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FDA Backs Novartis MS Pill Mayzent With Broad Label

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Novartis AG has won FDA approval for its eagerly anticipated multiple sclerosis drug Mayzent and won big, with the agency granting the green light for the therapy to be used across the spectrum for patients with relapsing forms of the neurological disease.

The thumbs-up from the FDA means that *Mayzent* (siponimod) is now the first oral treatment specifically indicated for active secondary progressive multiple sclerosis (SPMS) in adults. This was expected but the approval also states that the label on the drug, an improved version of Novartis' older therapy *Gilenya* (fingolimod), includes clinically isolated syndrome (CIS), defined as a first episode of neurologic symptoms that lasts at least 24 hours and is caused by inflammation or demyelination in the central nervous system, as well as relapsing-remitting MS.

In an interview with *Scrip* hours after the FDA approval was revealed, Novartis head of pharmaceuticals Paul Hudson said that when Mayzent is made available in the US in the next week, the emphasis will be very much on SPMS patients. Specifically, he spoke of those patients "who have had 10-15 years of the disease and face the 'heart sink moment' of sitting in front of their neurologist and they both know things are getting worse, though they can't always pinpoint a relapse."

However, the patient "knows they're struggling and the physician is desperate not to call it as SPMS because they have no medical treatment. However, we've reached the moment where now they do," Hudson added. He went on to say that Mayzent is "going to be fantastic for patients in trying to stop that descent into lack of mobility and preserving cognition, perhaps even bladder function, really terrible lifestyle-impacting burdens."

Hudson said that the principal aim was to get SPMS "properly characterized in the label" and "payers and providers want the confidence that comes from that and that's what we got." However Novartis got "slightly wider and we have to be responsible with that but there is a large group of progressive patients who start much earlier and that's why the wider label will give some physicians pause for thought about trying to address progression much earlier."

The approval of Mayzent, which selectively binds to the S1P1 and S1P5 receptors, is based on the Phase III EXPAND study in SPMS patients who had a mean age of 48 and had been living with MS for approximately 16 years. More than 50% had a median expanded disability status scale (EDSS) score of 6.0 and relied on a walking aid.

The drug significantly reduced the risk of three- and six-month confirmed disability progression, by 21% versus placebo, and favorable outcomes in other relevant measures of MS disease activity.

However, Hudson noted that while the patients in EXPAND had an EDSS of 6.0, there is data down to EDDS2, "which means that if you've got somebody who is progressing between relapses, you may say to yourself, what's the best treatment

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Activist investors win on CEO-Chairman split, but not yet (p16)

Signs Of Change?

Big pharma reports slow growth for list prices in 2018 (p21)

from the editor

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Data recently released by three big pharma companies – Eli Lilly, Merck & Co and Janssen Pharmaceutical Cos – show that the average US list price increases for their medicines have been falling since 2015. Net prices have actually gone into decline over the past couple of years (see report on p21; a full report with further charts is available on Scrip's website).

The pharma sector feels inherently precarious because of the high risk and cost of drug development. Price inflation was once a reliable and low-risk way for companies in the sector to keep on top of the growth imperative. But as Lilly, Merck and Janssen can attest, it isn't essential. At the same time as these companies reduced their net drug prices, they recorded an increase in their sales, not only globally but also specifically in the US, as well as in their pharmaceutical segment profits.

For big pharma, list prices, net prices and company revenues and profits are only loosely connected. All these companies were able to grow because they experienced strong uptake of newer products. Shrewd acquisitions and divestitures helped.

Elsewhere in this issue the array of new product approvals, positive clinical data, investment and partnering provides a snapshot of a lively and productive industry with good prospects. The overall health of the industry is good news for society, since it means new and better treatments are constantly becoming available. Given its self-regenerative powers, the R&D-based industry should not begrudge payers seeking to contain prices as medicines age (see p20 for more on biosimilar insulin glargine savings).

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publisher's spotlight

The 2019 Scrip Awards Is Now Open For Nominations

Come and celebrate your vital contribution to improving human health worldwide – the 2019 Scrip Awards is now open for entries.

Since they began, the Scrip Awards has sought to applaud the essential role that the pharmaceutical, biotech and other allied industries play in improving healthcare. Its trophies span the entire range of industry activities, from new drug launches and clinical trials, to innovative deals, outsourcing and fundraising.

This year, we have introduced a new category – MSD's Innovation Award (sponsored by MSD) – to acknowledge and celebrate the outstanding scientific or technological breakthroughs that have the potential to be transformative in the discovery or development of new medicines.

Over the past 15 years, the Scrip Awards has carved out a unique place in the industry calendar, with around 500 attendees coming from around the world to the prestigious ceremony, which this year will take place in the London Hilton on Park Lane in Mayfair on 4 December.

Our panel of 16 highly respected and independent experts from across the sector is waiting to judge the entries from the 16 categories in contention this year. You will find further details about our panel and how the judging process works on the Judges page.

The deadline for entries is 7 June. Now is the time to prepare your entry and make sure you take your place among the best.

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inside:

CONTINUED FROM PAGE 1

option here…we were encouraged by the regulator's opinion that there is a wider remit [and] if a physician wants to go earlier, they have the label." Still, he stressed that at least in the first year or so from launch, SPMS "is where our energy will go."

The list price for Mayzent is $88,500 per year, considerably lower than Gilenya ($98,500) and less than **Biogen Inc.**'s RRMS pill *Tecfidera* (dimethyl fumarate) which costs $93,700 at list price, according to Credit Suisse. Hudson told *Scrip* that "we have priced it at the lower end of the orals because we want the physician to make a clinical decision and not be encumbered by a price discussion."

He added that obviously "much depends on our relationship with the pharmacy benefit managers and the progress we can make with them on access, but I feel confident that that at least from a list price perspective, we have removed any burden." Novartis is also putting together programs to help those patients who will have problems affording Mayzent.

