P. Morgan conference in January but there was little movement and later Marrazzo told his counterpart that the company "would likely not consider a sale unless the offer value was well into the $80s." In the meantime, another big pharma contender, Party C, emerged.

Following more to-ing and fro-ing, Roche made a bid of $73 per share on Jan. 26 which was also rejected. To spice things up, Party C came in with a $75 per share offer on Feb. 4, while the day after, Party A said it was not going to put in an acquisition proposal. Feb. 8 saw Party B submit a collaboration proposal that included a $450m upfront payment to access Spark's hemophilia A candidates SPK-8011 and SPK-8016.

At this stage though, Spark decided against contacting Party B regarding a potential sale because it wanted to avoid disruption of negotiations around a hemophilia A collaboration. However the SEC filing also reveals that Spark discussed the likelihood that Party B would not be interested in the other parts of its business "and the uncertainty that Party B would have the ability to consummate an acquisition transaction of this size and nature."

Party C was not finished yet and upped its offer on Feb. 22 to $84 per share and the same day Roche put in what it designated as its best and final proposal of $91 per share. At this stage, however, the Spark board "discussed process considerations to attempt to maximize the value that these parties would offer to pay" and informed Roche and Party C that best and final offers would be due on the evening of Feb. 22 with one of the conditions being that the highest final bid should at least $2.00 per share higher than the other offer.

Party C submitted a revised proposal of $105.00 per share but this was comfortably trumped by Roche agreeing to $114.50 per share. The merger agreement was signed that same evening.

The tale shows the leadership of Spark in a good light, especially its ability to drive a hard bargain, as it managed to get a 122% premium out of Roche to its closing price of $51.56 on Feb 22, and a whopping 230% on its 52-week low. It also demonstrates the attractiveness of gene therapy companies and the desire of big pharma to get hold of them, with Roche's bid going up from $73 per share to $114.50 in less than a month.

Last year, Novartis acquired **AveXis Inc.** and its spinal muscular atrophy treatment *Zolgensma* for $8.7bn and earlier this week, **Biogen Inc.** bought the UK's **Nightstar Therapeutics PLC** for $800m. *(Also see "Biogen By Buying Nightstar Targets Ophthalmology As Emerging Growth Area" - Scrip, 4 Mar, 2019.)*

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Pro Vs. Con: A Side-By-Side Look At Investor Concerns, Bristol's Defenses Of Celgene Deal

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Bristol-Myers Squibb Co. has reviewed the value of its pending $74bn acquisition of **Celgene Corp.** for several months and believes – contrary to the views of some of its biggest investors – that the combined companies offer much more value to shareholders than either entity on its own.

Bristol released a letter to its shareholders and an investor presentation defending the deal on March 6 as materials to support an April 12 shareholder vote on the deal, which is expected to close in the third quarter of this year. Starboard Value LP also sent a letter to Bristol shareholders on March 6 urging investors to vote against the transaction; the correspondence reiterated five concerns about the acquisition previously outlined by the investment advisor.

Celgene represents the best opportunity to enhance Bristol's earnings potential over the long term more so than any of the other companies or combinations of companies that Bristol considered acquiring, the company claims. Bristol said in its new shareholder communications that it considered more than 20 different acquisition targets, including different combinations of smaller acquisitions, beginning

Side-By-Side: Starboard's Arguments Against The Celgene Deal Vs. Bristol's Rebuttals

