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Kåre Schultz

# Schultz Swings The Cleaver At Teva, Cutting 25% Of The Workforce

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**Teva Pharmaceutical Industries Ltd.** CEO Kåre Schultz is making fast, dramatic changes at the generic drug giant as an emergency response to stabilize the company. The announcement Dec. 14 that Teva will cut more than 25% of its workforce, or 14,000 employees, will reshape the company entirely.

Sweeping layoffs were anticipated as the company continuously failed to meet sales and earnings targets and now faces the mounting challenge of losing patent exclusivity for its blockbuster multiple sclerosis drug *Copaxone* (glatiramer), while confronting a growing debt crisis. But the level of layoffs is higher than some reports had suggested and show new CEO Schultz will be unapologetic about making massive changes.

"I'm confident that with the reduction in the cost base and with us protecting our revenue line, we will be able to manage in the short-to-medium term in a way where we can both address our financial obligations and ensure a solid, sustainable base for our business going forward," Schultz said in a same-day conference call outlining the changes.

The majority of the cuts will occur in 2018 and every business area and geography will be affected, Teva said. The company already is consolidating its support infrastructure, manufacturing, R&D and commercial operations. The restructuring initiative is intended to reduce Teva's costs by $3bn by the end of 2019, from an estimated cost base of $16.1bn at the end of 2017. More than half of the reduction is expected to be achieved by the end of 2018. Teva expects to spend $700m on the restructuring program.

In the US, Teva plans to consolidate offices from seven cities into one main campus (not including R&D or manufacturing facilities), with the location yet to be determined. The company has closed an office in Cambridge, Mass. and is in the process of closing offices in Washington, D.C., Horsham, Penn. and Manhattan, NY, the company said. The remaining offices are in Overland Park, Kan., North Wales, Penn. and Parsippany, NJ.

The company expects to close or divest manufacturing facilities in the US, Europe, Israel and growth markets. A number of R&D facilities also will be closed across geographies, the firm said.

"There is no alternative to these drastic steps in the current situation," Schultz said in an open letter to employees.

Schultz, previously CEO of **Lundbeck Inc.**, was appointed CEO in September, but only stepped into the role officially on Nov. 1. *(Also see "Teva Lands A CEO: Can Schultz Replicate Lundbeck Success?" - Scrip, 11 Sep, 2017.)* He unveiled a new organizational structure and corporate leadership team for Teva Nov. 27 in a move that opened the exit door to many of the people previously leading the company, including Head of R&D Michael Hayden, Global Specialty Medicines CEO Rob Koremans and Global Generic Medicines CEO Dipankar Bhattacharjee. *(Also see "A New Regime Takes The Reins At Teva" - Scrip, 27 Nov, 2017.)*

The big change to the organizational structure is that Teva will no longer have two separate global groups for generic and specialty medicines, but rather one

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## from the editor

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It's been a few years since widespread big pharma "right-sizing" was a regular topic in *Scrip*'s headlines. The arrival of Kåre Schultz at the helm of Teva has provided a less than happy reminder of how big company bloating can ultimately lead to unwelcome consequences for swathes of workers in an industry. But while the firm's radical rationalization included a cancellation of dividends for shareholders and widespread national strikes in its home county Israel, the share price shot up in recognition of Schultz's decisive action to bring long-overdue solutions to the company's troubles.

Some are predicting that tax reform in the US will lead to a new wave of big pharma consolidation. The last round of mega-mergers was almost a decade ago, and regular predictions that they are shortly to return have come and gone without realization for the past few years. This year the biggest deals have included Gilead's purchase of Kite, and Johnson & Johnson's purchase of Actelion: significant bolt-ons but a very different kettle of fish from diversified, scale-motivated deals of the past, like Merck/Schering Plough or Pfizer/Wyeth.

As well as our coverage of Teva's layoffs and an exclusive interview with Jane Griffiths, the J&J veteran appointed to lead Actelion (p21), we bring you further insights from the recent American Society of Hematology meeting, updates on the latest round of European product approval recommendations, industry concerns around Brexit and more besides. This is *Scrip*'s final issue of 2017: we wish our readers a happy Christmas and will be back on Jan. 5, 2018 with a double issue.

Scrip

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**Korea 2017 Review: Biosimilar Advances, R&D Progress Restore Confidence**
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Strong global advances in biosimilars and progress in new drug development as well as clampdowns on illegal rebate payments have dominated headlines in South Korea in 2017.

**How Novartis' For-Profit Social Business Is Reshaping Healthcare**
http://bit.ly/2AZvBsU

Amid glaring healthcare gaps in emerging markets like India, Novartis has scaled up its unique for-profit social business; similar initiatives are running in Kenya and Vietnam. Scrip brings you an on the ground report from rural India, where the Swiss multinational is trying to make a difference in a sustainable way.

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Vertex hopes to develop CTX001 as a treatment for sickle cell disease and beta thalassemia. Allergan adds stalled uterine fibroid candidate in buyout of troubled Repros, Juno licenses multiple myeloma candidate from Lilly.

# inside:



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# Family Comes First as BI Finance Chief Exits Over Future Direction

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Any notions that family-owned **Boehringer Ingelheim GMBH** may tap the markets for funds have been well and truly quashed with the news that chief financial officer Simone Menne is quitting after just over a year in the post because of differences over strategy.

Germany's second-largest pharmaceutical company – after **Bayer AG** – said that Menne, who is also a member of the board of managing directors as well as being responsible for finance, had decided to leave at the end of 2017. In a refreshingly frank statement, issued on Dec. 15, BI noted that "over the past year, in the course of discussions of the family-owned company's strategy, it has become clear that it has not always been possible to reconcile divergent views and perspectives."

The departure of Menne, who will pursue other career opportunities, is somewhat surprising not least because of the fanfare to which she was unveiled as CFO in September 2016. She joined having had a 25-year career at German airline Lufthansa, where she became the first female CFO on the DAX index, which comprises Germany's 30 biggest companies.

At the time of her appointment, Christian Boehringer, chairman of the shareholders' committee, described Menne as "a distinguished figure in the field of finance with many years of successful experience in Germany and abroad…she is therefore thoroughly familiar with the key tasks and challenges faced by a multinational corporation based in Germany." For her part, Menne has said in the past that one of the reasons she was brought on board was to apply her knowledge of the capital markets to the company, but her swift exit shows this is not an area that BI wishes to explore.

BI's chief executive Hubertus von Baumbach, who was CFO before Menne and is a great-grandson of founder Albert Boehringer, made it clear at the firm's annual press conference in April that maintaining the company's independence is paramount. For years, analysts have argued that a perceived conservatism at BI, and its lack of desire to embrace the public stock markets, is restricting its growth prospects but the philosophy of the company, which was founded in 1885, has been that outside influences could be detrimental to its long-term plans.

## REASONABLE SHAPE

Saleswise, BI is in reasonable shape, as first-half 2017 increased 27% to €9.2bn boosted by the contribution of **Sanofi**'s animal health business Merial, which was acquired at the start of the year in an asset swap that saw the French firm buy BI's consumer products brands, including its over-the-counter drugs and nutritional products business. On the pharma front, sales were up 12% at €6.1bn, boosted by its diabetes portfolio marketed with **Eli Lilly & Co.**- the *Tradjenta/Ondero* (linagliptin) and *Jardiance* (empagliflozin) franchises as well as *Basaglar/Abasria* (insulin glargine), a biosimilar of Sanofi's *Lantus* – jumping 59% to €1.2bn.

Clinically, BI has been busy too, and while a fairly recent entrant into cancer, its oncology pipeline has more than 10 assets in development for various tumor types. Liver disease is another area of focus with recent deals signed with **Dicerna Pharmaceuticals Inc.** and **MiNA Therapeutics Ltd.** looking at therapies for non-alcoholic steatohepatitis (NASH), and it is also seeking partners with early-stage, novel approaches to neuropsychiatry disorders.

Boehringer Ingelheim

*Different perspective: Outgoing CFO Simone Menne*

## PARTNERING RATHER THAN PURCHASING

Datamonitor Healthare analyst Edward Thomason told *Scrip* that BI's private status clearly has had implications on its strategy, noting that the asset-swap with Sanofi "was certainly smoother owing to having no public shareholders to please." He added that being private has shaped its deal-making strategy which differs from big pharma, "looking more to early-science for innovation rather than late-stage acquisitions."

Thomason said that being independent enabled BI to have more flexibility in making deals, and it had established an extensive global network of partnerships. This strategy will likely continue, given what appears to be a further declaration to remain private with Menne's departure, and BI has stated it was to spend €1.5bn in cooperation with external partners over the next five years."

CEO Von Baumbach's response to Menne's exit was amiable enough, saying in a statement that her "open and people-focused management style has been favorably received at every level of the organization. We greatly appreciate her contributions to the company and wish her all the best and much success in the future."

She will be succeeded by Michael Schmelmer, who since joining BI in February 2012 has served as head of the company's global IT organization. He holds degrees in aviation and space technology as well as industrial engineering and management, and von Baumbach said that "with his familiarity with a wide range of digital technologies and their applications," Schmelmer "will be able to share with us the benefit of his broad knowledge, experience and ideas in a time of profound change throughout the industry."

*Published online 17 December 2017*

CONTINUED FROM COVER

integrated commercial organization divided regionally into North America, Europe and Growth Markets. Some former global units will be integrated into the new structure while others will be made redundant.

"We are flattening our organization both top down and sideways, with fewer layers of management and increased accountability," Schultz said in the letter.

## PROFITABLE DRUGS OR DISCONTINUATION

The restructuring will involve rationalizing the generics portfolio globally, though mostly in the US, through price adjustments and/or product discontinuation, Teva said. The US generics business has been a particular problem for Teva; the business area has been under pricing pressure, in part due to a surge in ANDA approvals as FDA has worked its way through a backlog of applications and partly due to wholesaler consolidation. *(Also see "Generic Manufacturers Try To Up Their Game As US Pressure Persists" - Scrip, 16 Jun, 2017.)*

> 'There is no alternative to these drastic steps in the current situation'

Teva bought **Allergan PLC**'s generic drug business for $40.5bn in 2016 as a way to navigate through the US challenges, but it also increased the company's exposure to the problem. Allergan investors now view CEO Brent Saunders' decision to sell the generics business as a smart move.

"We are reviewing each and every product worldwide, and we will make pricing adjustments to the extent that this is necessary," Schultz said. "When we do that, we will in some cases … improve the profitability of the individual product and it will remain in the marketplace. In other cases, we might have to conclude that the product is not one that we will keep on manufacturing, and we will, therefore, discontinue these loss-making products."

He said Teva will hold an appropriate dialogue with customers to discuss economically viable pricing options. "I'm a big believer in margins over more than just volume," Schultz added.

As for the pipeline, Schultz said Teva was conducting a review of all generics and specialty R&D programs across the company to prioritize core projects and cancel others immediately. The company already began to sell off some non-core businesses before Schultz arrived, including women's health, but the chief executive said it would continue to evaluate other potential divestment opportunities. *(Also see "Teva Offloads Women's Health Business To Two Firms For $1.38Bn" - Scrip, 18 Sep, 2017.)*

The company will fully invest behind two commercial launches, he said: *Austedo* (deutetrabenazine) for movement disorders, including tardive dyskinesia, and fremanezumab for migraine, pending at FDA. "We are backing fremanezumab 100%," Schultz said.

In other cost-saving moves, Teva will immediately suspend dividends on ordinary shares and will not pay 2017 bonuses.

"A longer-term strategy will come later in the year," Schultz said. "However, in the near term we must remain focused on cash flow generation, short-term revenue and serving our debt."

## INVESTORS POSITIVE

Investors reacted favorably to the update, with the stock gaining 10% to close Dec. 14 at $17.30, though the stock has lost more than 60% of its value from a year ago.

"The surgeon has arrived and the cuts are major," Jefferies analyst David Steinberg said in a same-day research note.

Morgan Stanley analyst David Risinger said, "Teva announced greater-than-expected cost efficiencies, which is a positive."

But analysts agree a turnaround isn't going to be easy. "While Teva management suggests it could be on more solid footing within two years, we believe this will be a protracted turnaround and low growth/high leverage is likely to persist for the next several years," Oppenheimer analyst Derek Archila said.

*Published online 14 December 2017*

# Obituary: Barry Sherman

Source: Apotex

**Apotex Inc.** has paid its respects to the company's founder and chairman, Barry Sherman, 75, and his wife Honey, 70, after they were found dead at their home in Toronto on Dec. 15. The Canadian firm said it was with "profound sadness that we announce the unexpected passing" of Sherman, who founded privately-held Apotex in 1974.

"From its humble two-employee, 5,000 square-feet beginning in Toronto, the company Dr. Sherman founded grew into a global pharmaceutical organisation that today employs more than 11,000 people in research, development, manufacturing and distribution in facilities around the world," Apotex commented.