Hudson claimed that "Novartis is probably the best company in the world in neuroscience and we have produced unique data," noting that Biogen's *Tysabri* (natalizumab) failed in the SPMS patient population. He concluded by saying that Mayzent, which is widely expected to be a blockbuster, is the first of three expected US approvals for the firm this year (a European okay is forecast before the end of 2019), to be potentially followed by the gene therapy *Zolgensma* for spinal muscular atrophy and the ophthalmology treatment brolucizumab.

SURPRISING BREADTH

The breadth of label granted to Mayzent surprised analysts. In an investor note, Jefferies noted that the broad label, plus the unmet medical need of SPMS and "much less onerous first-dose monitoring requirements" could see the drug bring in worldwide peak sales of $1.25bn. The SPMS indication should be the main driver but it is a sizable one; around a quarter of the RRMS patients will transition to SPMS within 10 years, the broker noted, and over 75% will transition to SPMS after 30 years. It is estimated that at any one time around 30% of MS patients have SPMS.

Credit Suisse analysts said the 'in transition' patients represent "an additional early opportunity on top of our expectations…and we expect the company will focus on Mayzent's unique positioning in active SPMS and late-stage RRMS." As for the early MS marketplace, they noted that "this is a highly competitive area, increasingly dominated" by **Roche**'s game-changing infusion *Ocrevus* (ocrelizumab) "and where Mayzent has limited differentiation and only modest clinical data."

The approval, for which Novartis used a priority review voucher for the filing with the FDA, boosts the company's strong MS franchise. Gilenya is the company's biggest seller, with sales last year of $3.34bn and the company's CEO Vas Narasimhan told *Scrip* in January that while the legal situation around the drug's patents was "extraordinarily complicated," with several generics firms threatening at-risk launches, the company expects no copycat versions to hit the market this year.

Nevertheless, Gilenya generics are not that far away and the already-crowded MS market in the US can expect to see a few more entries in the next couple of years. In particular, Novartis will be keeping a close eye on **Celgene Corp.**'s ozanimod, which was re-filed with the FDA earlier this week and **Johnson & Johnson**'s ponesimod, which is forecast to get regulatory approval late 2020.

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Bluebird Bio's Zynteglo Flies Through Its CHMP Review

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Confirmation that **bluebird bio Inc.** has indeed received a green light for marketing in the EU of its lead product, the gene therapy Zynteglo (formerly LentiGlobin), at the Committee for Medicinal Products for Human Use (CHMP) meeting in Amsterdam this week puts the company on the path to its first commercial sales.

The final approval for treating beta-thalassemia should come in the second quarter and will be the first worldwide for the product; bluebird expects to start marketing it by the end of the year. Early reports that an positive opinion was in the offing came earlier this week following the first day's meeting of the CHMP, the European Medicines Agency's drug evaluation committee.

The MAA review broke records, thanks to the EMA's various programs designed to speed the development and review of potentially ground-breaking products. Since Zynteglo addresses an unmet medical need, it benefited from PRIME, EMA's platform for early and enhanced dialogue with developers of promising new medicines. "This interaction led to a more robust application package to demonstrate the medicine's benefits and risks, which allowed accelerated assessment of Zynteglo in 150 days, the fastest advanced-therapy medicinal product review time to date," the agency noted.

Bluebird CEO Nick Leschly told *Scrip* the company was "beyond impressed" with the EMA's processes. "It was incredibly efficient," he said, with "great questions, actually really informative questions, very reasonable questions. I wouldn't say it was enjoyable because this is always very hard work, very taxing and stressful, and it's nerve-racking, but at the end of the day we certainly feel a lot stronger for it."

An *ex vivo* gene therapy, Zynteglo (autologous CD34+ cells encoding β(A-T87Q)-globin gene) has specifically been given the go-ahead for patients 12 years and older with transfusion-dependent β-thalassemia (TDT) who do not have a β(0)/β(0) genotype, for whom hematopoietic stem cell (HSC) transplantation is appropriate but a human leukocyte antigen (HLA)-matched related HSC donor is not available. If approved, it will be the first gene therapy to treat TDT. The company has been preparing the ground for launch for some time, Leschly said, and the first sales are most likely to be in Germany by the end of the year.

"We've been spending a few years getting ready for launch in Europe and hopefully we're well on our way to getting ready in the US," he said. "With a product

like ours, not only do you have to make the virus, you have to set up the infrastructure to do the manufacturing, which is a real-time, very patient-involved and system-involved process, so we've been working on that country by country."

At the J.P. Morgan meeting in January, Leschly made the case for an innovative value-based installment pricing model for gene therapy, and suggested the price would be under $2.1m. Under the proposed plan, payers would pay for the therapy over five years. The first 20% would be paid up front while the rest would be paid in annual installments – but only if treatment is successful, based on a reduction in the number of blood transfusions – and there would be no payments after five years.

Bluebird is in pricing and reimbursement discussions in Germany, the UK, France and Italy but "the exact sequence of when we will be able to hopefully treat patients through that is a little bit to be determined," Leschly said. Germany is usually more of a known quantity, making it the most likely first market for launch, "but we are really thinking about this over a longer period of time of laying out the foundation in '19 and '20 for not only this product but hopefully future products," Leschly added. "We are at the start line here and it's just an exciting time."

The CEO noted that each country, and in some cases (especially in the US), each payer, would probably look at the pricing model differently. "Some will [find it] easier to digest, for certain reasons, some will be harder to digest so we are working payer by payer in the US and certainly in Europe."

While Europe could sometimes be thought of as being easier because it consists of mostly single-payer systems, such as the UK's NHS, to negotiate with, each region has its complexities, Leschly said.

"Everyone has their own unique path ways but we fundamentally believe that it is important that for a treatment like this, that is a one-time potentially curative treatment, that we establish a payment model that makes sense for all stakeholders, that shares risk, and that considers the fact that this will hopefully work for a lifetime," he said. "It is very different form the classic chronic treatment – you know: you give the drug, you get paid – and so we are trying to find a balance; that's what this model was all about."

Despite the prospect of booking sales by year end, Leschly said bluebird did not see itself as being at the cusp of a transition to a commercial business. "We are trying to actually think about it not that way. We are trying to say this is a natural extension and continued transformation of the system from the science and the way we run the studies to the way we bring [the product] to patients," he said.