STARBOARD'S CONCERN	BRISTOL'S RESPONSE
The Revlimid loss of exclusivity in a few years "will serve as a major overhang on [Bristol's] shares in the years to come. Based on our analysis, the patent cliff caused by Revlimid alone will require Celgene to replace over 60% of its total revenue in the next seven years."	Bristol is confident about Revlimid's prospects through at least 2022 when the first generics hit, based on a review of public and non-public information about ongoing patent challenges. However, the combined company will have nine products with more than $1bn in annual revenue, the number-one oncology and cardiovascular franchises among its peers, and be among the industry's top five immunology players. It will boast a late-stage pipeline of six key products that could generate $15bn in combined peak revenue and an early-stage pipeline of 51 compounds across key therapeutic areas.
The Celgene R&D pipeline is risky, since it requires a rebuilding of its entire revenue base over the next eight years, during which many currently marketed products will lose patent protection. "We believe this is an aggressive assumption" by Bristol.	Three of the five near-term product launches within Celgene's late-stage R&D portfolio have been de-risked in Phase III trials with US FDA filings on schedule or completed: ozanimod for multiple sclerosis (resubmission expected by the end of March), lisocabtagene maraleucel (liso-cel or JCAR017; filing expected in second half of 2019) and fedratinib for myelofibrosis (FDA accepted the filing and granted priority review). The payment of a contingent value right (CVR), bringing the Celgene acquisition's total value to $90bn, is dependent on these three programs. As for the company's other two late-stage assets, Celgene has said luspatercept for myelodysplastic syndromes and beta-thalassemia will be filed in the first half of 2019; pivotal data for bb2121 in multiple myeloma will be reported in late 2019, followed an FDA filing. *(Also see "Celgene Gives Reassurances That Key Products And Programs Remain On Track" - Scrip, 31 Jan, 2019.)*
"[T]his transaction was hastily construed and perhaps done to thwart potential strategic interest in Bristol-Myers. We believe that if the company remains independent, it is quite possible that there may be strategic interest in Bristol-Myers at a substantial premium to the current stock price."	Bristol first talked to Celgene in 2017, but it also considered 77 biopharma acquisition opportunities and prioritized 22 for further assessment in early and mid-2018. The company took a deeper look at seven opportunities in June (in parallel, it considered asset swaps and joint ventures with peer companies, but found this would have little strategic or financial impact). In September it identified Celgene as the best option to build value in line with Bristol's goals in and conducted an even deeper assessment and engaged in due diligence between October and December, before obtaining board of director approval for the deal in January.
Bristol's "analysis of the financial merits of the transaction – specifically its allocation of value between Celgene's marketed products, the combined synergies, and the Celgene pipeline – is potentially misleading based on our diligence."	In addition to the combined company's potential $15bn in peak revenue from six near-term approvals, including Bristol's immunology candidate BMS-986165, the portfolio of marketed Bristol and Celgene products is worth $55bn in sales by 2025 and the combined company will achieve $20bn in synergies, which justifies the $90bn deal cost, assuming the CVR is paid out.
"[T]here is a better path forward for Bristol-Myers, either as a more profitable standalone company with a more focused, lower-risk strategy, or in a potential sale of the whole company."	The transaction is more than 40% accretive in 2020 and remains accretive in all years through 2025. Net income for Bristol alone would grow from $7.1bn in 2020 to $11bn in 2025, but the combined company's net income will grow from $14.5bn to $19.6bn in that timeframe. Also, the deal will significantly diversify Bristol's portfolio with its top three products – *Opdivo* (nivolumab), *Eliquis* (apixaban) and *Orencia* (abatacept) – as a percentage of pro forma revenue dropping from about 70% to less than 50% in 2025. Bristol's non-GAAP operating income margin of 28% as a standalone company in 2018 would be 43% if it were combined with Celgene, after synergies.

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in early 2018 before determining that an acquisition of Celgene alone was the most attractive opportunity.

Indeed, Celgene was a long-term prospect, given that Bristol and the maker of multiple myeloma blockbuster *Revlimid* (lenalidomide) first began to talk about a merger of equals in 2017 before calling off the discussions. The companies then reconnected in late 2018 to negotiate a lower-valued Celgene buyout after several setbacks for the acquisition target. *(Also see "Bristol Approached Celgene Nearly Two Years Ago, Got A Better Deal Later" - Scrip, 1 Feb, 2019.)*

Bristol continues to insist that it has appropriately assessed the Revlimid risks, including both intellectual property risk from ongoing patent challenges and future revenue risk as generics cut into Revlimid sales and growth will have to come from new products.

The company's new shareholder presentation asks investors to put their faith in Bristol management, which has shown it can grow revenue even when key products fall over patent cliffs. Compound annual growth rates (CAGRs) across multiple metrics outpaced the company's peers during the past five years, including a more than 7% CAGR for revenue versus more than 3% for its peers.

"Bristol is clearly trying to convey that this transaction was not 'hastily construed,' as Starboard alleged," BMO Capital Markets analyst Alex Arfaei said in a March 6 note about the company's new investor presentation on the deal.

"While the presentation strengthens the fundamental argument for BMY+CELG, it doesn't address whether it was also done to thwart potential strategic interest in Bristol. Without a good bid for BMY, or strong opposition from proxy advisory firms, we believe BMY+CELG seems increasingly probable," Arfaei concluded.

Based on polls of clients and the mix of investors who hold a large amount of Celgene shares, including many Bristol shareholders, analysts continue to expect next month's merger vote to go in Bristol's favor, even with several high-profile investors continuing to express negative views of the deal. Enough shareholders may be willing to take the longer-term risk that late-stage Celgene pipeline programs will make up for Revlimid revenue declines anticipated when generics hit the market in 2022, rather than take the near-term risk that investors will lose a lot of money if the deal doesn't close.

"We continue to expect shareholders to vote in favor of the deal and expect it to close in 3Q19 as currently planned," Credit Suisse analyst Vamil Divan wrote in a March 6 note.

Divan pointed out that while Bristol investors have cited concerns that the company did not consider other potential acquisitions, the new investor presentation shows that several opportunities were reviewed in addition to Celgene.