As news of the deaths broke, publications including the *New York Post* reported that investigators were treating the case as a possible murder-suicide, a viewpoint disputed by the Sherman family. "We are shocked and think it's irresponsible that police sources have reportedly advised the media of a theory which neither their family, their friends nor their colleagues believe to be true," the family said in a statement that urged an "objective criminal investigation."

Following post-mortem examinations, Toronto police on Dec. 17 confirmed the identities of the deceased and stated that the cause of death in both cases was ligature neck compression. The division's homicide unit has taken over the "suspicious death investigation."

20 December 2017

*Editor's note: This article appears courtesy of Scrip's sister publication Generics Bulletin*

# Pfizer's Infliximab Biosimilar Approved In US But Won't Launch Against Inflectra

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**Pfizer Inc.**'s *Ixifi*, a biosimilar version of **Janssen Biotech Inc.**'s tumor necrosis factor inhibitor *Remicade* (infliximab), received FDA approval Dec. 13, but the big pharma, which already markets an infliximab biosimilar, is not planning to compete against itself for now.

Ixifi (infliximab-qbtx) is approved for all of the eligible indications on the Remicade label: adult and pediatric Crohn's disease, ulcerative colitis, rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis and plaque psoriasis.

The approval is notable for Pfizer because it marks the first US licensure of a biosimilar wholly developed by the big pharma company.

However, Pfizer currently markets another infliximab biosimilar, **Celltrion Inc.**'s *Inflectra* (infliximab-dyyb), in the US.

A Pfizer spokesman said the company is "committed to Inflectra" and although it is evaluating options with regard to Ixifi, "we are not currently planning to launch in the US."

Pfizer's decision means that the status quo remains for the US infliximab market, where two biosimilars, Inflectra and **Samsung Bioepis Co. Ltd./Merck & Co. Inc.**'s *Renflexis* (infliximab-abda), are struggling to gain ground against the still dominant Remicade.

## CELLTRION PARTNERSHIP

Pfizer gained commercialization rights to Inflectra through its September 2015 acquisition of **Hospira Inc.** *(Also see "Where's the value in Pfizer's $17bn Hospira buy?" - Scrip, 6 Feb, 2015.)*

At the time of the deal, Pfizer's infliximab biosimilar, known as PF-06438179, was in Phase III trials, and the European Commission required Pfizer to divest the product as part of its antitrust review.

Although **Sandoz Inc.** acquired rights to the product in Europe, Pfizer retained commercialization and manufacturing rights to its infliximab biosimilar in all countries outside of the 28 nations that form the European Economic Area.

In the US, the Federal Trade Commission did not find that the overlap between Hospira's and Pfizer's infliximab biosimilars would be anticompetitive and did not require divestment of either product.

FDA approved Inflectra in April 2016 and Pfizer launched the biosimilar seven months later at a 15% discount to Remicade.

> The Ixifi approval does not change anything with regard to the company's partnership with Celltrion

While Pfizer is sticking with Inflectra for now, the Ixifi approval gives it some options in the event there is a change in its partnership with Celltrion.

In addition, Pfizer does not have commercial agreements with the South Korean-based company in all markets and could opt to launch Ixifi in countries where it does not sell Inflectra.

The Pfizer spokesman said the Ixifi approval does not change anything with regard to the company's partnership with Celltrion, the terms of which are confidential.

## FIVE BIOSIMILAR APPROVALS

Ixifi becomes the ninth biosimilar licensed in the US and the fifth approved in calendar year 2017.

At least five other 351(k) applications are currently under review with user fee goal dates in the first half of 2018. *(See the Pink Sheet Performance Tracker for a listing of biosimilar submissions and approvals.)*

The Pfizer biosimilar was approved within the 10-month timeframe for applications submitted under the first iteration of the Biosimilar User Fee Act (BsUFA). That timeframe increased to 12 months under BsUFA II, starting with applications submitted on or after Oct. 1.

However, the increased pace of biosimilar submissions and approvals in the past few years has not translated into a bolus of new products reaching the US market due to ongoing patent disputes between reference product sponsors and biosimilar sponsors.

To date, only three products have launched: Inflectra, Renflexis and **Sandoz Inc.**'s *Zarxio* (filgrastim-sndz), a biosimilar of **Amgen Inc.**'s *Neupogen* (filgrastim) and the first 351(k) application to receive FDA approval.

## DIFFICULT COMMERCIAL ENVIRONMENT

Even for those that have launched, the commercial dynamics have proven challenging.

In September, Pfizer sued Janssen and parent company **Johnson & Johnson** alleging that the Remicade sponsor's exclusionary contracts and other anticompetitive practices have effectively blocked Inflectra from accessing 70% of the commercial market.

In November, J&J filed a motion to dismiss the lawsuit, asserting the complaint fails to adequately plead antitrust injury or harm to competition.

In a corrected memorandum of law supporting the dismissal motion, Janssen said Pfizer's lawsuit "seeks to dictate and circumscribe the nature of the price incentives Janssen can offer in order to reduce the degree to which Pfizer would have to price compete and cut into its own profits."

"Pfizer has not pled facts (as opposed to conclusory allegations) showing that Janssen's discounts and rebates, rather than Pfizer's own unwillingness to offer lower prices on Inflectra or bundled discounts on Pfizer's many profitable, billion-dollar products, are the cause of Inflectra's alleged poor record to date," the memorandum states. "Without such facts, Pfizer cannot plausibly plead that the cause of its alleged harm has been Janssen's competitive strategy."

Janssen asserts the complaint is silent on whether Pfizer has sought to compete against Janssen by offering bundled discounts on its own wide range of drug products, and whether it has actually offered a lower Inflectra net price to payers than the Remicade net price offered by Janssen after all discounts and rebates are taken into account.

Pfizer has until Jan. 12 to respond to the dismissal motion.

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# Semaglutide's CHMP Backing Stipulates Safety Studies

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**Novo Nordisk AS** has committed to conducting post-approval safety studies on semaglutide - including a long-term diabetic retinopathy outcome study - in return for regulatory backing for the GLP-1 therapy in Europe.

*Ozempic*, semaglutide's proposed brand name, is a glucagon-like peptide 1 (GLP-1) receptor agonist designed to improve glycemic control in adults, along with diet and exercise, in patients with type 2 diabetes.

In recommending the therapy, the European Medicines Agency's key scientific committee, the CHMP, said Ozempic's benefit included "its clinically relevant effect on glycemic control in patients with type 2 diabetes when used in combination with other glucose-lowering medicinal products or on its own when metformin cannot be used. Ozempic has also a beneficial effect on body weight."

The most common side effects are hypoglycemia when used in certain combinations and gastrointestinal side effects such as nausea and diarrhea, it added.

In October, a US FDA advisory committee wholly endorsed the drug's approval for type 2 diabetes and said a potential retinopathy risk with semaglutide is clinically manageable and can be adequately handled through product labeling.

Novo Nordisk believes its GLP-1 agonist promises to elevate the Danish group's product offering and market position. The Danish company expects to receive final marketing authorization from the European Commission in the first quarter of 2018 based on the CHMP recommendation.

"We believe Ozempic, with its unique clinical profile, has the potential to set a new standard for treatment of type 2 diabetes," Mads Krogsgaard Thomsen, Novo Nordisk's chief science officer said in a statement.

The CHMP recommended Ozempic be indicated as monotherapy when metformin no longer provides adequate treatment or is contraindicated, and as an addition to other medicinal products for the treatment of diabetes.

The label also reflects the superior reduction in body weight achieved with Ozempic relative to comparator treatments. *(Also see "Novo Nordisk's Great Hope Semaglutide Shines In Ph II Obesity Study" - Scrip, 26 Jun, 2017.)* It also noted the statistically significant reduction brought by its use in diabetic nephropathy, a complication of diabetes that is caused by uncontrolled high blood sugar.

The Danish company in a statement said that "as an integral part of the approval, Novo Nordisk has committed to conduct post-approval safety studies including a long-term diabetic retinopathy outcome study. Furthermore, as required for all long-acting GLP-1 products approved in the EU, Ozempic will be enrolled in the data collection for the registry of medullary thyroid carcinoma."

*Published online 15 December 2017*

# CHMP Negative On PharmaMar's Aplidin In Myeloma

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**PharmaMar SA**'s second product, the marine-derived anticancer agent *Aplidin* (plitidepsin), was knocked back by the EU's CHMP at its meeting this week (Dec. 11-14) for the treatment of patients with relapsed multiple myeloma, in combination with dexamethasone.

The disappointment was not unexpected for the company after it received a preliminary feed-back ("trend vote") from the EMA's scientific committee in early November.

Back then, however, it said it was left "deeply surprised" by the negative trend vote for a number of reasons:

- The pivotal Phase III ADMYRE trial, which was the basis of the MAA, had obtained EMA Protocol Assistance.
- ADMYRE met its primary end-point of progression-free survival, which was statistically significant (p=0.0054).
- The Rapporteur Day 180 Joint CHMP and PRAC Response Assessment communicated on Oct. 31, 2017, after a one-year assessment process, did not contain any major objection and had indicated that the MAA could be approvable.

Despite not having major objections in the referred report, the company said it was required to participate in an oral explanation on Nov. 7 before the CHMP. "The discussion was focused on certain statistical methodology applied to one of the secondary end-points of ADMYRE trial that had been previously accepted by the Rapporteurs," PharmaMar said. The company also participated in an oral explanation at the December meeting of the CHMP.

The company added that it was also surprised that the CHMP negative trend vote was verbally communicated to it by the EMA.

The EMA has given no reason for the rejection, saying on its website merely that questions and answers on Aplidin would be "published shortly".

PharmaMar will have to file a new marketing authorization application if it wishes to continue to pursue EU approval of plitidepsin, a substance derived from the ascidian (sea squirt) *Aplidium albicans*. PharmaMar says it specifically binds to the eEF1A2 protein, resulting in tumor cell death via apoptosis.

The EU filing was the product's first, but in October PharmaMar announced that it had also been submitted in Switzerland.

Nonetheless, this will be a significant delay for PharmaMar in what is already a crowded therapy area. It will also be unhelpful for the Spanish company's pursuit of commercial partners in markets such as the US and Japan – something that analysts say would be needed to boost its market share. This strategy was successfully employed by PharmaMar with its first product, *Yondelis* (trabectedin) which was licensed to Taiho Pharmaceuticals (now **Otsuka Pharmaceutical Co. Ltd.**) for Japan, and Janssen (**Johnson & Johnson**) for markets outside Europe and Japan.

*Published online 17 December 2017*

# Novartis Stockpiling Priority Review Vouchers

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**Novartis AG**'s purchase of priority review vouchers from rare disease developer **Ultragenyx Pharmaceutical Inc.** may indicate a strategy to build a stockpile of the coupons in order to race to market against potential competition.

Novartis now has two vouchers in hand after it agreed to pay $130m for Ultragenyx's rare pediatric disease priority review voucher (PRV), which allows the holder to gain an expedited review for any application it chooses, according to a Dec. 18 announcement from Ultragenyx.

Ultragenyx received the voucher as part of the approval of its *Mepsevii* (vestronidase alfa-vjbk), an enzyme replacement therapy for treatment of pediatric and adult patients with mucopolysaccharidosis VII (MPS VII), an ultra-rare disease also known as Sly syndrome.

Novartis' existing voucher was homegrown, gained from its approval of *Kymriah* (tisagenlecleucel) for treatment of B-cell precursor acute lymphoblastic leukemia that is refractory or in second or later relapse. It was the first CAR-T therapy to be approved.

A Novartis spokesperson confirmed the purchase of Ultragenyx's PRV, but declined to discuss how the company plans to use its vouchers.

The firm's decision to stockpile vouchers is particularly interesting given its history with the pathway. Novartis received the first-ever tropical disease PRV from FDA upon approval of the Malaria treatment *Coartem* (artemether/lumefantrine) in 2009 and redeemed it for a priority review of a supplemental indication for *Ilaris* (canakinumab) in gouty arthritis. FDA issued a complete response letter for that claim, however.

## COMPETITION MAY BE KEY TO FUTURE VOUCHER USE

Novartis has several products in late development stages, including some that may have competition on the horizon and thus might benefit from a voucher for a swifter review.

Brolucizumab is an anti-vascular endothelial growth factor (VEGF) single-chain antibody fragment in Phase III trials for age-related macular degeneration. The product met its primary endpoint in the HAWK and HARRIER trials and is considered a potential blockbuster even in a hotly contested field. It is expected to be submitted for approval in 2018. *(Also see "Novartis Back In AMD Game With 'Potential Blockbuster' Brolucizumab" - Scrip, 12 Nov, 2017.)*

And canakinumab might again be a candidate for a voucher; the company recently released new subgroup data for preventing cardiac events in heart attack patients with high levels of inflammation. *(Also see "Novartis Aims Canakinumab At Targeted CV Patients" - Scrip, 13 Nov, 2017.)*

Novartis seems keenly aware how priority review vouchers can change development dynamics, having just witnessed the obliteration of its review lead for erenumab, the calcitonin gene-related peptide (CGRP) antagonist for migraine headache treatment developed with **Amgen Inc.** *(Also see "Best-In-Class Or First-In-Class: CGRP Inhibitors Line Up To Win The Migraine Market" - Scrip, 8 May, 2017.)* Erenumab, which was submitted to the US FDA in May, is one of several CGRP inhibitors in development.