"We fundamentally believe our objective is actually not to sell drug. This is not about generating revenue and selling the drug. This is about educating the physicians and medical staff and the parents and kids about whether this is this the right choice for them based on their assessment of the pros and cons. Our job is to get to everyone as fast as we can, get them as informed as we can and let the chips fall where they may; it might be right for some patients and their families and it may not be." But still, he admitted, the company would like to make some money. "We do of course. We have unapologetically said that we believe in the value and what we do is very expensive but at the same time it's not the reason for being, it's not our purpose," he said: rather, it is an outcome of delivering "value to the patient and the system."

US FILING

Bluebird's EU application was supported by data from the completed Phase I/II Northstar (HGB-204) study and the ongoing Phase I/II HGB-205 study as well as available data from the Phase III Northstar-2 (HGB-207) study and the long-term follow-up study LTF-303.

The next big step is a US filing, again expected by year end. This is awaiting the full results of the Phase III Northstar-2 study which uses product made by a refined manufacturing process.

While the EU opinion covers the new manufacturing process, Leschly was pleased that the EMA was willing to look at the data from the earlier studies in parallel with the available data from the Phase III trial. "That's a lot easier from our perspective because you don't want two separate supply chains and certainly [this] will also be considered as the US filing starts to kick into gear," he said. LentiGlobin has US orphan drug status and breakthrough therapy designation for the treatment of TDT.

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AZ's Forxiga Gets Type 1 Diabetes EU Okay As Sanofi Suffers US Setback

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AstraZeneca PLC has stolen a march on **Sanofi** with Forxiga being granted approval in Europe as the first oral add-on to insulin in type 1 diabetes patients a few days after its French rival failed to get a similar green light for Zynquista across the Atlantic.

Having secured a positive opinion from the European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) in February, AstraZeneca has been given the thumbs-up to launch *Forxiga* (dapagliflozin) as an adjunct to insulin for patients with type 1 diabetes who cannot maintain blood glucose control using insulin alone, specifically those who are overweight or obese, i.e. with a body mass index (BMI) above 27. The approval is based on the Phase III DEPICT clinical program which showed that Forxiga 5 mg daily demonstrated significant and clinically meaningful reductions from baseline in average blood glucose levels HbA1c, weight and total daily insulin dose at 24 and 52 weeks. *(Also see "AZ Sees A Future For Forxiga In Type 1 Diabetes" - Scrip, 6 Mar, 2018.)*

Getting the thumbs-up in type 1 can only bolster the already-strong sales AstraZeneca books from Forxiga, a selective sodium

glucose cotransporter-2 (SGLT-2) inhibitor, in its main indication of type 2 diabetes. In 2018, the drug, known as *Farxiga* in the US, was the company's fifth biggest seller, bringing in $1.39bn, up 30% on the previous year, more than the other SGLT-2 inhibitors, **Johnson & Johnson**'s *Invokana* (canagliflozin) and **Boehringer Ingelheim GmbH/Eli Lilly & Co.**'s *Jardiance* (empagliflozin).

The company was coy when asked by *Scrip* about launch plans for Forxiga in type 1 diabetes, simply stating that "timing is variable and largely dependent upon each local health authority." As to how many type 1 patients in Europe could benefit, AstraZeneca noted that given the approval is for adults with a BMI of 27 or higher, "the potential market is limited."

News of the approval came as Sanofi suffered a setback in the US as the company announced March 22 that it received a complete response letter from the FDA for the dual SGLT1 and SGLT2 inhibitor *Zynquista* (sotagliflozin) partnered with **Lexicon Pharmaceuticals Inc.** for type 1 diabetes. *(Also see "Keeping Track: Thumbs Up For Zulresso And Sunosi, Thumbs Down For Zynquista And IV Meloxicam" - Pink Sheet, 24 Mar, 2019.)*

The decision was not a huge surprise given that an FDA advisory committee was split 8-8 vote in January this year on Zynquista being approved as an oral add-on to insulin. The principal concern of panellists centered around the risk of diabetic ketoacidosis (DKA) which was significantly higher among patients receiving Zynquista during clinical trials.

Speaking on an investor call, Lexicon CEO Lonnel Coats noted that "we only just received the letter and have not had any discussions with the FDA regarding the content of the CRL." Analysts at Wedbush issued a note March 25 saying that they have pushed back their potential US launch date for Zynquista from July this year to March 2021 to allow enough time to fulfill FDA requirements.

In the second quarter the broker is also expecting top-line results from the first of the nine ongoing Phase III studies for Zynquista in type 2 diabetes, with data from the remaining eight trials anticipated throughout 2019. The drug is seen as key to Sanofi's future prospects, particularly in diabetes where the firm has been hit by the loss of patent protection on the blockbuster *Lantus* (insulin glargine) and less-than-stellar uptake of its newer long-acting insulin product *Toujeo*.

It is not all woe for Sanofi and Lexicon however, given that earlier this month, the CHMP issued a positive opinion on Zynquista based on data from three Phase III studies which showed the drug could improve blood sugar control, as well as reduce weight and blood pressure. The agency acknowledged the risk of DKA, which can lead to acute kidney injury, respiratory failure and death when added to insulin, but is likely to approve the drug in the second quarter.

The Wedbush analysts noted that diabetes patients with higher BMIs have a greater risk of cardiovascular events so the weight loss benefit and higher use of insulin makes the DKA risk more acceptable. Pointing out that the CHMP did not recommend any post-marketing studies, they expect a potential EU launch in November this year and gross peak sales of about $235m.

DKA is also an issue for Forxiga and the CHMP noted that "despite precautionary measures, there is a considerable increase in the risk" of the potentially life-threatening complication, hence the approval limited to treatment in overweight or obese patients only and not for those with low insulin requirements. AstraZeneca acknowledged that the safety profile of the drug in the type 1 trials "was consistent with its well-established profile in type 2 diabetes, with the exception of a higher number of DKA events in Forxiga-treated patients," noting that it is a known complication that affects those with type 1 more frequently than with type 2.