Bristol's sum-of-the-parts explanation of the deal's $90bn aggregate value (including payout of the contingent value rights) – $15bn in sales from new launches, $55bn in sales from marketed products and $20bn from synergies – also should answer a big question about valuation for investors, he said.

"Based on our conversation with investors, most seem to agree that Bristol is paying a reasonable (if not favorable) price for Celgene," Arfaei noted.

Even so, additional investors are going public with their opposition of the deal, including the Loncar Cancer Immunotherapy Exchange-Traded Fund (ETF), which holds shares of Bristol, but not Celgene.

The Loncar ETF listed five reasons why it opposes the Bristol-Celgene transaction on March 6: reduced confidence in Bristol management's ability to run a larger company given recent clinical trial setbacks, a need for Bristol to focus on existing investments, likely R&D cuts that could undermine Bristol's value, Bristol could adopt poor Celgene business practices, and Celgene's track record could mean there are more R&D pipeline surprises coming for Bristol investors.

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Concert Says Phase II Alopecia Drug Could Beat Pfizer's Candidate To Market

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Concert Pharmaceuticals Inc. believes it may be positioned to move ahead of **Pfizer Inc.** in the race to bring the first drug for alopecia areata to market, but the biotech also must stave off a patent challenge from **Incyte Corp.** regarding its rights to bring a deuterium-modified version of ruxolitinib to market.

Concert presented Phase IIa data for CTP-543, its deuterated formulation of Incyte and **Novartis AG**'s myelofibrosis drug *Jakafi*, dosed at 8 mg twice-daily for 24 weeks in patients with alopecia areata at the American Academy of Dermatology (AAD) annual meeting March 2. The drug demonstrated statistically significant hair growth compared to placebo based on the number of patients who showed a 50% or greater improvement in Severity of Alopecia Tool (SALT) score from baseline.

In an interview, Concert CEO Roger Tung said his company has pretty much determined the minimally effective dose of its drug, which is an important factor considering the US FDA's emphasis on correctly balancing the safety and efficacy of Janus kinase inhibitors. CTP-543 is an oral, selective inhibitor of JAK1 and JAK2, while Pfizer's PF-06651600 is a selective JAK3 inhibitor. Although CTP-543 is a reformulation of ruxolitinib, it is expected to be considered a new molecular entity (NME).

Pfizer moved its drug into the pivotal ALLEGRO study last September, but Tung believes the pharma will need to conduct an additional confirmatory study in order to file PF-06651600 for approval due to the FDA's safety emphasis in the JAK inhibitor class.

Concert expects to complete its dose-ranging work with CTP-543 before the end of 2019, which should mean it can initiate

pivotal Phase III work in 2020, he explained. "Pfizer has demonstrated that they have a compound, a JAK3 selective inhibitor, which shows efficacy against AA, however they've only studied it in a single dosing regimen," Tung told *Scrip*. "They started [Phase II] with a loading dose of the compound for a 28-day period and then backed off to one-quarter of that loading dose for the ensuing five months of that study."

COMPLEX STUDY WILL NEED TIME TO FIND BEST DOSE

Pfizer's ALLEGRO study is investigating seven arms – some with induction doses followed by maintenance doses of PF-06651600 and others only testing a maintenance dose. The study is expected to report out data in 2021. Of note, Pfizer obtained breakthrough therapy designation for the drug in alopecia areata – an unmet medical need – last September.

"What [the trial design] really indicates is that they don't know how to use the drug yet," Tung asserted. "They know there's activity there, but they don't know where or how they will get to understand the minimally effective dose." Because of that, he believes Pfizer will be required to run a confirmatory Phase III trial with an as-yet undetermined dose of PF-06651600, which "gives us a substantial time advantage compared to Pfizer."

While continuing its clinical development program with CTP-543, however, Concert also will need to deal with a patent challenge from Incyte. The US Patent Trial and Appeal Board has granted Incyte a rehearing on the issue, which will occur on or before April 9, the outcome of which will determine CTP-543's revenue tail, JMP Securities analyst Liisa Bayko said in a Feb. 14 note. Concert intends to pursue continued development of the drug no matter the hearing's outcome, but Incyte claims a broad patent on ruxolitinib including deuterated forms of the molecule.

"The question remains whether CTP-543 can be commercialized without any obligations to Incyte," Bayko said. "At this point, it is difficult to predict a winner one way or the other given the multiple iterations involved, but [Concert] management has committed to its development regardless of the outcome, as the compound would, at a minimum, have five years of exclusivity as a new chemical entity (NCE), enough time to make it a commercially viable opportunity."