**Teva Pharmaceutical Industries Ltd.** redeemed a priority review voucher in October to speed the review of its fremanezumab, putting it almost neck and neck with erenumab in the race for approval.

## SALE FITS WITH RECENT PRICE RANGE

Ultragenyx President and CEO Emil Kakkis said in a statement that the voucher revenue will provide "an important source of non-dilutive capital to help advance" its pipeline of rare and ultra-rare disease therapies. The company is expected to a receive a lump-sum payment at the close of the transaction.

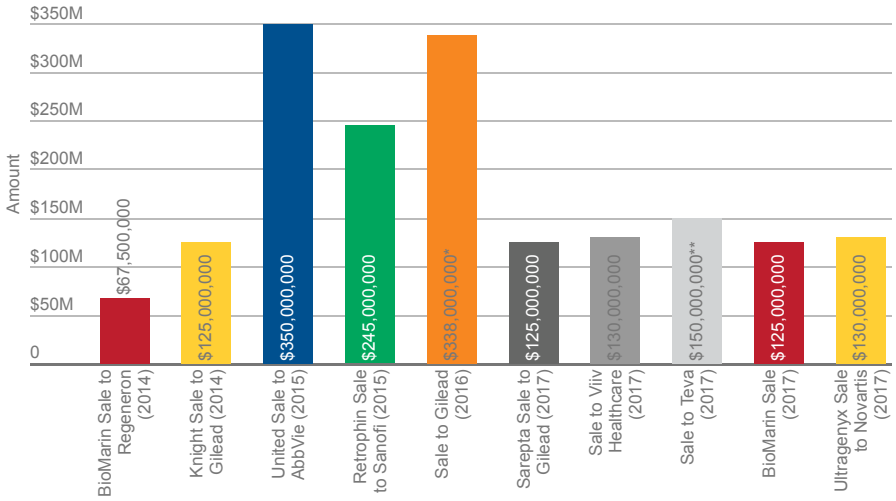
A company spokesperson said the funding will not benefit any specific development program.

The Ultragenyx sale confirms the present voucher valuation, in line with values of the previous four disclosed purchases, which all fell between $125m to $150m. (*See chart.*) That followed a period in 2015 and 2016 where two of three PRVs sold for more than $300m.

And while a stable price can offer some reassurance to buyer and seller alike, the new lower set point may be changing the financing model for small rare disease companies.

*Published online 19 December 2017*

## Priority Review Voucher Prices Seem Stable




*Note: One known voucher sale does not appear on this chart since the terms of Wellstat's sale of a voucher to AstraZeneca in 2014 were not disclosed.*

**Gilead did not disclose the exact amount of the voucher purchase or the seller, but could have paid less than $338m for it.*

*** Teva did not disclose exact amount but is known to have paid up to $150m.*

*Source: Company statements and public filings*

# Commercial Fallout From Merck's Failed Keytruda Gastric Cancer Trial May Be Limited

**EMILY HAYES** emily.hayes@informa.com

The failure of **Merck & Co. Inc.**'s Phase III KEYNOTE-061 study of *Keytruda* in second-line advanced gastric cancer may wind up having little commercial downside, as there will be no change in labeling.

The KEYNOTE-061 study tested Keytruda (pembrolizumab) as a monotherapy against paclitaxel chemotherapy in the treatment of 592 patients with advanced gastric or gastroesophageal junction adenocarcinoma, following first-line platinum and fluoropyrimidine chemotherapy.

Keytruda failed to show a significant improvement in overall survival in patients testing positive for PD-L1 expression – the primary endpoint – although there was a trend in the right direction (the hazard ratio was 0.82, the p-value was 0.042 and the confidence interval was 0.66-1.03). There was also no significant improvement in progression-free survival (PFS), the company reported Dec. 14. No new safety signals were identified.

Keytruda received accelerated approval from the US FDA in third-line PD-L1-positive advanced/metastatic gastric cancer (for use after fluoropyrimidine- and platinum-containing chemotherapy and, if appropriate, HER2/neu-targeted therapy) in September. The filing was supported by response rate data from a single-arm Phase II study.

FDA's approval letter guided the company to conduct and submit the results of "one or more randomized trials to verify and describe the clinical benefit of pembrolizumab over standard therapy based on a clinically meaningful improvement in overall survival in patients with PD-L1 positive, microsatellite stable/mismatch repair (MMR) proficient metastatic gastric or gastroesophageal junction adenocarcinoma."

Merck said in its statement about the KEYNOTE-061 failure that "the current indication remains unchanged" and that it continues to evaluate Keytruda in two Phase III studies. The KEYNOTE-062 study tests Keytruda as a monotherapy or in combination with chemotherapy against chemotherapy alone in PD-L1+ advanced gastric or gastroesophageal junction cancer; KEYNOTE-585 is evaluating Keytruda with chemotherapy against chemotherapy in the neoadjuvant/adjuvant setting.

The company confirmed to *Scrip* that it already has discussed the KEYNOTE-061 study with FDA and does not expect any changes to the gastric cancer indication at this time.

Either KEYNOTE-061 or KEYNOTE-062, which is expected to read out in February 2019, were positioned to serve as a confirmatory study for the third-line approval in September.

BMO Capital Markets analyst Alex Arfaei said in a Dec. 14 note that the studies of Keytruda in earlier lines of therapy "have a better chance of showing an OS benefit."

"This is based on KN-061's narrow OS miss, and the fact that the OS benefit seen with IO therapies typically increases in earlier disease. Moreover, KN-062 is in an all PD-L1+ patient population, and perhaps Merck will select a higher PD-L1 threshold for the primary endpoint analysis based on findings from KN-061," the analyst said.

Gastric cancer is a small indication for PD-1/L1 inhibitors relative to other tumor types, but collectively the modest market approvals add up and the major sponsors of checkpoint inhibitors have been active in developing their drugs for this disease.

**Bristol-Myers Squibb Co./Ono Pharmaceutical Co. Ltd.**'s PD-1 inhibitor *Opdivo* (nivolumab) demonstrated a modest improvement in overall survival in the Phase III ONO-4538-12 study, which tested the drug against placebo in patients with advanced gastric cancer refractory to or intolerant of standard therapy.

**Merck KGAA** and partner **Pfizer Inc.** announced in November that their PD-L1 inhibitor *Bavencio* (avelumab) failed to improve overall survival compared to chemotherapy in the Phase III JAVELIN Gastric 300 study of third-line advanced gastric cancer.

While the results of KEYNOTE-061 are unfortunate, expectations were low given the recent failure of avelumab in third-line gastric cancer, BMO Capital Markets' Arfaei said. "Further, gastric cancer is a relatively small market," he added.

Meanwhile, investors remain focused on the larger non-small cell lung cancer (NSCLC) market. Results for Keytruda in the KEYNOTE-042 NSCLC study are due in the first quarter of 2018 and could broaden the drug's monotherapy label, Arfaei noted.

KEYNOTE-042 tests Keytruda against platinum-based chemotherapy in PD-L1+ advanced or metastatic NSCLC.

## JUST THE LATEST PHASE III FAILURE

The failure of the KEYNOTE-061 gastric cancer study may reinforce clinical concerns in some quarters about early approvals of checkpoint inhibitors based on surrogate measures.

The KEYNOTE-061 gastric cancer is the not the first time Keytruda has failed in an earlier line of treatment after being approved in a later line, nor is it the only PD-1/L1 inhibitor to do so.

Keytruda received accelerated approval for recurrent or metastatic head and neck cancer in August 2016, a filling supported by response rate data in the single arm KEYNOTE-012 study. However, in July of this year the company announced the failure of Keytruda to show a significant survival benefit in the Phase III KEYNOTE-040 head and neck cancer study, which tested Keytruda against investigator's choice of chemotherapy. As with gastric cancer, the company said it did not expect a label change, despite the trial's failure. *(Also see "Merck's Keytruda Gets Benefit Of Doubt, Despite Failing in Head & Neck" - Scrip, 24 Jul, 2017.)*

Accelerated approval of **Roche**'s PD-L1 inhibitor *Tecentriq* (atezolizumab) in bladder cancer in May 2016 was followed by the drug's failure in May of this year to demonstrate an improvement in overall survival over chemotherapy in the Phase III IMVigor211 confirmatory study in the second-line setting.

At the time, Roche explained that the performance of the chemotherapy arm was better than expected. Tecentriq has maintained its approval in the indication.

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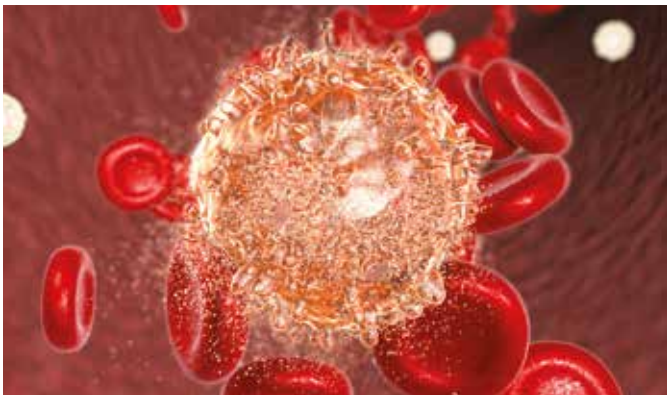
# ASH In Review: Roche Refreshes Hematology Portfolio With Robust New Drugs

**EMILY HAYES** emily.hayes@informa.com

Data presented at the American Society of Hematology meeting fleshed out the profile of **Roche**'s newly approved hemophilia drug *Hemlibra* for physicians, promised to catapult chronic lymphocytic leukemia drug *Venclexta* from a low sales base and introduced polatuzumab vedotin as a robust therapy for diffuse large B cell lymphoma.



Shutterstock: Kateryna Kon

This year's American Society of Hematology (ASH) meeting from Dec. 9-12 in Atlanta capped a year of portfolio renewal at Roche following US FDA approval in November for Hemlibra (emicizumab) as a weekly injection to treat hemophilia A in patients with inhibitors as well as the release of positive results for the PD-L1 inhibitor *Tecentriq* (atezolizumab), execs said during a Dec. 13 investor call. *(Also see "Roche's Tecentriq-Avastin Combo Improves PFS In Kidney Cancer Too" - Scrip, 11 Dec, 2017.)*. The Swiss pharma unveiled data from the IMpower150 and IMmotion151 studies of Tecentriq in lung cancer and renal cancer during the meeting. *(Also see "Roche Powers Forward With First-Line Tecentriq In Advanced NSCLC" - Scrip, 7 Dec, 2017.)*.

In the 20 years since approval of the anti-CD20 antibody *Rituxan* (rituximab), which revolutionized the treatment of B cell disease, the company has improved upon the CD20 mechanism of action with the follow-on drug *Gazyva* (obinutuzumab), Chief Medical Officer Sandra Horning noted during the call. Roche also built its presence in chronic lymphocytic leukemia (CLL) through the oral BCL-2 inhibitor Venclexta (venetoclax), which is in Phase III across three diseases and four indications, and the company positioned Tecentriq for hematologic malignancies and solid tumors, Horning said.

New assets promise to reinvigorate the company's hematology pipeline. One of Roche's highlights at ASH was data from a Phase II study of the antibody-drug conjugate (ADC) polatuzumab vedotin in relapsed/refractory diffuse large B cell lymphoma (DLBCL). The candidate consists of an anti-CD79b monoclonal antibody conjugated to monomethyl auristatin E, a microtubule disrupting agent via a protease-cleavable peptide linker.

The study tested polatuzumab vedotin with bendamustine chemotherapy and Rituxan (BR), a standard therapy, against BR alone in 80 patients with an average age of 70, equivalent to 75% of the patient population in the refractory setting.

The primary endpoint was complete response, as assessed with PET-CT scans six to eight weeks after the end of treatment. The outcome on this measure was 40% for VR versus 15% for BR, a statistically significant result. The objective response rate was significantly improved at 70% for VR versus 33% for BR.

Median progression-free survival (PFS) was 6.7 months in the polatuzumab combination arm and two months in the BR arm (HR=0.31). Median overall survival (OS) was 11.8 months versus 4.7 months, respectively (HR=0.35). Both the PFS and OS results were statistically significant.

"If you look across the subgroups, they are all consistent. And the safety profile was in line with that observed for bendamustine and Rituxan," Horning said.

On the safety front, the rate of Grade 3/4 events was 85% for the polatuzumab/BR arm vs. 67% for BR. Grade 3/4 events included thrombocytopenia, neutropenia and anemia. The rate of dropouts related to adverse events was 33% for the polatuzumab/BR arm vs. 15% for BR.