It will be interesting to see what the FDA makes of the DKA issue when it makes a decision on Farxiga for type 1 in the second half of this year. The drug is also currently under regulatory review in Japan and a decision is expected there in the first half of 2019.

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AstraZeneca's Imfinzi Cements Market Position In Lung Cancer Segment With UK NICE Okay

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Heralded as the "biggest advance we've seen for a number of years in treating locally advanced non-small cell lung cancer," **AstraZeneca PLC**'s checkpoint inhibitor, *Imfinzi* (durvalumab), has been recommended for use in the UK's National Health Service in a small subgroup of patients – around 165 individuals in the first year – by the health technology assessment body, NICE.

With the National Institute for Health and Care Excellence (NICE)'s technology appraisal committee being advised by clinical experts that durvalumab was a "potentially curative treatment", a positive appraisal was perhaps more than likely, although NICE's draft final guidance, issued on March 28, 2019, comes with caveats, principally that Imfinzi treatment should be reimbursed by the government-backed and ring-fenced Cancer Drugs Fund, and not by the NHS itself.

That's because the clinical trial data on which the appraisal was based, the PACIFIC study, were "still immature," NICE said. "Because of the high level of uncertainty in the clinical evidence supporting the appraisal, NICE was unable to conclude that the most plausible ICER fell within the range usually considered to be a cost-effective use of NHS resources. However, it met the criteria for being recommended for use in a specific subset with the Cancer Drugs Fund," the appraisal says.

Drugs are funded by the UK's Cancer Drugs Fund if there is plausible potential to satisfy the criteria for routine commissioning, but significant remaining clinical uncertainty which needs more

investigation, through data collection in the NHS or clinical studies. Durvalumab will be made available and reimbursed via the Cancer Drugs Fund while more clinical data are collected from the PACIFIC study; final analyses of that study are expected in September 2021, at which point the NICE guidance will be reviewed.

Imfinzi was approved for unresectable Stage III (locally advanced) NSCLC in by the European Commission in Oct. 2018, and in the US in February 2018, and AstraZeneca recorded sales of $663m for the drug in 2018, the majority of sales being in the US.

"The favorable impact of additional potential launches in other markets is yet to come," the company commented in its 2018 year-end results. Analysts have been predicting blockbuster sales for Imfinzi, driven by its potential in locally advanced NSCLC where there are no treatment options to delay or stop the disease progressing after chemoradiation. Analysts at *Datamonitor Healthcare* are predicting peak sales of $3.5bn for Imfinzi in 2024, the majority from use in Stage III NSCLC.

Other checkpoint inhibitors such as **Merck & Co. Inc.**'s *Keytruda* (pembrolizumab) and **Bristol-Myers Squibb Co.**'s *Opdivo* (nivolumab) have established positions in metastatic lung cancer, but not in locally advanced disease.

UNDISCLOSED DISCOUNTING

In the draft final guidance, NICE recommends durvalumab as a monotherapy in patients with locally advanced unresectable NSCLC in adults whose tumors express PD-L1 on at least 1% of tumor cells, and whose disease has not progressed after concurrent platinum-based chemoradiation, and the conditions of a (confidential) managed access agreement are followed. AstraZeneca is to make durvalumab available at an undisclosed discount to the NHS list price of £592 per 120 mg/2.4 ml vial, and £2,466 per 500 mg/10 ml vial.

> Analysts have been predicting blockbuster sales for Imfinzi, driven by its potential in locally advanced NSCLC where there are no treatment options to delay or stop the disease progressing after chemoradiation.

The appraisal makes a distinction between concurrent and sequential platinum-based chemoradiation; better results were seen in PACIFIC with concurrent therapy, the less common form of chemoradiation scheduling in the UK. Durvalumab may be of more benefit after concurrent chemoradiation because that form of treatment is used in healthier patients, the appraisal speculates. Alternatively, concurrent chemoradiation may in fact produce better outcomes and have different adverse effects than sequential chemoradiation, clinical experts told the appraisal committee. NICE concluded that the PACIFIC data on concurrent chemoradiation could not be generalizable to a population undergoing sequential chemoradiation.

In their analysis of data from the PACIFIC study, the appraisal noted that median progression free survival was 23.9 months in the durvalumab arm and 5.6 months in the standard care arm. The hazard ratio was 0.44 with a 95% confidence interval (CI) of 0.31 to 0.63. Durvalumab also lengthened overall survival compared with standard care, producing a hazard ratio of 0.54 (95% CI 0.35 to 0.81).

Clinical experts advised that the duration of treatment effect due to durvalumab was uncertain because the data were immature, but that experience with other immunotherapies showed that a five-year duration of treatment effect was plausible. They also noted that durvalumab was a potentially curative treatment. However, in some patients, durvalumab might delay disease progression rather than curing the disease.

As well as calling durvalumab the biggest advance in lung cancer for a number of years, consultant clinical oncologist Fiona McDonald, of the Royal Marsden NHS Foundation Trust in the UK, said that durvalumab would have an immediate impact on clinical practice, and would become the standard of care for eligible patients.

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Blackstone Bets On Pharma In First Japan Buy, But Why?

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Funds under The Blackstone Group are buying the private specialty firm **Ayumi Pharmaceutical**, in a signal that the US private equity giant sees attractive returns down the road from what is its first controlling private investment in Japan.

The transaction, expected to close in the calendar second quarter for a reported (but unconfirmed) sum of around JPY100bn ($910m) including debt, is significant on several counts. Ayumi's focus area of pain has not historically seen significant M&A activity globally, while major investments by private equity (PE) groups have not traditionally been an important part of Japan's pharma landscape.

Even with around $472bn in assets under management worldwide, the new investment marks a substantial commitment by Blackstone, and is the first large transaction by the company's new Asia-focused investment fund, set up in late 2017 and which has so far raised around $2.3bn, and is also said to be eyeing multi-sector opportunities in China and India. Blackstone stated in media interviews last year that it was planning to step up its so far limited investments in Japan, apparently spying acquisitions and other opportunities from the spin-off by large companies of non-core assets, and among family-owned or domestic-focused firms facing business challenges.