TECHNOLOGY'S POTENTIAL ILLUSTRATED BY VERTEX DEAL

Concert's business model, based on creating deuterium-modified versions of already approved drugs, already has proven lucrative, as it obtained $160m up front from **Vertex Pharmaceuticals Inc.** in 2017 for its deuterated version of ivacaftor, the active ingredient in Vertex's cystic fibrosis drug *Kalydeco* and several combination therapies for CF. [See Deal]

When the deal was struck in March 2017, Vertex generally was viewed as having played defense to protect its CF franchise. At the time, Tung told *Scrip* that Concert planned to keep other candidates from its *Deuterium Chemical Entity* (DCE) platform in-house by developing outside the approved indications for their original formulations, citing CTP-543 specifically.

Tung said the DCE platform can alter the therapeutic characteristics of a drug, making it efficacious at smaller doses and/or providing a longer half-life. The technology was able to achieve both of those ends with deuterated ivacaftor.

Concert is also working to bring D-serine into human studies for the first time with a deuterated version that may address the amino acid's renal toxicity issues. Previous attempts to make a D-serine-based drug have ended in preclinical testing due to toxicity, but Concert thinks its formulation could other a new therapeutic option in neuropsychiatric diseases, such as schizophrenia.

The Phase IIa work with CTP-543 continues, as Concert expects to report out data from a 12 mg twice-daily cohort in the third quarter. It is also in the process of initiating a study to compare the safety and efficacy of 8 mg twice-daily – which the company believes is an approvable dosage – against that of 16 mg once-daily, with data expected this year.

"By the end of the year, we hope to understand the dose range with respect to what we could take forward and we also will have a lot more information regarding the dosing characteristics in terms of once- versus twice-daily," Tung said.

Bayko thinks demonstrating a once-daily dosing capability would only add to CTP-543's commercial potential. "This makes sense as it gives the company another option to potentially take into a Phase III study with the added benefit of being a more patient-friendly regimen with reduced dosing frequency," she said.

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Allergan Endures Another R&D Setback With Rapastinel Failing Three Pivotal Studies

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Clinical development failures in major depressive disorder (MDD) are nothing new, but **Allergan PLC**'s trio of unsuccessful Phase III studies with NMDA receptor modulator rapastinel might be more damaging because of the company's recent litany of R&D setbacks, along with **Johnson & Johnson**'s US approval in the same class with *Spravato* on March 5.

Allergan announced top-line results late in the day March 6 showing that rapastinel – a driver of its $560m purchase of **Naurex Inc.** in 2015 – failed to meet the primary and secondary endpoints as adjunctive MDD therapy in three Phase III studies enrolling 1,500 patients. The candidate appeared unlikely to meet endpoints in an ongoing, open-label relapse-prevention study as well. Allergan spoke optimistically about rapastinel during the J.P. Morgan Healthcare Conference in January and had named it one of the six "stars" of its pipeline.

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While the latest studies investigated rapastinel as adjunctive therapy to oral standard-of-care antidepressants in patients with inadequate clinical response, Allergan has a Phase III program with the candidate as MDD monotherapy and a Phase II proof-of-concept study in MDD patients with imminent risk of suicide under way.

Chief Research and Development Officer David Nicholson said in a statement that Allergan will evaluate the impact of the adjunctive therapy data on those programs and decide sometime in 2019 whether to continue the studies.

The company listed rapastinel, during its fourth quarter/full-year 2018 earnings call on Jan. 29, along with the recently launched neuropsychiatric drug *Vraylar* (cariprazine) and the Phase III oral CGRP antagonists ubrogepant and atogepant as key pieces of its strategy for surviving the coming patent cliff for its dry eye stalwart *Restasis* (cyclosporine ophthalmic emulsion 0.05%). *(Also see "Allergan Thinks It's Ready To Withstand Restasis Generics" - Scrip, 29 Jan, 2019.)*

Credit Suisse analyst Vamil Divan said in a March 6 note that safety data for ubrogepant in acute migraine expected in May at the American Academy of Neurology meeting now looms large as Allergan's next R&D inflection point.

Divan called rapastinel "a star we thought would shine bright" and said optimism around the drug had been high "given the legacy the Allergan team has in the CNS space and in depression in particular."

Both Divan and SVB Leerink analyst Marc Goodman speculated that the disappointing data might increase investor pressure on Allergan's management and board heading into the company's May 1 annual meeting.

Prior to rapastinel's disappointment, Allergan suffered late-stage trial disappointments with cenicriviroc in nonalcoholic steatohepatitis (NASH) and abicipar in wet age-related macular degeneration (AMD), and received an FDA complete response letter for ulipristal acetate (marketed in Europe as *Esmya*) in uterine fibroids. *(Also see "Allergan's Ulipristal, Dogged By Liver Concerns, Gets An FDA Rejection" - Scrip, 22 Aug, 2018.)*