"It's important to note that this study was conducted in a heavily pretreated population with few options. The majority of participants were refractory to their last treatment, and none were eligible for hematopoietic stem cell transplant. Patient safety is our highest priority, and no unexpected safety signals were observed with the addition of polatuzumab vedotin to BR," the company explained to *Scrip*.

In a Dec. 11 note about the study, Credit Suisse analyst Rebekah Harper described polatuzumab vedotin's efficacy as strong and the safety as acceptable. Credit Suisse is forecasting peak sales of $1bn.

Polatuzumab vedotin has a breakthrough therapy designation from the FDA in DLBCL and is being tested in the Phase III POLARIX study in first-line DLBCL; the first patient was dosed in November. Roche is discussing its earlier-stage refractory/relapsed data with regulatory authorities.

Autologous chimeric antigen receptor T cell (CAR-T) therapies also are being tested in DLBCL and analysts on the call asked the company to explain positioning of polatuzumab versus CAR-T. Horning said polatuzumab is a more universal therapy as opposed to CAR-T therapies, which are manufactured over a period of two to three weeks using a patient's own T cells. She also noted that Roche's ADC can be administered to patients of any age, though the company's study tested it in an older population. The CAR-T therapies have been tested in a younger patient population by comparison.

"If you see a patient in the clinic and they need treatment immediately, you can write a prescription, theoretically, and treat that patient as he or she needs, maybe the same day or within the week. And that timed treatment is an important differential," Horning said. Also, in the CAR-T setting, patients receive therapy before the CAR-T treat-

ment to get the disease under control as they wait for a referral to a transplant center to receive the new, reengineered T cells. Roche believes that polatuzumab could be used as a bridging therapy for these patients, so it may not come down to a choice between one or the other.

She also stressed the potential for polatuzumab as an effective frontline therapy, due to the high rate of complete responses and overall survival benefit.

"And what we're really excited about is the potential of polatuzumab to make a difference and boost the cure rate in the first line," Horning said.

## DEEP RESPONSE WITH VENCLEXTA

Another major highlight for Roche at the ASH meeting was the release of data from the Phase III MURANO study of Venclexta with Rituxan versus bendamustine with Rituxan during a late-breaker session on the last day of the meeting.

Venclexta received accelerated approval in April 2016 for CLL with 17p deletions, a small, high-risk population, and this study tested it in a broader patient population of relapsed/refractory CLL. *(Also see "After MURANO: Roche/AbbVie Map Venclexta's Expansion Past CLL" - Scrip, 12 Dec, 2017.)* Roche and partner **AbbVie Inc.** guided for sales of $125m in 2017, so the drug needs to be expanded to larger populations to attain blockbuster status.

In MURANO, treatment was given for a fixed period (a maximum of two years) and it resulted in a statistically significant improvement in investigator-assessed PFS (HR=0.17, a highly significant result). The companies highlighted impressive results in terms of those with minimal residual disease (MRD) in the blood, meaning a deep response. About 60% in the VR arm were MRD-negative versus 5%-10% in the BR group. The data suggest that that the therapy could be curative, Horning said.

"And we saw also that there was consistency across all of the subgroups with this primary endpoint. And if you look at the two-year data, it's 84.9% versus 36.3% progression-free," Horning added.

Overall survival data are not yet mature with 24 months of follow-up, but there was a trend in favor of the VR arm (HR=0.48).

Horning stressed during the call that the VR regimen is chemotherapy-free and treatment is for a finite period. Other drugs, notably **Johnson & Johnson** and AbbVie's BTK inhibitor *Imbruvica* (ibrutinib), are given indefinitely.

Safety was consistent with Venclexta's known profile. Cases of life-threatening tumor lysis syndrome were problematic early in the drug's development, but this risk is now successfully managed through a ramp-up in dosing over five weeks and other prophylactic measures.

Horning also noted that the results compare well to studies of other agents in CLL, including Imbruvica and **Gilead Sciences Inc.**'s PI3 kinase inhibitor *Zydelig* (idelalisib).

The Phase III CLL14 study is testing venetoclax with the company's next-generation CD20 antibody Gazyva against Gazyva with chlorambucil chemotherapy.

Roche plans to submit a supplemental filing based on the MURANO data by the end of the first quarter of 2018. The company also is developing the drug for a range of other indications and presented encouraging data in acute myeloid leukemia and multiple myeloma at ASH.

## HEMLIBRA HOLDING UP OVER TIME

The ASH meeting also provided an opportunity to build up the profile of Hemlibra, approved in November, with physician attendees. The filing was supported by the Phase III HAVEN 1 trial, which tested the drug in patients aged 12 and older who had hemophilia A with inhibitors, and the open-label HAVEN 2 study, which enrolled patients under the age of 12. *(Also see "Roche's Hemlibra Priced And Labeled To Beat Competition, Safety Concern" - Scrip, 17 Nov, 2017.)*

Soon after approval, the company announced positive results for the therapy in the HAVEN 3 study of patients with hemophilia A and no inhibitors.

Updated data from the HAVEN 1 study presented at ASH show that bleed rates in patients treated with prior bypassing agent prophylaxis improve over time, Levy said. Whereas the reduction in treated bleeds was 79% previously, updated data with an additional 10 months of follow-up show an 88% reduction.

Gallia Levy, global development team leader for Hemlibra, said it's great to see that the data from HAVEN 1 are holding up and, if anything, are looking better over time.

An updated analysis of HAVEN 2 with 40 additional patients and an additional six months of follow-up also show that bleeding rate data are holding up and confirming an earlier analysis, the company reported. Importantly, the drug was well tolerated with no thromboembolic or thrombotic microangiopathy events reported, Levy said.

## BENEFITS OF MONTHLY DOSING

Roche reported positive interim results for Hemlibra on Dec. 7 from the Phase III HAVEN 4 study, which tested a new monthly dose of the injectable drug in hemophilia A with and without inhibitors to factor VIII.

"At this interim analysis after a median of 17 weeks of treatment, Hemlibra prophylaxis showed a clinically meaningful control of bleeding," the company said in a statement.

The data are consistent with pivotal trial results from Hemlibra dosed once weekly or every two weeks, Roche said. No new safety signals were observed and there were no thrombotic microangiopathy or thrombotic events in the trial, the company reported.

Roche presented pharmacokinetic modeling data at the ASH meeting showing that the efficacy with four-week dosing was similar to what would be seen with dosing every one or two weeks. The study is fully enrolled and the company plans to present interim results at an upcoming meeting, Levy said.

Roche did not present additional data for HAVEN 3 at the ASH meeting, but the top-line data have been "extremely well received by the community with a lot of excitement," and Roche will be showing full data next year, Levy said.

Cristin Hubbard, lifecycle leader for Hemlibra, noted that the product launch is in its early days, but said early indicators are encouraging. The drug's safety and efficacy profile has been well-received by patients and physicians and discussions are ongoing with payers to support the company's strategy for broad and rapid access to Hemlibra, the exec said.

*Published online 17 Dec 2017*

A Star Is Born? HERCULES Data Shine At ASH For Ablynx's Caplacizumab: **http://bit.ly/2BfjkEO**

# What's New And What's Next In CAR-T After ASH

**Novartis AG** and **Gilead Sciences Inc.**'s recently acquired subsidiary **Kite Pharma Inc.** have the only two approved chimeric antigen receptor T cell (CAR-T) therapies, but **bluebird bio Inc.** and its partner Celgene Corp. were the stars of the recent American Society of Hematology (ASH) annual meeting.

Both Novartis' *Kymriah* (tisagenlecleucel) and Gilead/Kite's *Yescarta* (axicabtagene ciloleucel) are comprised of patients' own T cells reengineered to target cancer cells expressing CD19 in leukemia and lymphoma. That's why there was a lot of interest at ASH from Dec. 9 to 12 in Atlanta, Ga. in bluebird and Celgene's bb2121 against the novel target B cell maturation antigen (BCMA). **Juno Therapeutics Inc.** has its own early-stage BCMA-targeting candidate in development, but its most anticipated news at ASH was the latest data for its come-from-behind CD19 program JCAR017 with partner Celgene.

*Scrip* spoke with Novartis Senior Vice President and Global Head of the company's cell and gene therapy business Pascal Touchon along with Novartis Senior Vice President David Lebwohl, Franchise Global Program Head for CAR-T therapies, while the executives were attending ASH to talk about the latest Kymriah data and the product's launch.

New results from 81 patients in the Phase II JULIET clinical trial in relapsed or refractory diffuse large B cell lymphoma (DLBCL) showed an overall response rate (ORR) of 37% and a 30% complete response (CR) rate at the six-month follow-up, that was down from the best response rates: 53% ORR and 40% CR rate. However, the six-month data were stable compared with three-month results showing 32% of patients had a CR.

"We're seeing a high rate of responses, including complete responses, and we're seeing a good safety profile. And importantly, at this point, based on the patients who were in complete response at three months, almost all of them were still in response at six months," Lebwohl said.

He noted that the JULIET results were consistent with a 28-patient trial conducted at the University of Pennsylvania (UPenn), which was published in the *New England Journal of Medicine* on Dec. 10. Six of the 14 patients with DLBCL (43%) and 10 of the 14 patients with follicular lymphoma (FL; 71%) achieved complete remission in the academic study. With a median of 29.3 months of follow-up (a range of 7.7 to 37.9 months), all patients in CR at six months remained in remission at their last assessment.

In terms of safety in JULIET, 12% of patients experienced Grade 3 or 4 neurotoxicity and 23% had Grade 3 or 4 cytokine release syndrome (CRS), but no patients died from these severe adverse events, which are common in patients treated with CAR-T therapies. In fact, 26% of patients were treated in the outpatient setting, where they stayed close to the treatment center for two weeks after infusion with the CAR-T cells rather than in the hospital to monitor side effects.

## SAFETY SUPPORTS OUTPATIENT TREATMENT

Touchon said it was reassuring to see in the clinical trial that patients' side effects could be managed without admission to the hospital in some cases. He noted that in the commercial setting some patients have been treated with Kymriah both in the outpatient setting.

"Different diseases have different amounts of toxicity," Lebwohl said. "The experience in DLBCL is very different relative to ALL; it depends on the burden of the disease and the location of the disease." Patients at lower risk may be eligible for outpatient treatment.

The US FDA approved Kymriah in August to treat relapsed or refractory children and young adults with acute lymphocytic leukemia (ALL) and Novartis submitted a supplemental biologic license application (sBLA) in October for FDA approval to treat adults with DLBCL. Kymriah as a treatment for relapsed or refractory children and young adults with ALL and adults with DLBCL is under review at the European Medicines Agency (EMA) and approval is expected in mid-2018.

In addition to training oncologists in the collection and transport of patients' T cells for manufacturing its autologous cell therapy, Novartis also is required by the risk evaluation and mitigation strategy (REMS) on the FDA-approved Kymriah label to train staff at specially certified cancer treatment centers how to manage CRS and neurotoxicity associated with CAR-T therapy.

"We have indicated that we wanted to certify initially 32 sites and out of the 32 sites 13 were sites with clinical trial experience for ELIANA," Touchon said, referring to the trial that supported Kymriah's first indication. "It has been really, so far, a very nice and progressive development of onboarding these sites. We have 21 that are fully operational and we have been treating commercial patients at these sites."

"The other thing that we have achieved is 22 days manufacturing time in the commercial setting," he continued. "We have been very reliable and fast in ensuring that the patient is treated on time according to our manufacturing process. Altogether we are very pleased with the progress so far of our launch."

Novartis worked with payers in anticipation of the Kymriah launch and continues to communicate with them post-launch "to make sure we can offer access to the patient. We have been progressively moving from managing individual cases to coverage" under the product's label, Touchon said. He noted that the majority of US patients eligible for treatment are able to get their treatment covered by their private health insurance or Medicare.

## PAYER ISSUES FOR GILEAD/KITE?

While one media report after ASH suggested that patients eligible for treatment with Gilead/Kite's Yescarta have had trouble getting access to the CAR-T therapy, Gilead indicated to Scrip that negotiations with public and private payers are ongoing. Yescarta was approved for relapsed or refractory large B cell lymphoma, including DLBCL, in October.

"Kite and Gilead are focused on ensuring patient access to Yescarta," Gilead said in a statement. "Kite is diligently engaged with payers to ensure they are prepared for this novel therapy and we are confident that Yescarta will be covered by payers. We anticipate the payer mix to be about 50%-60% commercial and about one-third Medicare. To date, the vast majority of the commercial payers have confirmed coverage. We have met with many individuals representing Medicare to help inform their reimbursement decisions around Yescarta, and we continue to engage actively with Medicare to ensure we are doing all we can to support access."