In common with other PE groups, Blackstone typically provides capital, management expertise and contacts to help

expand a business and facilitate licensing deals and overseas expansion. Like its peers, there is a clear focus on a profitable exit at an appropriate stage, usually through divestment to an acquirer or initial public offering.

The real estate-focused company does have some prior history when it comes to pharma, and for instance was part of a group of investors that acquired **Nycomed SPA** from Nordic Capital for an undisclosed sum in 2002.

In that case, Nordic acquired back a controlling interest in the European-based pharma firm in 2005, and eventually sold Nycomed to **Takeda Pharmaceutical Co. Ltd.** for €9.6bn in 2011.

In 2013, Blackstone sold an equity stake in **Emcure Pharmaceuticals Ltd.** to another investor, Bain Capital, which holds its stake in the Indian generics firm to this day.

More recently, Blackstone funds plowed $250m into startup **Anthos Therapeutics Inc.**, which is starting life with an antithrombotic asset licensed from **Novartis AG**.

But what's so attractive about Ayumi?

AYUMI'S APPEAL

A little background. So far, Ayumi has been privately owned by two Japanese investors, the independent private equity group Unison Capital and the medical information services provider M3.

Blackstone's Japan private equity head Atsuhiko Sakamoto said that the company is looking forward "to working with the company to leverage Blackstone's global footprint and expertise in this sector", to help Tokyo-based Ayumi meet growing demand and investment needs.

Ayumi president and CEO Ouchi Hikaru stated simply: "We will need more investment for future growth."

The company was formed in 2015 as a new venture after Unison purchased ophthalmic specialist **Santen Pharmaceutical Co. Ltd.**'s anti-rheumatic drug division. The new company was then enlarged by the acquisition and merger later that year of small Japanese firm's Showa Yakuhin Kako's business, which brought an analgesic portfolio.

Ayumi is not large, employing only around 400 people, but specializes in the manufacture and sale of pain, rheumatism and orthopedic drugs, a focus on a potentially growing sector that may have attracted Blackstone.

Its main product is *Calonal*, the leading prescription preparation of acetaminophen (paracetamol) in Japan for chronic pain and which came from Showa.

Otherwise, the line-up includes first-line therapies for rheumatoid arthritis and a biosimilar infliximab product launched in 2017, a sodium hyaluronate preparation for osteoarthritis, raloxifene and minodronic acid for osteoporosis, and biosimilar etanercept.

Although it releases no sales data, this specialty focus may have attracted Blackstone, given forecasts of Japan's aging population will drive increased demand for pain management products in conditions including arthritis, diabetic neuropathy and cancer - particularly for cost-effective products.

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From the editors of PharmAsia News.

To read this story in full please go to: **https://bit.ly/2U709EW**

Alios Buy Best Forgotten For Johnson & Johnson As RSV Failure Costs It Dear

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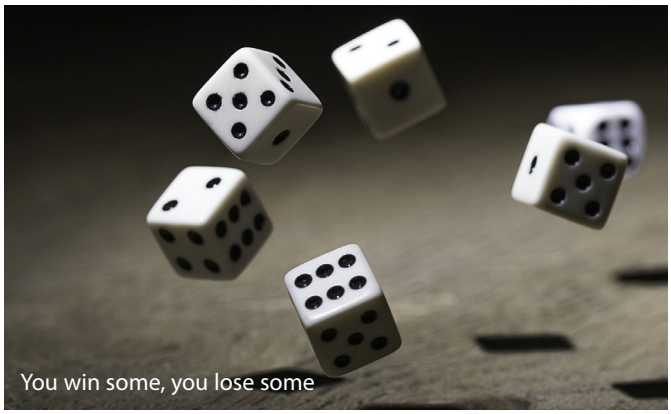
Johnson & Johnson has taken a further $700m impairment charge after the failure of its respiratory syncytial virus (RSV) asset AL-8176 (lumicitabine) which it obtained via its 2014 acquisition of **Alios BioPharma Inc.** for $1.75bn.



You win some, you lose some

The new charge, which represents the remaining intangible asset value related to AL-8176 and will be reflected in the company's first quarter 2019 financial results, follows a previous impairment charge of about $630m booked in its Q3 2018 accounts. That followed the suspension of the Phase IIb study, pending analysis of the data. The decision now to discontinue the product prompted the latest charge, as noted in an SEC filing dated March 21.

It all adds up to a bad bet by J&J on Alios. It bought the private biotech also in a large part for its hepatitis C nucleoside analog products, AL-516 and AL-335, but these fell victim to the profound changes in the hepatitis market that revolutionized treatment of that disease earlier this decade and have already been dropped.

Lumicitabine, an orally bioavailable nucleoside analog, was one of a number of products highlighted by J&J as part of its growth plan back in mid-2017.

Its failure also leaves a gap in the late-stage RSV treatment pipeline. Earlier this month, Novavax's RSV vaccine ResVax, its lead product, missed its endpoint in a first Phase III trial in infants; it is still in studies in other populations. All other products in development, both vaccines and drugs, are at Phase I or II, and vaccines make up the majority of these. J&J also has a small-molecule fusion inhibitor JNJ-8678 for the treatment of RSV infection in Phase I.

Current approved treatments include **AstraZeneca PLC**'s *Synagis* (palivizumab), a monoclonal antibody that targets the RSV F protein, and is used for prophylaxis against RSV disease in high-risk infants. AstraZeneca also markets *Respigam*, an immunoglobulin product for the prevention of RSV disease in children under 24 months with bronchopulmonary dysplasia or a history of prematurity.

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Good DREAMM-1 Data Keeps GSK On Track For Multiple Myeloma Filing This Year

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GlaxoSmithKline PLC confirmed plans to file its investigational anti-BCMA antibody-drug conjugate GSK2857916 with regulators by the end of this year, as further positive data from the DREAMM-1 study in relapsed/refractory multiple myeloma confirmed that nearly two thirds of patients responded to the drug after an extra year's follow-up.

Announcing updated data from the DREAMM-1 study, published in *Blood Cancer Journal*, GSK said "these new data confirm that 60% of patients receiving GSK2857916 achieved an overall response rate (ORR)."