Abicipar demonstrated non-inferiority to *Lucentis* (ranibizumab) in a pair of Phase III studies last year but also showed a side-effect profile that caused analysts to question its market potential. *(Also see "Allergan's Abicipar Effective With Fewer Injections, But More Inflammation In AMD" - Scrip, 19 Jul, 2018.)* Cenicriviroc, focus of the $1.7bn buyout of **Tobira Therapeutics Inc.** in 2016, failed to show a fibrosis benefit in a Phase IIb readout in late 2017. *(Also see "Allergan's Two-Year NASH Data Fail To Show Fibrosis Benefit" - Scrip, 22 Sep, 2017.)*

The succession of disappointments plus concerns about financial performance after Restasis' loss of exclusivity have led to activist investors pushing for changes in Allergan's management structure. *(Also see "Allergan Fights Generic Headwinds, Activist Investors" - Scrip, 26 Jul, 2018.)*

PHASE IIB PROMISE NOT REPEATED IN LARGER INVESTIGATION

In the three studies, a 450 mg bolus intravenous injection of rapastinel administered weekly was tested along with ongoing oral antidepressant therapy compared to placebo – one of the three trials also included an arm testing a 225 mg weekly rapastinel dose. Although the drug showed rapid onset of action and duration of effect in a Phase IIb study reported in 2014, in Phase III rapastinel failed to better placebo on change from baseline Montgomery-Asberg Depression Rating Scale score at both three weeks and one day, the primary and secondary efficacy measures.

Allergan did not release detailed data from the three studies, but said it will do so at a future scientific meeting.

Biomedtracker downgraded rapastinel's likelihood of approval by 13 percentage points to 41% upon the release of the Phase III adjunctive therapy data and called the "washout" a significant blow for both Allergan and MDD patients, because rapastinel has posted a fairly clean safety profile with no indications of psychomimetic effect.

The approval of J&J's *Spravato* (esketamine) carries an enhanced Risk Evaluation and Mitigation Strategy (REMS), because of ketamine's historical risk for psychomimetic effects. "Considering that rapastinel was well tolerated without any signal of psychotomimetic side effects across its Phase III trials, this would have been a competitive advantage over Spravato, which produced dissociative side effects in clinical trials," Biomedtracker asserted. "Furthermore, these negative data threaten the outlook for rapastinel's remaining clinical trials in depression. As highlighted by key opinion leaders, rapastinel has less opportunity in MDD since there is a plethora of oral antidepressants at first line and physicians would be less inclined to initiate newly diagnosed patients on a less-established, intravenous, and likely more expensive antidepressant."

ANALYST: SETBACK 'NOT SURPRISING'

Morgan Stanley analyst David Risinger called the rapastinel setback "not surprising" in a March 6 note, but pointed to Allergan's Phase III oral NMDA modulator AGN-241751 as a reason for optimism. Allergan in-licensed that compound from Naurex successor **Aptinyx Inc.** in May under an existing option agreement.

In his own March 6 note, SVB Leerink's Goodman predicted that after an initial downturn in its stock price due to the rapastinel data, Allergan shares would uptick quickly due to expectations of change at the company's general meeting in May. Allergan finished the trading day March 7 up 4% to $143.

Aptinyx, which is developing NMDA modulators that weren't sold to Allergan in the Naurex transaction, fell 10.6% to close at $4.65. The company's stock is down 72% year-to-date after a Phase II trial failure in January. *(Also see "Aptinyx Says DPN Setback Just A Step In Seeking Chronic Pain Indication" - Scrip, 16 Jan, 2019.)*

Speaking at SVB Leerink's Global Healthcare Conference on Feb. 27, Allergan CEO Brent Saunders expressed guarded optimism for rapastinel and the potential of NMDA modulation in depression.

"We're excited to learn more about [this mechanism of action]," the exec said. "We're excited to get the data from the oral [candidate], which is in Phase II. We think this mechanism is a viable mechanism for development. And it could be among the most promising, if not the most exciting things we've ever been involved in."

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Alnylam Ramps Up Commercial Planning For Givosiran Based On Phase III Data

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Alnylam Pharmaceuticals Inc. expects to launch its second commercial drug and the second RNAi therapeutic in the US in early 2020, after announcing positive Phase III data on givosiran in patients with the ultra-rare disease acute hepatic porphyria (AHP).

The company already has launched a disease awareness initiative and is providing genetic testing support for patients through its Alnylam Act program. A revised timeline for givosiran's filing with the US FDA has been a bit of a step back, however, as Alnylam had been hoping to file early based on interim data released last year, but was hung up by early safety signals, which have not been eliminated.

Management discussed the positive top-line results of the ENVISION study in a call March 6, outlining why the company thinks givosiran could be used in a wide range of the small number of patients with AHP while downplaying some worrisome adverse events impacting the kidney and liver. Renal and liver impairment are among the manifestations of the disease, which is why the company believes there was an increased incidence of chronic kidney disease and higher liver enzymes in study patients treated with givosiran versus placebo.