## CAR-T Data At ASH And Upcoming Milestones

| DRUG / DEVELOPER | ASH UPDATES | NEXT MILESTONES |
|---|---|---|
| Kymriah/Novartis | Novartis also presented a cost-effectiveness analysis of Kymriah in relapsed or refractory pediatric ALL. The product outperformed clorafarabine, clorafarabine combination therapy, **Amgen Inc.**'s *Blincyto* (blinatumomab), other salvage chemotherapies and allogeneic stem cell transplant in terms of quality-adjusted life years (QALY). UPenn investigators also reported data in chronic lymphocytic leukemia (CLL) that showed minimal residual disease (MRD) responses (no evidence of cancer in the bone marrow). | While awaiting FDA approval for DLBCL and EMA approval for DLBCL and pediatric ALL, Novartis will kick off multiple new studies in 2018, including pivotal trials in CLL, FL and adult ALL. A study in combination with a PD-1 inhibitor will be initiated in 2018 as well. Novartis also plans to start a trial in multiple myeloma next year for a BCMA-targeting CAR-T therapy from its partnership with UPenn. |
| Yescarta/Gilead | Gilead/Kite also presented Phase I/II ZUMA-3 results in relapsed or refractory adult ALL. Seventeen out of 24 patients with at least eight weeks of follow-up (71%) had complete remission and all with a CR had no detectable MRD. These patients were relapsed or refractory to chemotherapy or a hematopoietic stem cell transplant. Grade 3 or higher CRS and neurotoxicity was observed in 28% and 52% of patients, respectively. | The EMA is reviewing Yescarta in DLBCL, FL and primary mediastinal B cell lymphoma (PMBCL) with a decision expected in the first half of 2018. Phase II studies are under way in indolent NHL and mantle cell lymphoma (MCL). Ongoing Phase I studies are in DLBCL (in combination with a PD-L1 inhibitor), adult ALL and pediatric ALL. A Phase I study recently was initiated for the BCMA-targeting candidate KITE-585 in multiple myeloma. |
| JCAR017 (lisocabtagene maraleucel)/Juno and Celgene | Data from the Phase I TRANSCEND study in relapsed or refractory NHL, including a pivotal cohort in DLBCL were reported. For 19 patients treated with dose level 2 (100m cells) the ORR was 74% at three months with a 68% CR. Among 91 patients across all TRANSCEND cohorts, there were 32 cases of CRS (35%) and one case of severe CRS (1%) with 17 reports of neurotoxicity (19%), including 11 patients with severe neurotoxicity (12%). | Data from the ongoing pivotal cohort of TRANSCEND in DLBCL will support a filing with the FDA in the second half of 2018 with approval anticipated in late 2019. A Phase I/II study of JCAR017 in CLL is under way. Juno plans to initiate studies during 2018 in ALL, DLBCL with JCAR017 plus the **AstraZeneca PLC** PD-L1 inhibitor *Imfinzi* (durvalumab), and in combination with a BTK inhibitor for CLL. Juno also will run its first study in 2018 for JCARH125, a CAR-T targeting BCMA for multiple myeloma. |
| bb2121/bluebird and Celgene | Results from the first 21 relapsed or refractory multiple myeloma patients across multiple doses in an ongoing Phase I trial: 17 out of 18 patients (94%) treated with bb2121 dosed at 150m, 450m or 800m cells achieved an objective response; 16 out of 18 had a very good partial response (89%) and 10 out of 18 had a CR (56%). Nine out of 10 patients evaluable for MRD were MRD negative. Safety: CRS was reported for 15 out of 21 patients (71%), including two cases of Grade 3 CRS (9%); there was one case of Grade 4 neurotoxicity. | A pivotal trial for bb2121 in multiple myeloma was initiated earlier this month in the fourth-line setting. It could be the first CAR-T therapy approved for these advanced multiple myeloma patients; a 2020 FDA decision is anticipated. A Phase III study is planned to test bb2121 plus Celgene's *Pomalyst* (pomalidomide) and dexamethasone in the third-line setting. The first study for a next-generation BCMA-targeting CAR-T known as bb21217 is enrolling patients. |
| UCART19/**Cellectis SA**, **Pfizer Inc.** and **Servier SA** | One of the first allogeneic CAR-T candidates in the clinic, the off-the-shelf CD19-targeting therapy is made from donor T cells. Data at ASH from two Phase I studies in relapsed or refractory adult and pediatric ALL revealed an 83% complete remission rate as of 28 days post-infusion. Five out of seven adults were MRD negative and five out of five children were MRD negative four weeks after receiving UCART19. One patient each in the adult and pediatric studies had Grade 1 graft versus host disease. There was no severe neurotoxicity and most cases of CRS were mild, but one adult patient had Grade 4 CRS and neutropenic sepsis and died at day 15. | The Phase I studies for UCART19 are ongoing; Servier acquired global rights to this candidate from Cellectis and licensed US rights to Pfizer. A clinical hold on Cellectis' UCART123 due to a patient death was announced in September and lifted in November. |

With Novartis' sBLA pending at the FDA, Gilead/Kite probably has only a few months to sort out any payer issues, manufacturing delays or safety training for Yescarta before it has a competing CAR-T on the market for DLBCL.

Sattva Neelapu, co-lead investigator for Gilead/Kite's ZUMA-1 clinical trial in refractory large B cell lymphoma (including DLBCL) and professor at the University of Texas MD Anderson Cancer Center, told *Scrip* that "we have recently collected cells from several patients at our center, but we have not infused anybody [with Yescarta] yet. There is a steep learning curve in administering this therapy or any CAR-T therapy, [but] most transplant centers should be able to handle this."

Long-term ZUMA-1 data presented at ASH showed an ORR of 42% and CR of 40% among patients followed for at least one year after infusion with Yescarta. At 18 months, 52% of the 108 patients were still alive.

*Published online 17 December 2017*

# Sanofi Sees Cemiplimab As Path To Relevance In IO

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With promising data from a Phase II trial in advanced cutaneous squamous cell carcinoma (CSCC), **Sanofi** has begun a rolling Biologics License Application (BLA) for cemiplimab, a PD-1 inhibitor that is one of two clinical candidates it is counting on to make a competitive play in immuno-oncology.

Cemiplimab is part of the French pharma's 2015 IO partnership with long-time collaborator **Regeneron Pharmaceuticals Inc.**[See Deal] The company reported top-line data showing an overall response rate of 46.3% in the 82-patient EMPOWER-CSCC 1 study in three types of patients with CSCC, the second most common and the most-lethal form of skin cancer in the US. While the study is still ongoing for duration of response, Sanofi execs said during an analyst day Dec. 13 that cemiplimab would move toward approval under a rolling BLA to be completed during the first quarter of 2018, with an EU filing also expected during the first quarter.

CEO Olivier Brandicourt told attendees that cemiplimab and isatuximab, an anti-CD38 checkpoint inhibitor in four Phase III trials for multiple myeloma, comprise "the base for our rebuild in oncology," a key strategic goal for Sanofi.

Sanofi expects 2018 to be landmark year in that rebuilding effort, anticipating approval of cemiplimab – which has FDA breakthrough therapy designation in CSCC – and a US filing for approval in multiple myeloma with isatuximab. In addition, the pharma says the year's cancer milestones will include: six programs entering Phase I development (including two combo therapy regimens incorporating cemiplimab), work toward proof-of-concept in 14 indications, four potential POC readouts, and nine pivotal studies ongoing or planned.

In overviewing the firm's oncology strategy, Senior VP and Global Head of Development Jorge Insuasty said that while cancer had been a strongpoint for Sanofi in the past, it "missed the boat" in immuno-oncology, trailing clear leaders such as **Merck & Co. Inc.**, **Bristol-Myers Squibb Co.** and **Roche/Genentech Inc.** The company had a presence in chemotherapy but struggled to develop targeted therapies and stayed out of the IO space early on.

"We have made the decision that we would like to play [in IO] and that we think we can actually establish a strong presence in oncology," the exec said. "We actually have proprietary scientific platforms that are allowing us to generate products, assets that are targeting different molecular pathways that are of interest in oncology."

In the meantime, Sanofi is winding down its monoclonal antibody partnership signed in 2007 with Regeneron, he added, but it is continuing to work with the US biotech in the checkpoint inhibitor space. It comes to the newer Regeneron collaboration with different set of capabilities, though, as Sanofi can now generate its own antibody candidates thanks to a "strong translational medicine group" it has developed.

## TARGETING FIRST-LINE NSCLC WITH CEMIPLIMAB

Sanofi and Regeneron's longer-term strategy with cemiplimab is to obtain an indication for first-line non-small cell lung cancer, something of a great white whale in the IO spectrum. During its third quarter earnings call Nov. 8, Regeneron Chief Scientific Officer George Yancopoulos noted that only Merck's *Keytruda* (pembrolizumab) has managed to add first-line NSCLC to its label among the five anti-PD-1/L1 agents that have reached market.

Roche, however, may be a factor in first-line lung cancer as well. It reported on Dec. 7 that its PD-L1 inhibitor *Tecentriq* (atezolizumab) was associated with a 38% reduction in the risk of disease worsening or death when used in combination with chemotherapy for previously untreated advanced non-squamous non-small cell lung cancer in the IMpower150 study.

The Sanofi/Regeneron strategy around cemiplimab is to first get to market in CSCC, which although it has no currently approved drug therapy is estimated only to be a "modest" market opportunity in the range of a few hundred-million dollars in peak annual sales, according to Morgan Stanley analyst Vincent Meunier. Then, the firms plan to target two other cancer indications currently unserved by checkpoint inhibitors – second-line advanced metastatic basal cell carcinoma and platinum-refractory cervical cancer, Insuasty said.

Meunier's projections of the CSCC market do not reflect consensus, however. Bryan Garnier analyst Eric Le Berrigaud unveiled modeling Dec. 13 based on the top-line Phase II data suggesting that cemiplimab could achieve peak US sales of $1bn in CSCC if it was priced at $130,000 for a nine-month course of therapy and 30% market penetration. Le Berrigaud gives the drug a 50% likelihood of success.

Sanofi hopes to report data for the basal cell carcinoma indication during the second half of 2018, and for cervical cancer during the first half of 2020, Insuasty said. Meanwhile, it will undertake a trio of studies in first-line NSCLC with cemiplimab.

The top-line Phase II data Sanofi unveiled for the anti-PD-1 candidate in CSCC serve as the pivotal data for the rolling NDA, the exec added. The candidate compiled a safety profile generally consistent with approved anti-PD-1 agents in the study, he said, while demonstrating a promising ORR. Median duration of response has not been reached yet, however, as 32 of 38 responses to therapy are ongoing. All patients have at least six months of follow-up to date, he added.

EMPOWER-CSCC 1 is a single-arm, open-label study in which approximately two-thirds of the participants had progressed following systemic chemotherapy or radiation therapy. Patients received a 3 mg/kg dose of cemiplimab every two weeks.

## A DISMAL PROGNOSIS FOR METASTATIC CSCC

Insuasty noted that no other anti-PD-1/L1 candidate in development is pursuing this indication, even though it is the second most common skin cancer in the US and the prognosis for metastatic patients is grim. There are 200,000-400,000 new cases annually in the US and the standard of care is surgery. Metastasis occurs in between 1%-6% of patients, and these patients have what Insuasty called a "dismal prognosis" with median survival of less than two years.

Sanofi's rationale for pursuing the first-line NSCLC indication over the longer term is based on an assumption that the treatment landscape in this setting is still evolving. It believes the current standard of care is unlikely to be in place five to 10 years from now, with combination regimens likely to take a dominant position eventually, Insuasty said.

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# UK Life Science 'Needs Manufacturing Incentives, NHS Access' After Brexit

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The UK needs to learn from Singapore and Ireland and offer better incentives to the life sciences industry if it wants to attract future innovative processes and successfully compete in the pharma sector once the country leaves the European Union.

That's the view of two key opinion leaders – Sir John Bell, Regius Professor of Medicine at University of Oxford, and **Merck Sharp & Dohme Ltd.**'s research laboratories head Roger Perlmutter. The pair spoke exclusively to *Scrip* on the day the UK government unveiled its industrial strategy for the sector.

The duo flagged many issues deemed important to the pharma sector ahead of Brexit – an event slated to occur in March 2019.

But Bell and Perlmutter said they were particularly keen on seeing on the UK make itself more attractive to medical manufacturing in Britain. Another was tapping into the National Health Service (NHS) for its innovative potential and clear synergies that that would offer the life sciences sector generally.

## MANUFACTURING INCENTIVES

They said the UK needs to play 'catch up' and draw drug manufacturers to the country. They added that the eventual terms and conditions of Brexit will help determine whether that is possible.

"The UK has lost the plot when it comes to life sciences manufacturing," Bell said.

"A lot of the small-molecule manufacturing has moved to places like Ireland and Singapore – low-tax environment plus the facilitation offered by those places; those countries provide space, some of the time they pay for capital assets while the UK has been pretty placid about fighting to hold on to that activity."