"That ORR was identical to the rate previously reported in the interim analysis, after more than a year of follow-up, and demonstrates not only the potential efficacy of the medicine but the durability and depth of response," GSK said in a statement.

The number of patients achieving a complete response increased to 15% over the additional one-year follow-up period.

Relapsed/refractory multiple myeloma is a malignancy of antibody-producing plasma cells often characterized by anemia, hemorrhages, recurrent infections, and weakness.

Relapsed, or recurrent, multiple myeloma is the term for when cancer returns after treatment or after a period of remission. Since multiple myeloma does not have a cure, most patients will relapse at some point. Refractory multiple myeloma refers to when the cancer does not respond to therapy.

BCMA has become an exciting novel drug target in multiple myeloma, with a number of active programs in development.

GSK's '916 was awarded PRIME status by the European Medicines Agency (EMA) and breakthrough designation by the FDA in 2017. The UK drug maker hopes it can reach the market in mid-2020, based on results from the DREAMM-1 trial. Still, the therapy faces stiff competition in an increasingly crowed multiple myeloma market.

BB2121 VS GSK'S '916

Datamonitor Healthcare analyst Hardik Patel says **Celegene**'s chimeric antigen receptor T-cell (CAR-T) therapy bb2121 will pose the biggest challenge to GSK's candidate.

"While its difficult to compare across trials, especially trials with small patient pools, the available evidence seems to suggest that bb2121 may be more effective than GSK's '916," Patel told *Scrip*.

He noted that in a Phase I trial in relapsed/refractory multiple myeloma patients who had received at least three prior lines of therapy, treatment with bb2121 at active doses (≥150 x 10^6 CAR-T cells) led to an ORR of 95.5%, a complete response (CR) rate of 50%, and a median progression free survival (PFS) rate of 11.8 months.

"GSK2857916's DREAMM-1 study had a similar patient population, and while the median PFS was similar at 12 months, the ORR and CR rate shown by GSK2857916 of 60% and 15%, respectively was much lower than that shown by bb2121," Patel said.

> BCMA has become an exciting novel drug target in multiple myeloma, with a number of active programs in development.

"Also, the outcomes presented for GSK2857916 in patients who had received prior treatment with **Johnson & Johnson**'s *Darzalex* (daratumumab) were less impressive, showing median PFS of 7.9 months and an ORR of 38.5%," he said.

"In contrast, the majority of patients in the bb2121 trial had received prior treatment with Darzalex, and the results of that trial were still overwhelmingly positive," Patel aded.

This is an important distinction, as Darzalex has become a primary treatment option for multiple myeloma patients in the earlier lines of therapy, and the majority of patients in later lines of the treatment are likely to have received at least one regimen containing the drug.

The DREAMM-1 study is small. But GSK is waiting for further data from its DREAMM-2 trial in multiple myeloma patients who have already been treated with Darzalex, which is an anti-CD38 antibody,

One advantage that GSK2857916 does hold over bb2121 is that its antibody-drug conjugate approach will likely allow the drug to be priced much more cheaply than bb2121, which is a CAR-T cell therapy.

"Assuming both drugs successfully make it to market, and the efficacy demonstrated by each drug in these early-phase trials is replicated in subsequent studies, the uptake of each drug may depend on each stakeholder's opinion of their cost-to-benefit ratio," Patel said.

AND SELINEXOR

Another emerging therapy in the multiple myloma market is **Karyopharm Therapeutics Inc.**'s selective inhibitor of nuclear export (SINE) selinexor, which is also vying for a similar patient population as that studied in GSK2857916's pivotal DREAMM-2 trial, as well as bb2121's pivotal KarMMa trial.

"All are examining so-called 'triple class refractory' patients who have previously received a proteasome inhibitor, an immunomodulatory agent and an anti-

CD38 antibody, and have received at least three prior regimens," said Datamonitor Healthcare Michael Ramirez.

However, there is reason to doubt selinexor's competitive position against GSK2857916, as selinexor recently received an unfavorable reaction at its advisory committee meeting, where panelists voted to delay an approval decision until results from the Phase III BOSTON trial were released, which pushed a potential approval decision back to early 2020. The PDUFA date for selinexor has since shifted to July 6, as more existing data was submitted in an attempt to expedite approval, however. "Though the data for selinexor may not look as impressive as either GSK2857916 or bb2121 - it showed an ORR of 26.2%, median prior lines of therapy = 7 - if selinexor was to end up getting approved for the highly refractory population, pricing could be an important consideration," Ramirez told *Scrip*.

"As a small molecule inhibitor, selinexor could conceivably be priced even cheaper than GSK2857916.

"However, even if approved, one of the doubts the FDA has around selinexor is a fairly unfavorable safety profile. This may also come into consideration in the case that all three drugs are approved for the highly refractory setting," Ramirez said.

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Otsuka's Avanir Encouraged By First Peek At Treatment For Alzheimer's Agitation

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In a matter of days since patients with Alzheimer's disease suffered their latest blow from **Biogen Inc.** and **Eisai Co. Ltd.**'s decision to discontinue the Phase III clinical trials testing aducanumab in mild cognitive impairment, some brighter news is, potentially, around the corner. *(Also see "Why Biogen/Eisai's Aducanumab Failure Is Not The End Of Amyloid Hypothesis" - Scrip, 21 Mar, 2019.)*

Avanir Pharmaceuticals Inc., a California-based subsidiary of **Otsuka Pharmaceutical Co. Ltd.**, has announced "encouraging" results from the first of a pair of Phase III clinical trials investigating the efficacy of AVP-786 for the treatment of moderate-to-severe agitation in patients with Alzheimer's dementia.

The study, which used s sequential parallel comparison design (SPCD) demonstrated a significant improvement on the primary endpoint on the Cohen-Mansfield Agitation Inventory for one of the two doses being evaluated. The other dose demonstrated numerical but not significant improvement on the SPCD analysis. Similar improvements were also observed on the key secondary endpoint. SPCD is a trial design used in conditions which are subject to moderate-to-high rates of placebo response, such as addiction, pain or mental illness.