"We are encouraged by the overall safety profile, especially in this disease setting where there are no approved treatments," CEO John Maraganore said. "The efficacy and safety results together support regulatory submission of givosiran, which we aim to complete in mid-2019." Under a rolling new drug application (NDA) submission, Alnylam already has completed the CMC and nonclinical portions of the NDA, he said.

The company is pushing ahead with early commercialization plans, even as some investors were unsure about the benefit-risk data. The company's stock closed 4% lower at $84.75.

"This is a terrible disease with enormous burden," President Barry Greene told the call. AHP is a family of rare, genetic diseases caused by a genetic deficiency of one of the enzymes of the heme biosynthesis pathway in the liver, resulting in build up of two neurotoxic heme intermediates, of which aminoleyulinic acid (ALA) is believed to be responsible for causing attacks. Those attacks include severe abdominal pain, weakness, nausea and fatigue that can frequently lead to hospitalization and is often misdiagnosed. Long-term complications result in chronic neuropathic pain, hypertension, chronic kidney disease and liver disease.

There are estimated to be only 1,000 patients in the US and EU with recurrent attacks, but Greene said Alnylam also plans to target another 5,000 patients in the US and EU who experience sporadic attacks and chronic manifestations.

EFFORTS UNDERWAY TO IDENTIFY AND DIAGNOSE PATIENTS

"Given the current diagnosis rate is as low as 20%, the patient journey is around 15 years," he said. "We believe with better education and patient-finding efforts, there is a significant potential for growth in the number of properly identified and diagnosed patients. Alnylam has initiated physician and patient education initiatives to spread the word, targeting gastroenterologists, hematologists and neurologists. The company also launched the physician-focused website porphyriadiagnosis.com, providing an overview of the disease and outlining symptoms and diagnosis. The site also provides information about genetic testing and the Alnylam Act program, under which Alnylam provides financial support for testing and services by independent third parties.

Under the genetic testing program, 305 physician tests already have been submitted, of which 31 individuals with pathogenic AHP mutations have been identified, Greene said.

"This is just the beginning of our Alnylam Act program," he said. "We are very encouraged to see an approximate 10% positive mutation identification rate."

Alnylam also is exploring social media as a way to inform patients about the disease and build awareness.

KIDNEY AND LIVER EVENTS REMAIN A CONCERN

But before Alnylam can treat the patients it finds, the company will need to get givosiran across the FDA approval finish line. The top-line data from ENVISION suggest there will be questions that need to be answered around safety.

The study enrolled 94 patients, including 89 with genetically-confirmed acute intermittent porphyria, the most common subtype of the disease. ENVISION met its primary efficacy endpoint of reduction in annualized rate of composite porphyria attacks versus placebo at six months. The company expects to present further details of the study at the EASL International Liver Congress in April.

The trial also achieved statistically significant positive results on five of nine secondary endpoints, including urinary ALA levels at three and six months in AHP patients, annualized attack rate in AHP patients and annualized days of administered hemin doses in AIP patients. Hemin is one option used to treat patients but chronic use can cause renal insufficiency and iron overload, which can cause liver cancer.

Four other secondary endpoints did not reach statistical significance, including daily worst pain, daily worst fatigue, daily worst nausea and the physical component summary of the health survey in AIP patients.

But it was the adverse events that caused some concern among investors, even though those issues were noted in an interim look at the Phase III data last year.

Serious adverse events were reported in 10/48 (20.8%) of givosiran patients veresus 4/46 (8.7%) of placebo patients. Adverse events reported in greater than 10% of givosiran patients and more frequently than in placebo included chronic kidney disease, as well as nausea, injection-site reactions and fatigue. CKD was reported in five givosiran-treated patients, but all of the cases were in patients with renal dysfunction at baseline and patients continued on the

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study drug. Increases in liver transaminase of more than three times the upper limit of normal (ULN) were also observed in 14.6% of patients on givosiran versus 2.2% of those on placebo. All had evidence of iron overload or liver disease at baseline, the company reported. One patient discontinued treatment due to an increase in alanine aminotransferase levels greater than eight times ULN; it subsequently resolved. All of the other patients enrolled in the ENVISION open-label extension study, which management said highlights the clinical benefit versus the risks.

"Let's be clear, if a patient suffers damage to their kidneys or impaired renal function associated with a drug than the normal practice is you reduce the dose of the drug or you take the patient off the drug. That did not occur here," Chief Medical Officer Pushkal Garg pointed out.

"The nature of those changes were not sufficiently concerning from a clinical perspective, and we anticipate – we don't know – but we anticipate the overall benefit they were getting was so remarkable that the physicians decided to keep the patient on the drug," he said.

Morgan Stanley analyst David Lebowitz remained positive on the prospects, noting in a same-day note that the tolerability is likely acceptable given the high unmet need.

"Despite the disappointment from management's inability to file on the interim data presented in 2018, we see a strong path to market with potential approval by 2020," he said.