"Brexit will make that even more difficult because, if you've got a variety of custom barriers to get API in or formulation out, then it just gets really complicated," said Bell, who played a key role in formulating the Life Sciences Sector Deal with the Conservative government under prime minister Theresa May.

"We've suggested that the UK pull itself together and try to get itself in a strong position for manufacturing, and in particular focus on some of the new platforms for therapeutics," Bell said, adding that the UK-based pharma industry bore some responsibility for lost time – and opportunities.

> 'The UK has lost the plot when it comes to life sciences manufacturing.' – Sir John Bell

"We completely missed the train in antibodies development because the pharma companies in the UK just didn't see it; that whole thing is now gone, so we need to look at new things downstream," Bell said.

Perlmutter agreed, and said UK politicians will need to act if a solution is to be found. "To make that happen there will need to be a change in approach by the UK government and the way it views the attractiveness of those manufacturing facilities because other countries are very eager to have such manufacturing facilities and are prepared to provide incentives of the kind that the UK has not been offering," he said.

Bell said more incentivization in the form of tax relief would help, and that the pay back would be "huge" in terms of trade.

"The first criteria for a manufacturing base is a low-tax environment because you don't want to pay tax on stuff you're churning out and selling all over the world." He said the UK currently offers innovative pharma companies around a 10% net tax rate. "That is starting to get competitive with even the best players, but probably not as good as Singapore because they'll build a whole facility for you there. But it gets you in the top rank in terms of the net tax rates. Most countries, like Ireland, will give you money to build the facilities there and they'll give you the piece of land and they'll lay it all out for you. The UK needs to get better at that if they want to have serious manufacturing in this space," Bell said, adding: "I don't think anyone is going to be making any big bets on manufacturing until Brexit is signed and its terms are clarified."

## REGULATORY HEADACHES

While it's still not known what the outcome of the Brexit talks will be, the pair said the worst-case assumption at present is that the UK becomes a third country and may need to set up its own regulatory system to approve innovative drugs that in the EU are submitted, evaluated and authorized centrally.

MSD's Perlmutter said that would cause him big headaches, not least in the manufacturing of product for clinical trials. "If I knew for sure right now that the release of materials in the UK would be acceptable to the European Union, well fine because we have a substantial manufacturing footprint in the UK and we're doing that… [If not], then I've got to move everything. And I can't do it overnight. It's very complicated and we're already rubbing up against the time."

He said his operations were dependent on the continued free movement of top talent, and that that was also key for the UK life sciences to be viable in future.

"For MSD, it's very appealing to be in the UK, due largely to the Golden Triangle of Oxford, Cambridge, London for discovery research," Roger Perlmutter said.

"But if people cannot come in and out, if they cannot interact with discovery scientists in those major centers, if the Crick Centre isn't open because people can't get across the border, well it then doesn't matter that you've established this brilliant facility. The UK just will not be able to compete. The UK by itself is not a large enough market to dictate to anybody else. It must be part of the whole," Perlmutter concluded.

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# Time Is Running Out For Industry To Prepare For Brexit, Firms Begin to Feel Staffing Effects

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Stakeholders are worried that a failure to ensure post-Brexit regulatory alignment between the UK and the EU could hit drug approvals, clinical research, trade and many other areas. It could also force the UK to set up its own regulatory regime in parallel with that of the EU.

Brexit negotiations have been proceeding at a snail's pace since the UK triggered Article 50 in March 2017, formally signaling the country's intention to leave the EU. In December it was finally agreed that the UK had made "sufficient progress" on the "divorce" issues to allow the talks to move on to the post-Brexit UK-EU relationship and a possible transition period after March 2019.

With the continuing uncertainty and some influential politicians still openly pushing for a "no-deal" outcome, concern is mounting over the effects of Brexit on the UK life sciences sector – and particularly the people who work in it.

The implications of limiting the free movement of people for sectors such as the National Health Service and university research have been a concern since the June 2016 EU referendum. The concerns are shared by those working in both the regulatory arena and the life sciences industry. The continuing uncertainty also seems to be leading many EU citizens to consider their future prospects in the UK.

But of course, in life sciences as in many other sectors, Brexit is an EU as well as a UK problem. Just ask the European Medicines Agency, which as a result of Brexit is having to relocate from London to Amsterdam. Also ask national regulators in the other member states, many of whom are taking on new staff to deal with the expected increase in workload when the UK agency, the MHRA, is no longer part of the network.

While Amsterdam was among the top five cities in a survey of EMA staff earlier this year, it could still be some time before it's clear exactly how many of the staff will choose to relocate there. The survey found that for the five cities in group 1 (those most favoured), retention rates would be 65% or above, while for group 2 it would be between 50% and 65%, and for group 3, 30-49%.

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> 'I had my first conversations where I started to become worried about the impact of Brexit on our employees'

The figures are important because they will determine the extent to which the agency is able to carry out its activities during and after the relocation. For the cities in group 1, which included Amsterdam, the agency said that core activities such as new drug approvals and safety monitoring would largely be maintained, albeit with possible delays. However, its ability to carry out strategic activities in areas like antimicrobial resistance, collaboration with HTA bodies, and medicines availability would be significantly affected.

The EMA has already suspended some operations under its business continuity plan, which was published in full on Oct. 13 and set out two scenarios in the face of what the agency calls "this unprecedented situation." These are ensuring a "business as usual" scenario as far as possible during the relocation or, failing that, invoking a range of compensatory measures in the plan such as prioritizing its activities and re-allocating freed-up resources.

## INDUSTRY WORRIED

The continuing uncertainty over the Brexit outcome now appears to be starting to cause recruitment problems within the UK pharmaceutical industry. This would be a major headache given that companies operating in the UK rely heavily on talent from across the EU.

Confirmation of this trend came in October when Mene Pangalos, an executive vice president at Anglo-Swedish giant **AstraZeneca PLC**, told a House of Lords Science and Technology Committee hearing that "I had my first conversations where I started to become worried about the impact of Brexit on our employees" – both UK employees in Sweden and elsewhere in Europe, and EU employees working for the company in the UK.

"They are worried about the uncertainty, and obviously we are being as positive as we can be, in terms of saying 'we will look after you', but the fact that we have no idea what is going to happen is a real, real problem, and we are starting to see people turn us down now in the UK because they don't

know what the outcome will be in terms of future employment," Pangalos said. "Even though we tell them we have no doubt that great talent is going to be accepted down the road, they haven't got that certainty and so they are saying until we've got it we'd rather go and work somewhere else."

These concerns were echoed by Dave Allen, a senior vice president at **GlaxoSmithKline PLC**, who told the committee it was important to think hard about the effects of Brexit on the science base and the UK's ability to attract talent. "With a population of 65 million, we cannot expect to have all the talent we need all of the time," Allen said. Companies are asking people to come to the UK to become part of the life science infrastructure "and we need to make it simple for them to do that." The skills they bring are critical, Allen said, and without them "we are not going to compete with countries that are prepared to make it much easier for people to move and thrive in those countries."

## FUTURE OF REGULATION

As for the future of the UK and EU regulatory system itself, companies and regulators alike have made it clear that their preferred option is some kind of collaboration agreement that preserves the current alignment of UK and EU regulations over time – and preferably allows the UK to continue its input into the EMA.

In July industry was encouraged by a letter to the *Financial Times* in July from two senior ministers who said the UK "would like to find a way to continue to collaborate with the EU, in the interests of public health and safety." In a return letter, a number of top pharmaceutical company executives said that "patient safety and public health throughout Europe rely on the current pan-European regulations and standards applying to the research, development, manufacture and supply of medicines."

But the ministers also said that if the "desired relationship" with the EU failed to materialize, the UK would have to establish its own regulatory system. Pretty much everything therefore hangs on the final outcome of the Brexit process. In the event of a "soft" exit – for example, continued membership of the EU single market and customs union, if only for a transitional period – the UK could probably carry on playing a part in the EU regulatory system in some form or other. But if the outcome is "no-deal" and the UK simply crashes out of the EU, the situation would be entirely different. EU centralized drug approvals would no longer be valid in the UK, and the country would have to revamp its regulator, the Medicines and Healthcare Regulatory products Agency, to act as an independent body carrying out its own new drug assessments, with all the resource implications this would entail.

There are risks too for the UK's attractiveness as a location for clinical research. At present the country is routinely included in multinational trials in the EU, but this could change once the UK is no longer a member state. It may also not be able to benefit from the new EU Clinical Trial Regulation, which will streamline the system by offering companies a single submission portal and a central clinical trials database.

As reported in October, the UK is planning to adopt a "Withdrawal Bill" that will transpose all pre-Brexit EU legislation onto the domestic statute books and repeal the European Communities Act of 1972, which gives EU law supremacy over UK domestic law. But because of delays with the portal/database system, the provisions of the CTR will not now apply until the second half of 2019, i.e., after the formal Brexit date of March 29, 2019. According to the Department for Exiting the EU, this means the CTR will not be included in the bill, which would effectively exclude the UK from the proposed system, unless some other regulatory arrangements could be reached.

## COMPANIES, BE PREPARED

The longer the negotiations take to move on from the so-called "divorce settlement" that the UK will have to pay as part of Brexit to the nature of the future relationship, the more likely it is that life science companies will need to prepare for a "no-deal" scenario in which the UK abruptly leaves the EU and automatically falls under World Trade Organization rules.

If no reciprocal regulatory arrangements have been agreed, companies in the UK with marketing authorizations or orphan designations for centrally approved drugs will need to transfer them to a license holder established in the EU if they want to carry on marketing them there. Similar transfers of responsibility will be required in the case of the Qualified Person for Pharmacovigilance, and the UK will become a third party as far as exports of APIs and finished products to the EU are concerned.

To help companies plan for these and other eventualities, the EMA has produced a Brexit Q&A document, which was complemented in November with new practical guidance on how to go about transferring their MAs and other functions.

But time is running out, and while the biopharmaceutical industry has called on the negotiators to agree a transitional period after Brexit, companies have been advised to take action now rather than gamble on such a period being agreed. As the EMA's Agnès Saint-Raymond told companies at a Drug Information Association meeting in October: "You will have to decide whether to implement some changes now."

But when is now? Virginia Acha of the UK Association of the British Pharmaceutical Industry pointed out at a TOPRA symposium that same month: "Negotiators have until 2019. We don't… so at what point do we say 'you just passed my no-go'?"

Companies that fail to make their own preparations risk being left behind in the mayhem that a chaotic Brexit could bring.

The nightmare scenario on what's being called "Day 1" is potential drug shortages for patients if drugs are stuck at borders, allowed neither into the UK from the EU or into the EU from the UK. Nobody wants that.

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# Roche's Neuroscience Franchise Gets Lift From Huntington's Breakthrough

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Following the release of favorable Phase I/IIa results with **Ionis Pharmaceuticals Inc.**'s antisense compound, IONIS-HTT$_{Rx}$, in patients with Huntington's disease on Dec. 11, analysts have been positive about **Roche**'s decision to exercise its option on the drug, with the big pharma now being responsible for all future development and commercial activities.

"The Roche decision is a win for Ionis," said analysts at Leerink, who estimated the market for Huntington's disease therapies could be worth up to $5bn in 2025.

However, various commentators noted caveats, including whether doses of the antisense product can be found that inhibit the mutant Huntingtin protein, believed to be the cause of the disease, while retaining a certain level of normal Huntingtin production. And can sufficient levels be attained and maintained in the CNS to affect the clinical course of what is a progressively debilitating inherited genetic disease?

Further details of the Phase I/IIa study are expected to be presented at a scientific conference in the first half of 2018.

Analysts at BMO Capital Markets noted that Roche could conduct a more conservative Phase II dose finding study first before it moves into a large Phase III study. IONIS-HTT$_{Rx}$ knocks down both mutant protein and normal huntingtin levels by binding to mRNA, and a balance might have to be struck to retain sufficient levels of normal huntingtin protein. Laidlow & Co analysts noted that Huntington's disease is a slowly progressive disease, and it might take up to 18 months before a change in disease progression is detected.

That said, the antisense compound should become an important member of Roche's neuroscience pipeline, which has more than a dozen investigational agents in clinical studies including potential therapies for multiple sclerosis, Alzheimer's disease, spinal muscular atrophy, Parkinson's disease and autism. *(Also see "Roche Delivers Strong Quarter On Ocrevus Launch, Pipeline Promise" - Scrip, 27 Apr, 2017.)*

But Roche may not have the Huntington's disease sector all to itself. In a recent "Market Spotlight" on Huntington's disease, analysts at Datamonitor Healthcare report other potential Huntington's disease therapies are in early-stage clinical studies including WVE-120101 from **Wave Life Sciences Ltd.**; a monoclonal antibody targeting semaphorin, VX15, from **Vaccinex Inc.**; and a vasopressin-targeted molecule, SRX246, from **Azevan Pharmaceuticals Inc**. A Phase II study of **Teva Pharmaceutical Industries Ltd.** /**Active Biotech AB** Active Biotech's *Nerventra* (laquinimod), the LEGATO study, is due to report in 2018.