There are two more Phase III studies ongoing in the AVP-786 clinical development program, which use a conventional parallel-arm design, as opposed to the SPCD used in this first study.

While Avanir was guarded in details of the study, not providing details regarding which dose showed significant improvement (18 mg or 28 mg) for example, the limited study results are the farthest along in the clinic a company has successfully come in this setting.

Pamela Spicer, senior analyst on *Datamonitor Healthcare*'s CNS and Immunology and Inflammation team, commented that while it isn't unusual for a company to remain tight lipped about the doses of an investigational drug while the study is ongoing, the fact that Avanir had not divulged which dose demonstrated a significant response "raises an eyebrow to the possibility that it could have been the lower dose, which would make you question why the higher dose didn't work."

A glimmer of hope in a challenging indication

The 12-week study enrolled 410 US patients aged 50-90 with moderate-to-severe agitation and probable Alzheimer's dementia.

The most common adverse events in patients receiving AVP-786 versus placebo were falls, urinary tract infection, headache and diarrhea. Overall, mortality during the study was low and none of the deaths were considered related to treatment.

AVP-786 is a combination of deudextromethorphan (an uncompetitive NMDA receptor antagonist, sigma-1 receptor agonist and inhibitor of the serotonin (SERT) and norepinephrine (NET) transporters), and an ultra-low dose of quinidine.

AVP-786 is a next-generation formulation of Avanir's only approved product *Nuedexta* (dextromethorphan and quinidine) for pseudobulbar affect (PBA), a neurologic condition that can occur when there is damage to areas of the brain and may interrupt brain signalling resulting in sudden, frequent and involuntary episodes of exaggerated crying and/or laughing.

Incorporation of deuterium into the dextromethorphan molecule has been shown to reduce first-pass liver metabolism. By having a lower rate of metabolism, deudextromethorphan requires an ultra-low dose of quinidine (an inhibitor of the enzyme CYP 2D6) in the AVP-786 formulation.

POTENTIAL COMPETITORS

Avanir is not alone in developing a therapy of agitation in AD sufferers, an unmet medical need.

Parent company Otsuka and **Lundbeck Inc.** have studied schizophrenia drug *Rexulti* (brexpiprazole) in two Phase III trials in fixed and flexible dose but the results were not convincing, and they have now started a third Phase III trial after discussions with the FDA.

Axsome Therapeutics Inc. is trialling AXS-05 (bupropion plus dextromethorphan) in a Phase II/III study which is 40% enrolled, results are expected in 2020. **Tonix Pharmaceuticals Holding Corp.** is ready to start trials of a low dose of *Tonmya* (cyclobenzaprine hydrochloride) in pivotal Phase II trials. The drug was granted fast track designation from the FDA in July 2018.

Sanjay Dubé, Avanir's vice president of R&D and head of clinical development and scientific strategy, said: "Currently there is no FDA-approved treatment for agitation in patients with Alzheimer's dementia. Any advancement in the treatment and management of agitation in patients with Alzheimer's dementia would help to bridge the treatment gap in these patients."

According to Informa's R&D research engine *Biomedtracker*, AVP-786 is also being studied in Phase II trials in schizophrenia, neurobehavioral disinhibition in traumatic brain injury and psychiatric disorder. Trials have been suspended in major depressive disorder and neuropathic pain.

AVP ORIGINS

In February 2012, Avanir and **Concert Pharmaceuticals Inc.** entered into an exclusive license agreement that afforded Avanir worldwide rights to develop and commercialize Concert's deuterium-modified dextromethorphan (d-DM) for the potential treatment of neurological and psychiatric disorders. The agreement included the rights to multiple deuterium-modified dextromethorphan compounds, including AVP-786. *(Also see "Avanir gains rights to Concert's 'heavy' Nuedexta dextromethorphan" - Scrip, 1 Mar, 2012.)*

Under the terms of the agreement, Concert is eligible to receive an upfront payment and additional milestones upon achievement of certain predefined clinical, regulatory and commercial targets as well as tiered royalties on worldwide sales of products containing d-DM. Avanir has overall responsibility for research, development and commercialization of d-DM.

Approval of AVP-786 could provide a steady stream of royalties, $100m at peak, to Concert, according to analysts at JMP Securities. This would provide funding for development of Concert's pipeline of proprietary deuterated products, led by CTP-543 in alopecia areata.

In December 2014, Otsuka bought Avanir for $17.00 per share in cash, valuing Avanir at $3.5bn.

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Acadia, Neuren Headed To Phase III With Trofinetide In Rett Syndrome

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Partners **Acadia Pharmaceuticals Inc.** and **Neuren Pharmaceuticals Ltd.** have unveiled positive Phase II data for pediatric Rett syndrome patients that puts their molecule, trofinetide, on track for launch of a Phase III study later this year.

No drugs are approved to treat Rett, meaning patients are treated with more general therapies specific to one of the symptoms of their disease. However, data from an 82-patient Phase II study in female Rett syndrome patients ages 5-15 that are being published in the April 16 edition of *Neurology* – and were posted online on March 27 – show efficacy across three syndrome-specific measures for trofinetide.

A 27-patient cohort treated with a 200 mg/kg twice-daily dose of the drug – a novel synthetic analog of the amino terminal tripeptide of IGF-1 – met statistical significance compared to placebo on three out of five measures. Overall, while the 200 mg/kg dose did not hit the other two. The companies did give results for the 50 mg/kg and 100 mg/kg doses but they will not be taken forward in Rett syndrome.

The largest dose met statistical significance on the caregiver assessment Rett Syndrome Behavior Questionnaire (RSBQ; p=0.042) and on two clinician assessments – the Clinical Global Impression Scale-Improvement (CGI-I; p=0.029) and the RTT-Clinician Domain Specific Concerns Visual Analog Scale (RTT-DSC; p=0.025).

RSBQ and CGI-I will be used as the co-primary endpoints in a planned 180-patient Phase III study of Rett syndrome patients aged 5-20 scheduled to launch in the second half of 2019, after the sponsors complete manufacturing scale-up activities.