If Alnylam does manage to launch givosiran then it will be on track to reach its goal of being a global multi-product company with a deep clinical pipeline by the year 2020. As Maraganore pointed out during the call, "this is a profile rarely achieved in biotech history." Alnylam's 2020 goal has been modified a bit since it was announced in 2015. Then, Maraganore laid out a goal for the company to get three drugs to market by 2020.

The company's first drug, *Onpattro* (patisiran), debuted with a lot of fanfare last year, as the first RNAi therapeutic approved in the US and the first drug for hereditary transthyretin-medicated amyloidosis (hATTR), another rare genetic disease.

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Bayer Bosses Beg Risk-Averse Europe To Rethink

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Bayer AG bosses believe that the firm is well placed to be at the head of the innovative advances that will drive pharmaceuticals development in the near future but have expressed concerns about the environment, particularly in Europe, to ensure that innovation is nurtured and rewarded.

Speaking to *Scrip* at the German group's annual press conference in Leverkusen on Feb. 27, head of innovation Kemal Malik noted that Bayer, not least with the discovery of aspirin, was a key player at the birth of the modern pharmaceutical industry, and small molecule chemistry, in the nineteenth century. Now, just as the group was there at the start, "we want to be at the forefront of the activities in cell and gene therapy," he said, an area which represents the next wave of innovation in the sector.

The company currently has a Phase II trial underway with partner **Ultragenyx Pharmaceutical Inc.** looking at a gene therapy for hemophilia A, for which Malik said recruitment is ongoing. He also referenced **Roche**'s recently proposed $4.8bn acquisition of **Spark Therapeutics Inc.** and its hemophilia programs as an example of the huge interest in the space, adding that "literally every week we hear about something happening in gene therapy."

He went on to speak about the group's 'Leaps by Bayer' initiative which has so far invested some €600m in start-ups that offer "really radical breakthrough innovation", and about the companies it has set up with other partners, notably **Casebia Therapeutics**. The latter is a joint venture with the gene editing company **CRISPR Therapeutics AG**, which earlier this week announced (along with partner **Vertex Pharmaceuticals Inc.**) the initiation of clinical trials in beta thalassemia and sickle cell disease of CTX001, their Crispr/Cas9 gene-edited stem cell therapy.

As for Casebia, Malik said an application would be made to start trials next year

Kemal Malik

in autoimmune conditions. It plans also to move forward in ophthalmology and potentially cardiovascular indications, "so we are very much at the forefront of gene therapy and gene editing." He also spoke about **BlueRock Therapeutics**, a joint venture with Versant Ventures, which hopes to move a stem cell-based therapy for Parkinson's disease into clinical trials later this year.

Malik went on to mention the antisense project with **Ionis Pharmaceuticals Inc.** in thrombosis, "an area where we are the market leader, so when you bring all of these activities together, you can see how Bayer will be one of the leading cell and gene-based therapy companies in the world."

However, how much of Bayer's activities in these new areas will take place in Europe, particularly in gene editing, is up in the air. Chairman Werner Baumann used part of his address at the Leverkusen meeting to air his concerns that the continent is not keeping up when it comes to adapting to "far-reaching changes [which] have been taking place in the world that demand answers."

These include the acceleration of innovation cycles through digitalization and other disruptive technologies, he said, and also include "the decline in Europe's significance as an economic center of gravity. But if you follow public debate in Germany and Europe, you don't get the impression that

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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, 1–7 MARCH 2019

Event Stage	Lead Company/Partner	Drug Name	Indication	Comments	Change To LOA (%)	LOA (%)
Phase III Published Results	Novo Nordisk A/S	Ozempic (semaglutide)	Diabetes Mellitus, Type II	SUSTAIN 9; The Lancet Diabetes & Endocrinology, March 1, 2019	0	100
Phase III Published Results	Indivior plc	Sublocade (buprenorphine)	Substance Use Disorder	Journal of Addiction Medicine, March 4, 2019	0	100
Phase IIIb Updated Results	Eli Lilly & Co	Taltz (ixekizumab)	Genital Psoriasis	IXORA-Q; Clinical Improvement	0	100
Phase III Updated Results	Sun Pharma	Ilumya (tildrakizumab-asmn)	Psoriasis	reSURFACE 1, 2	0	100
Phase III Updated Results	Dermira Inc.	Qbrexza (glycopyrronium tosylate)	axiliary hyperhidrosis	Extension Study (ARIDO); Sustained Responses	0	100
Phase III Updated Results	Endo International plc	Xiaflex (collagenase)	Cellulite	RELEASE-1,-2;Met Clinical Endpoints	0	66
Phase III Updated Results	AbbVie/Boehringer Ingelheim	Skyrizi (risankizumab)	Psoriasis	IMMhance, IMMvent; Effective And Well Tolerated	0	98
Phase III Updated Results	Almirall/Athenex	KX2-391	Actinic Keratoses	AK004; Achieved Primary Endpoint	0	70
Phase III Updated Results	Verrica Pharmaceuticals, Inc.	VP-102 (cantharidin)	Molluscum Contagiosum	CAMP-1,-2; Positive Results	0	71
Phase III Updated Results	Sesen Bio, Inc.	Vicinium	Bladder Cancer	VISTA; Clinical Activity Sustained	4	39
Phase III Updated Results	Novartis AG	Cosentyx (secukinumab) Vs. Stelara (ustekinumab)	Psoriasis	CLARITY; Further QoL Data	0	100
Phase III Updated Results	Alnylam Pharmaceuticals, Inc.	givosiran	Porphyria	ENVISION; Positive Further Data	-1	92
Phase III Updated Results	ViiV Healthcare	cabotegravir/rilpivirine	HIV/AIDS	ATLAS, FLAIR; Positive Data For Once-Monthly Injections	0	67