And there has been some progress in controlling some of the unpleasant symptoms associated with the condition: Teva's *Austedo* (deutetrabenazine) was approved in the US in April 2017 for chorea associated with Huntington's disease. *(Also see "Teva's Austedo Positioned To Compete With A Generic Rival" - Scrip, 4 Apr, 2017.)*

Ionis has received $45m from Roche exercising its option, adding to the $55m in upfront and milestone payments it has already received, and the US biotech is also eligible to receive additional milestones and royalties on sales if the product is commercialized. The company's antisense platform has been pioneered by the approval and launch of the spinal muscular atrophy therapy, *Spinraza* (nusinersen), that is marketed by another licensee, **Biogen**, and Ionis has a pipeline of antisense drugs in late-stage clinical development including inotersen for hereditary TTR amyloidosis and volanesorsen for familial chylomicronemia.

## ATTACKING UNDERLYING CAUSE

IONIS-HTT$_{Rx}$ is the first drug in clinical development aimed at the underlying cause of Huntington's disease, the production of the toxic mutant huntingtin protein (mHTT), and in the global Phase I/IIa study, led by Sarah Tabrizi, professor of clinical neurology at University College London's Huntington Centre, administration of the antisense compound reduced levels of huntingtin protein in the nervous system by an unspecified amount. IONIS-HTT$_{Rx}$ was also safe and well tolerated, Ionis noted.

The study enrolled 46 patients with early Huntington's disease in nine centers in the UK, Germany and Canada, who received four doses of either IONIS-HTT$_{Rx}$ or placebo by intrathecal injection, with the doses of drug increasing over time. The patients are now being offered continued therapy with the drug in an open-label extension study.

Tabrizi said the key is now to move quickly to a larger trial to test whether IONIS-HTT$_{Rx}$ slows disease progression. IONIS-HTT$_{Rx}$ has been granted orphan drug designation by the US FDA and EU's EMA for the treatment of Huntington's disease.

Huntington's disease is a genetic neurodegenerative disease that currently affects around 30,000 individuals in the US. In the disorder, a three-nucleotide sequence in the huntingtin gene is mistakenly repeated up to 36 times, and the resulting mutated protein damages neurons in the brain, causing patients to exhibit declining mental and physical abilities from about the age of 30 years onward.

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# Mereo On The Move With Strong COPD Data And US Listing Plan

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**Mereo BioPharma Group PLC.**'s model of acquiring then developing assets from big pharma looks to be paying dividends again, highlighted by impressive data on its chronic obstructive pulmonary disease (COPD) drug acumapimod, bought off **Novartis AG**, and plans to list in the US.

Last week, the UK company announced positive top-line results from a Phase II trial with acumapimod in acute exacerbations of COPD which showed that the p38MAP inhibitor more than halved rehospitalizations, potentially filling a gaping hole in the COPD market. There are no approved therapies for the treatment of acute exacerbations of COPD and Mereo noted that most treatment is directed at relieving symptoms and restoring functional capacity of the airways.

Specifically, 282 eligible patients were randomized to receive either two different doses of acumapimod, codenamed BCT-197, or placebo (with three doses over five days). The primary endpoint, a comparison of change in forced expiratory volume in one second (FEV1) from baseline to day seven within each arm of the study, was met for both doses of the drug, while a number of secondary and exploratory goals were also reached, including the >50% reduction on the high dose of rehospitalizations.

Speaking to *Scrip*, Mereo CEO Denise Scots-Knight noted that at the moment, patients who end up in hospital will get antibiotics in case of infection, additional steroids and additional bronchodilation "but that is it and that treatment regime really hasn't changed for decades." Acute exacerbations of the disease account for about 63% of all COPD-related hospital admissions, representing more than 1.5 million emergency room visits in the US alone, Mereo noted, so the cost as well as clinical effectiveness of acumapimod has gone down well with the respiratory community.

One of its leading lights, Wisia Wedzicha from Imperial College London and principal investigator in the trial, described the results as exciting. In particular, she said in a statement that "the potential of short-term BCT-197 treatment to impact beyond the acute exacerbation and benefit the clinically meaningful outcomes of treatment failure and recurrent exacerbations, brings the possibility of a step change in management for patients with COPD."

This enthusiasm was echoed by analysts at Cantor Fitzgerald who said in an investor note that the "respiratory field would benefit enormously" from a therapy that minimizes the debilitating effects of exacerbations that leads to a reduction in hospitalizations, "providing attractive health economic benefits."

Achieving these goals is not going to harm Mereo's chances of finding a partner for acumapimod, which was acquired from Novartis in 2015. Scots-Knight said "as you can imagine, we've had a few phone calls," and once the company has gone through the full data set, with more expected in the first quarter, "we will be engaging with potential partners."

She added that the side-effect profile was also encouraging. The p38MAP class has been associated with adverse events such as elevated liver enzyme levels and rash when tested as a chronic treatment for inflammatory conditions such as rheumatoid arthritis and COPD but the Mereo study "looks pretty clean," Scots-Knight noted.

The lack of any serious adverse events was expected, she added, given the short-term exposure to the drug. Scots-Knight went on to say the data represent an important milestone for the firm "as it is the first clinical readout from a product we have acquired, so we are very pleased."

## IPO IN US IN FIRST HALF OF 2018

These are interesting times for Mereo and on Dec. 18, the company, which is already listed on London's AIM, said it planned to conduct an initial public offering in the US during the first half of next year. The number of shares and price of the proposed offering "have not yet been determined," it added.

Mereo will have plenty of projects other than acumapimod to spend the proceeds on if the IPO in the US does go ahead. Its most advanced project, and the most promising according to Cantor Fitzgerald, is its anti-sclerostin antibody BPS-804 (setrusumab) for osteogenesis imperfecta, or brittle bone disease, which last month was granted PRIME designation by the EMA.

## NEW ASSESSMENT TECHNIQUE

A potentially pivotal Phase IIb study is currently underway whereby the drug will be assessed by a relatively new imaging technique, HR-pQCT, as opposed to using bone fracture as an endpoint. BPS-084 has already been accepted into the agency's adaptive pathways program and Cantor Fitzgerald, which believes that the drug could have peak sales of $1.2bn, expects a filing in 2019 – the analysts also believe Mereo will retain rights and self-market. *(Also see "What Progress In The Rare Disease, Osteogenesis Imperfecta?" - Scrip, 22 Feb, 2017.)*

In October 2017, Mereo signed a license agreement with **AstraZeneca PLC**, which has become a shareholder, for AZD-9668 (alvelestat), an oral inhibitor of neutrophil elastase to treat the genetic orphan disease alpha-1 antitrypsin deficiency, with an option to acquire the product following the initiation of pivotal studies. A Phase II trial will start next year, while the first quarter of 2018 will see top-line data from a Phase IIb study of BGS-649 (leflutrozole), acquired from Novartis for the treatment of hypogonadotropic hypogonadism in obese men.

Mereo is also looking for opportunities to further expand and diversify its product portfolio and said it is evaluating "a number of innovative clinical stage products for the potential treatment of rare diseases from large pharmaceutical and biotechnology companies." That particular strategy seems to be working well and, as the Cantor Fitzgerald analysts stated, "So far, so good."

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# Forge Therapeutics Excites Big Guns In Antibiotic World

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**Forge Therapeutics** may be barely two years old, but it has attracted the attention of many experts in the antibiotic development world thanks to its team's work targeting metalloenzymes.

Infectious disease drug developers have long been trying to develop antibacterial medicines that target a zinc metalloenzyme called LpxC. This enzyme plays a key role in the formation of the outer membrane of most Gram-negative bacteria but is not found in Gram-positive bacteria or human cells. However, the target has proven difficult to drug because the "warhead" chemistry called hydroxamic acid that most companies have used to bind to the metal tends to get degraded in the body before it can reach its bacterial targets, and increasing the dose causes toxicity.

## LPXC BREAKTHROUGH?

San Diego-based Forge has taken a different approach, starting with metal-ligand interactions to identify selective metal-binding "warhead" pharmacophores from a proprietary library, then using a novel platform of bioinorganic and medicinal chemistry to develop non-hydroxamate inhibitors. Forge's scientific co-founder and scientific advisory board member Professor Seth Cohen (of University of California, San Diego), initiated the process for incorporating fragment-based drug discovery with the focused library of metal binding pharmacophores, which the company industrialized and has used to develop a discovery and preclinical pipeline initially focused on LpxC inhibitors targeting a range of bacterial infections.

"LpxC has been a high priority target for Gram-negatives for the past 20 years. When we tell our story to scientists who have actually worked on the target, who have worked on metalloenzymes and know the chemistry limitations, it really resonates," CEO Zachary Zimmerman told *Scrip*. "They say 'Hey Zak, you've got the chemistry solution to the metalloenzyme problem,' and they want to become part of it." If successful, an eventual product from this program could represent the first of a new class of Gram-negative antibiotics in several decades.

The LpxC program includes preclinical work for *Escherichia coli, Klebsiella pneumonia and Proteus mirabilis* urinary tract infections, and discovery work with a range of bacterial types for intra-abdominal, respiratory and gonorrheal infections, as well as for biodefense applications. The aim is to begin Phase I human studies by 2020, and with FDA accelerated approval a possibility for drugs to treat superbugs, successful Phase II trials could make way for early approval.

The novelty and success to date of Forge's approach, which has seen it garner high hit rates from its proprietary fragment library across 50 metalloenzyme screens, enabled the company to enlist several prominent experts to join its advisory board in July.

These include Lynn Silver, who was involved in the discovery of the first inhibitors of LpxC and the development of the antibiotic *Invanz* at **Merck & Co.**; Andrew Tomaras, former LpxC program leader at **Pfizer**, now VP and director of microbiology at *in vitro* diagnostics firm BacterioScan Inc.; John Rex, former head of antibiotic development at **AstraZeneca**, former chief strategy officer at the US-UK antibacterial research public-private partnership CARB-X and chief medical officer of antifungal development firm **F2G Ltd.**; and Karen Joy Shaw, formerly SVP biology at **Trius Therapeutics** and antibacterial team leader at **Johnson and Johnson** and **Schering Plough** and currently chief scientific officer of **Amplyx Pharmaceuticals**, among others.

"Our scientific advisors know the unmet need, they know it's only getting worse, and they also know the pipelines of companies are empty and there are very few solutions [to the rising challenge of superbugs and antibiotic resistance] out there. They want to work together to accelerate this as fast as we can, because there are patients that need this today."

## EVOTEC PARTNERSHIP

When it comes to speed of R&D, Zimmerman believes the company has a strategic advantage thanks to the partnership it has with **Evotec AG**, which saw Forge's presentation at a scientific conference and realized that the San Diego team may have cracked a problem that it had itself spent years trying to address. The German company signed a strategic alliance with Forge in December 2016 focused on lead optimization of the LpxC inhibitors identified by the US firm. That partnership was then expanded in October 2017 with the launch of the BLACKSMITH platform to discover additional novel metalloenzyme inhibitors against three additional antibiotic targets (RNAP, DXR and PDF), with the potential to expand to a wider range of diseases.

According to Zimmerman, Forge's partnership with Evotec's anti-infectives team based in Alderley Park, UK has created a rapid and efficient conveyor belt for novel antibiotic classes. The arrangement ties Forge's early chemistry with Evotec's microbiology and established expertise in drug discovery and preclinical development in a 24-hour continual process. "We're able to do this very fast cycle of design, make and test. We design things on a Monday and Tuesday, make things in our laboratories on a Wednesday and Thursday, and test them on a Friday. And then go back and do it again the next week. Whereas if we were in a large organization, these things would literally take months and months," Zimmerman said, outlining the way that the baton is handed between the UK and US on a daily basis.

The partnership with Evotec sees both companies involved in decision making, while Evotec employees working on Forge projects are paid by Forge and the IP and data generated remain with Forge. Evotec meanwhile is an investor in the San Diego company, having participated in the company's series A financing this year. Evotec's COO Mario Polywka is on Forge's board of directors.

## FINANCING AND FUTURE

With money raised this year, Forge is expanding. "We're going from a 10-person company with just around a thousand square foot of lab space to doubling and tripling our headcount over the next year and moving into new state of the art lab space in San Diego that's just under 10,000 square foot," Zimmerman told *Scrip*.

Forge Therapeutics received a significant grant from CARB-X in March 2017 (which could total $8.8m over time and upon achievement of milestones), and followed up with a $15m series A financing in April. "Right now with our financing we have enough runway to get us into 2020," Zimmerman said.

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# Actelion CEO Aims To Drive 'Small Big Company' To Greater Growth In J&J

**KEVIN GROGAN** kevin.grogan@informa.com

**Actelion Pharmaceuticals Ltd.** is clearly a leader in pulmonary arterial hypertension but chief executive Jane Griffiths believes that following the Swiss biotech's acquisition by **Johnson & Johnson**, there is still a lot of value to be created in that space.