Source: Biomedtracker | Informa, 2019

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people realize this. While other countries are working to shape the future, many people here view advances in technology with suspicion. While people willingly take advantage of things that are useful, the technologies themselves – or the effects that accompany them – are frequently rejected."

The main target for Baumann's ire was a ruling by the European Court of Justice last year which reached the conclusion that gene editing technologies such as Crispr/Cas are to be considered as genetic modification and regulated accordingly. He said the ruling "makes working with this fantastic, highly promising new technology unattractive in Europe. It's up to the politicians to find a solution quickly, otherwise Europe risks falling behind in this area as well."

He went on to say "this is about nothing less than securing our prosperity. For that, we need improved conditions for companies and technological innovation, including an appropriate regulatory process that enables new technologies to emerge and does not over-emphasize the precautionary principle, which is right and proper."

Baumann claimed that "our employees come up with an average of 450 inventions a year for which Bayer files patent applications. That's more than two inventions every working day. New things that promise to make the world a little bit better. Of course, not every idea or every new molecule turns into a product but having a lot of good ideas is essential for delivering innovation."

When asked by *Scrip* about the political will in Europe to reward innovative medicine with decent prices, Bayer's head of pharma Stefan Oelrich said that there needed to be a lot more discussion about the value created by life sciences, and more particularly pharma, in Europe. He added that "in my country, we continue to talk about the car industry when it has basically been reduced to inventing batteries."

"We need to look at how we can secure value creation through new modalities in pharma because if you look at the basic research coming out of Germany, the UK, France, Switzerland and so on, we have still world class researchers in the academic setting in Europe yet when you look at where the value is created, it's all in the US. All the start-ups, all the venture capitalists, they all go to the US," Oelrich said. He added that "I think we have some work to do, together with governments, to better explain the value that we bring to the future, not just by curing people, but also by employing people."

READY FOR 'IRRESPONSIBLE' BREXIT

How long the UK will be mentioned in the same breath as the rest of the Europe remains to be seen with just over four weeks to go before the country is scheduled to leave the European Union. On Brexit, Baumann told *Scrip* that personally speaking, he felt those politicians who had called the referendum back in June 2016 have behaved in a "highly irresponsible way," but if "March 29 is the D-Day, we are prepared for it."

He added that Bayer has inventory ranges of 8-12 weeks "which will help us navigate the initial imponderables and chaos at the customs borders." Baumann noted that additional preparations for drugs that cannot be stockpiled such as the prostate cancer radiopharmaceutical *Xofigo* (radium 223) had been made and he hopes that the latter type of treatments will not need special approval to be imported. He did not give a specific figure but said that Bayer had spent "several millions" on its Brexit preparations.

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APPOINTMENTS

Executive	To Company	New Role	From Company	Previous Role	Effective Date
Victoria Smith	Amphivena Therapeutics Inc	Chief Scientific Officer	Gilead Sciences	Leader, Biologics and Target Biology Group	3/5/19
Michael Raffa	Astellas Pharma Us Inc	Senior Vice President, Head, IP Innovation and New Technologies	Haug Partners LLC	Partner	4/1/19
Jessica Christo	Constellation Pharmaceuticals	Chief Product Development Officer	Verastem Oncology	Senior Vice President, Development Operations	3/4/19
Keld Flintholm Jorgensen	H. Lundbeck AS	Executive Vice President, Chief Business Officer	Roche	Head, Strategic Partnering	4/4/19
Martine Nolan	Kiadis Pharma	Head, Quality Assurance	Amgen	Head, Quality Operations	3/5/19
Nicholas Draeger	Novaremed	Chief Executive Officer	Nurevas International	Chief Executive Officer	3/5/19
Priya Singhal	Zafgen	Head, Research and Development	Biogen	Senior Vice President, Global Head, Safety and Benefit Risk Management	3/4/19

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