*Jane Griffiths*

It is six months since Actelion was bought by J&J's Janssen unit in a deal valued at around $30bn and Griffiths took over the reins. A high-profile and well-respected figure in the industry, she joined Johnson & Johnson in 1982 and was most recently company group chairman of Europe, Middle East and Africa (EMEA) for Janssen but this is her first CEO post.

"By nature, I like to do different things; in my everyday life I want to do one thing a week I've never done before, and this is one thing in my career I've never done before," she told *Scrip* in a recent interview at the J&J Innovation Center in London. Griffiths has also been immersing herself in PAH, "a very nasty disease with huge unmet need and to be involved in what else we can do there is very interesting."

The PAH franchise has been the source of pretty much all of Actelion's revenues since its first drug, the blockbuster *Tracleer* (bosentan) was launched back in 2001. It is now off-patent but the follow-up products, *Opsumit* (macitentan) and *Uptravi* (selexipag) are enjoying healthy growth and consensus estimates of peak sales for both drugs are in the region of $2bn apiece.

Griffiths noted that the PAH assets have had a dramatic effect in tackling the disease with five-year survival increasing from around 32% to 65% but that still leaves a sizeable population that is not receiving the treatment they need.

"There is still a lot to do in PAH," she says and one key area is earlier and better diagnosis. Griffiths said one problem is that the symptoms are not dissimilar to respiratory diseases. "You start with breathlessness, so what do you think – it could be asthma or chronic obstructive pulmonary disease," so patients often start with asthma medication, then after three months they are put on a different one, then they are sent – possibly after a long wait – to a chest physician.

"Before you know where you are, it's a year or 18 months by which time there has been a lot of damage done to your heart," Griffiths said. Therefore, using an easy-to-use diagnostic at point of care – even if it means sending a much smaller population for a right heart catheterization, i.e. to get a definitive PAH diagnosis – would represent a major advance.

The Actelion CEO noted that the company was looking to see if there are start-ups working in this area "but there are lots of things you could look at, whether there is something in the exhaled breath that is different, can you monitor the pressure without invasive tests, some sort of pressure sensor outside your rib cage. We need to think what isn't there now that could exist in the future."

Griffiths added that the goal was to have diagnostic tests and patient monitoring systems that can catch people much earlier "where you intervene in a disease and cost the system less. If you have someone with a chronic condition for 30 years, that's a long time."

As for therapies, "we have got good medicines in an area of unmet need," she noted and there is scope for further growth, adding that in Europe, "access negotiations" for Uptravi are ongoing. Griffiths also pointed out that most patients, if not all, will transition from one medicine, then two and three "but at the moment only 20% are getting that third medicine." Most will need it because as symptoms get worse and patients need a different mechanism to control them, she added.

In the last few years, Actelion has tried to reduce its reliance on PAH and Griffiths told *Scrip* that such a strategy was perfectly understandable for a smaller company that wants to diversify and spread its risk. However, now it is under the J&J umbrella, a major shift away from its core area of expertise is unlikely.

Griffiths said that despite the advances in PAH, a significant number of people are dying earlier than they should, "so the first thing is to look at what other pathways are involved in PAH which are not addressed by the mechanisms that are currently in place and there are a number that are very interesting and we are looking at those."

## LOOKING AT DISEASES ALLIED TO PAH

Actelion is going to be exploring new indications and formulations for the current assets. Also, "if something caught our eye that was outside PAH but still addressed the same customer population we would take a look so we can build on our current footprint."

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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**

## Selected clinical trial developments for the week 8–14 December 2017

| LEAD COMPANY/PARTNER | COMPOUND | INDICATION | COMMENTS |
|---|---|---|---|
| **Phase III Results Published** | | | |
| Pfizer Inc. | *Trumenba* vaccine | meningitis | *NEJM*, Dec. 14, 2017. |
| Daiichi Sankyo Co. Ltd. | edoxaban | cancer-associated venous thromboembolism | Hokusai-VTE CANCER; *NEJM* online, Dec. 12, 2017. |
| Takeda Pharmaceutical Co. Ltd./ Seattle Genetics Inc. | *Adcetris* (brentuximab vedotin) | Hodgkin lymphoma | Echelon-1; *NEJM* online, Dec. 10, 2017. |
| **Phase III Completed** | | | |
| Cyclacel Pharmaceuticals Inc. | sapacitabine | acute myeloid leukemia | SEAMLESS; mixed results. |
| **Phase III Interim/Top-line Results** | | | |
| Pfizer Inc. | talazoparib | breast cancer | EMBRACA; PFS extended. |
| Ampio Pharmaceuticals Inc. | *Ampion* (LMW human serum albumin fraction) | severe knee osteoarthritis | Met primary endpoint. |
| Dova Pharmaceuticals | avatrombopag | immune thrombo-cytopenic purpura | Study 302; durable platelet responses. |
| Glenmark Pharmaceuticals Ltd. | *Ryaltris* (olopatadine/ mometasone furoate) | allergic rhinitis | Efficacy and safety endpoints met. |
| **Updated Phase III Results** | | | |
| Roche/AbbVie Inc. | *Venclexta* (venetoclax) | chronic lymphocytic leukemia | MURANO; PFS extended. |
| Ablynx NV | caplacizumab | thrombotic thromb-ocytopenic purpura | HERCULES; clinically meaningful responses. |
| Johnson & Johnson/Genmab AS | *Darzalex* (daratumumab) | multiple myeloma | ALCYONE; improved outcomes. |
| Emmaus Life Sciences Inc. | *Endari* (L-glutamine) | sickle cell anemia | Reduced crises. |
| Geron Corp./Janssen Biotech NV | imetelstat | myelodysplastic syndromes | Initial efficacy signs. |
| Kyowa Hakko Kirin Co. Ltd. | mogamulizumab | cutaneous T-cell lymphoma | MAVORIC; PFS improved, objective responses. |
| PharmaMar SA | *Aplidin* (plitidepsin) | multiple myeloma | ADMYRE; PFS and overall survival increased. |
| Shionogi Inc. | lusutrombopag | thrombocytopenia | Met all endpoints. |
| Verastem Inc. | duvelisib | chronic lymphocytic leukemia | DUO; improved PFS. |
| Roche | *Hemlibra* (emicizumab-kxwh) | hemophilia A with inhibitors | HAVEN 1,2 4; reduced bleeds. |
| Cytokinetics Inc. | tirasemtiv | amyotrophic lateral sclerosis | VITALITY-ALS; missed primary endpoint. |
| MediciNova Inc. | ibudilast | amyotrophic lateral sclerosis | Signs of efficacy. |
| **Phase III Initiated** | | | |
| Corbus Pharmaceuticals Holdings Inc. | anabasum | scleroderma | RESOLVE-1; an international study. |
| Pfizer Inc. | PF-04965842 | atopic dermatitis | JADE-Mono-1; a JAK1 inhibitor. |
| BioMarin Pharmaceutical Inc. | valoctocogene roxaparvovec | hemophila A | GENEr8-1; an open-label study. |
| Clementia Pharmaceuticals Inc. | palovarotene | fibrodysplasia ossificans progressive | MOVE; a multinational study. |
| Regeneron Pharmaceuticals Inc./ Sanofi | cemiplimab | non-small cell lung cancer | Combined with ipilimumab or chemotherapy. |

*Source: Biomedtracker*

CONTINUED FROM PAGE 21

Those allied diseases could include pulmonary hypertension and chronic thromboembolic pulmonary hypertension (CTEPH) and as Griffiths told *Scrip,* "You know what the J&J model is, this innovation center here is all about having teams of scouts investing in very early start-ups and biotechs who are tasked with spotting molecules of interest."

Aside from PAH, Actelion has high hopes for ponesimod, an investigational oral treatment for multiple sclerosis. The Phase III program for the sphingosine-1-phosphate receptor 1 modulator includes a superiority study comparing ponesimod to placebo in subjects with active relapsing MS who are being treated with **Biogen Inc.**'s blockbuster pill *Tecfidera* (dimethyl fumarate).

When asked if the compound fits well in Actelion's pipeline, Griffiths noted that "we've got neuroscience in J&J so there is an obvious collaboration there and we are very excited about it." For cadazolid, a quinolonyl-oxazolidinone antibiotic for *Clostridium difficile*-associated diarrhea which is in Phase III, Actelion is evaluating its options.

And as for the relationship with Idorsia, the new R&D venture set up by Actelion founder Jean-Paul Clozel with the earlier-stage assets left over from the $30bn acquisition, Griffiths said there are transition agreements in place, providing services both ways, and a lot of obvious informal links given that many Idorsia staff have come from Actelion - They are next door, we share their canteen, and there's a lot of respect." Last week, J&J agreed to pay $230m to **Idorsia Pharmaceuticals Ltd.** to co-develop the latter's investigational hypertension drug aprocitentan, a metabolite of Opsumit.

Interesting times for the new boss and Griffiths told *Scrip,* "A big part of my job is to show our people what benefits J&J will bring to their organization at this point in its life. It is 'a big small' company that needed to make that transition and having a ready-made big company to tap into that has the resources you need is a good thing."

J&J has paid a hefty price for Actelion but Griffiths concluded by saying: "You buy the assets but you also buy a group of very talented people who we acknowledge as absolute leaders in this space. Their relationship with the key opinion leaders in PAH is very tight and over the last 20 years these physicians have grown up with Actelion and that closeness to the patient, the disease, the science and the customer is highly valued by us."

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## APPOINTMENTS

The **IFPMA** has appointed ***Greg Perry*** as its new assistant director general, effective mid-February. Perry will have responsibility for IFPMA's external outreach and stakeholder engagement in global health topics including innovation, access, and the international regulatory environment. Perry brings more than 20 years' leadership and advocacy experience in the public healthcare arena, most recently as executive director of the Medicines Patent Pool. Before that Perry was director general of the European Generic Medicines Association (1999-2013) in Brussels.

***Dr. Petra Wicklandt*** is to take over the leadership of **Merck KGAA**'s newly created corporate affairs unit as of January 1, 2018. She will report to ***Stefan Oschmann***, executive board chairman & CEO of Merck. Corporate affairs consolidates the government and public affairs of the three business sectors as well as the corporate responsibility and global health activities of the group. Wicklandt joined Merck in 1994 and most recently served as head of global chemical and pharmaceutical development.

**Ergomed plc** has appointed ***Stephen Stamp*** as chief executive officer and ***Dr Jan Petracek*** as chief operating officer and a director with immediate effect. ***Dr Dan Weng*** has decided to step down as CEO. Stamp has been Ergomed's chief financial officer, and member of the board, since January 2016. Prior to this, he spent more than 30 years in corporate finance and general management in the UK and US and, as CFO, led the IPO of Shire on the London Stock Exchange and NASDAQ. Petracek has been CEO of Ergomed's pharmacovigilance subsidiary PrimeVigilance since April 2017 and is the former head of risk management section at the European Medicines Agency.

**Spectrum Pharmaceuticals** has terminated its chief executive officer CEO ***Dr. Rajesh C. Shrotriya*** "without cause". ***Joseph W. Turgeon***, the current president and chief operating officer, has been named president and CEO and elected to the board, and current director ***Dr. Stuart M. Krassner***, has been named chair. In addition, ***Thomas J. Riga***, who currently serves as executive vice president, chief commercial officer and head of business development, has been named COO. Turgeon has more than 30 years of experience in the pharmaceutical industry, including various executive leadership roles at Amgen Inc. Riga brings over 15 years of pharmaceutical sales and management experience in various positions at Amgen, Eli Lilly and Dendreon. Krassner has served as a director of Spectrum since December 2004.

**Astellas** has promoted ***Anthony Fiordaliso*** to vice president, Americas finance, reporting to Stephen Knowles, senior vice president, finance and information technology. Previously, Fiordaliso served as executive director, commercial finance. Prior to joining Astellas, Fiordaliso was director, US financial operations at Schering-Plough (now Merck). Before Schering-Plough, he served as senior internal auditor at Warner-Lambert (now Pfizer).

**Laboratoris Sanifit**, a clinical-stage biopharmaceutical company focused on treatments for calcification disorders, has appointed ***Dr. Alexander M. Gold*** chief medical officer and president of its US subsidiary Sanifit Inc., based in San Diego. Gold is a cardiologist with over 16 years' experience in development of new therapies, and is also an adjunct professor at Stanford University School of Medicine. Gold was most recently senior vice president and head of clinical development at Portola Pharmaceuticals.

**Audentes Therapeutics Inc.**, a biotechnology company focused on gene therapies, has appointed ***Dr. Mark A. Goldberg*** to its board. Goldberg brings over 20 years' experience developing and commercializing products to address serious unmet medical needs. Previously, he served as the executive vice president, global medical and regulatory strategy at Synageva, and as senior vice president for clinical development and global therapeutic group head for oncology and personalized genetic health at Genzyme Corporation.


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