Australian firm Neuren previously showed efficacy with the candidate in adult Rett syndrome patients. It licensed North American development and commercial rights to trofinetide to San Diego-based Acadia in August, getting $10m up front and up to $455m in milestone payments. Trofinetide is thought to address Rett syndrome by reducing neuroinflammation and supporting synaptic function. In the current study, all three doses were generally safe and well tolerated, the companies said.

Study author Daniel Glaze, director of the Blue Bird Circle Rett Center at Texas Children's Hospital, said Rett patients and their families currently face a significant therapeutic burden both in terms of cost and the potential side effects of multiple therapies to treat the individual symptoms of the syndrome. These can include motor function deficits, cognitive issues and gastrointestinal (GI) problems. A therapy specifically addressing the core symptoms of Rett syndrome should provide significant benefit to patients and their families, he told *Scrip*. "These are individuals who lose the ability to utilize spoken language to communicate in an effective way, so if we can improve their communication abilities, if we

Trofinetide is thought to address Rett syndrome by reducing neuroinflammation and supporting synaptic function. In the current study, all three doses were generally safe and well tolerated, the companies said.

can improve their attention, it will be helpful to them," Glaze said. "In addition, it probably will have an effect on behavior as well as improving attention and cognitive function and motor function."

When Rett patients have seizures, generally they are given anti-epileptic medications, he noted, and special diets are used to address the disease's GI manifestations. "The standard of care is specific to the symptom," Glaze explained. "For example, many of the children and adult patients have a variety of GI problems, so we can address that, whether it be constipation, gastroesophageal reflux, nutritional problems, failure to gain weight. There are standards for treating those problems in general, but not Rett-specific standards."

He added that the study's significance is increased because efficacy was demonstrated on both clinician and caregiver assessments. That is why one of each was chosen for the Phase III program. "Having three different measures completed by two different groups of individuals with different experiences and backgrounds indicates that this is strong evidence that this will be an effective medication for Rett syndrome," Glaze said.

Biomedtracker lists four candidates in clinical development for Rett syndrome, although one – **BioElectron Technology Corp.**'s EPI-743 – has not reported data since 2014. Besides trofinetide, the others are **Newron Pharmaceuticals SPA**'s Phase I/II sarizotan, a serotonin 1A agonist, and **Biohaven Pharmaceutical Holding Co. Ltd.**'s Phase I BHV-5000, an NMDA receptor antagonist.

Glaze said trofinetide is the first Rett candidate to demonstrate both safety and efficacy in the clinic. Neuren retains rights to the drug outside North America; Acadia had an option to bid on those rights, but Neuren decided late in 2018 to hold onto them. The Australian firm also has completed a Phase II study with trofinetide in Fragile X syndrome. *Published online 27 March 2019*

Boost For Daiichi's Oncology Ambitions As AZ Agrees Huge $6.9bn Deal For Lead ADC Asset

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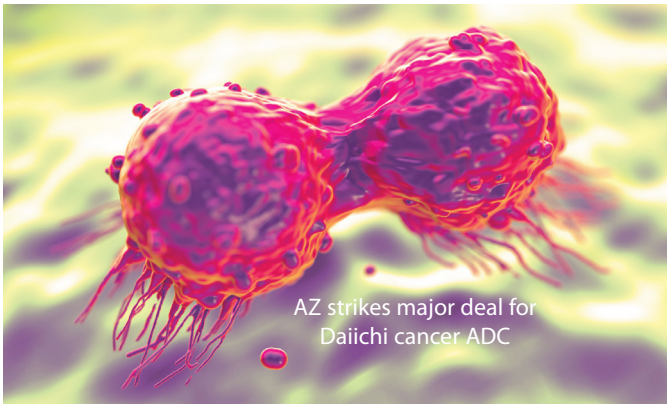
In what should provide a massive fillip to **Daiichi Sankyo Co. Ltd.**'s ambitions to build its worldwide presence in oncology, **AstraZeneca PLC** has picked up global rights to one of the Japanese firm's lead development assets in the sector.



The massive deal will see the UK-based multinational pay $1.35bn upfront (half on execution, the remainder 12 months later), and up to $6.90bn in total, for trastuzumab deruxtecan (DS-8201), an antibody-drug conjugate (ADC) now in multiple pivotal trials for breast and gastric cancer.

Daiichi Sankyo shares surged by 15.9% in morning trading in Tokyo on March 29 just after the deal was announced, reflecting what is likely to be a transformational moment for the company's international oncology aspirations.

The ADC, developed using proprietary technology, has potential as both monotherapy and combination therapy across a range of HER2-expressing malignancies, and is also being investigated for colorectal and non-small cell lung cancer.

This broad global potential and a desire to maximize development and access across this range of settings was the main driving force behind the decision to seek an alliance with AstraZeneca, according to Stuart Mackey, Daiichi Sankyo's global business development head.

"We have had interest from various third parties since the really encouraging data started coming out, and wanted to reach DS-8201's full scope and potential," he told *Scrip*.

"We made the decision to bring on a collaborator, and AstraZeneca can bring a wealth of global expertise to accelerate and expand use, and also has the commercial capability. They recognized the value [of DS-8201] and importantly share our vision for the drug."

The total non-upfront payouts will be dependent on future regulatory and other contingencies (totaling up to $3.8bn) and sales-related milestones (up to $1.75bn). Daiichi retains exclusive rights in Japan and will be responsible for all manufacturing and supply globally.

As part of the deal, the two companies will share equally global development and commercialization costs and profits (except in Japan), and Daiichi will book sales in the US and in certain European countries and other markets where it already has business affiliates.

Sales in other markets globally, including Russia, China, Australia and Canada, will be booked by AstraZeneca.

FIRST FILING THIS YEAR

Daiichi said that it plans to submit a biologics license application in the US in advanced/refractory HER2-positive metastatic breast cancer treated previously with ado trastuzumab emtansine (T-DM1; **Roche**'s *Kadcyla*) in the fiscal 2019 first half (ending Sept. 30).

In its statement on the deal, AstraZeneca said the first regulatory filing "is scheduled for the second half of 2019."

Speaking to *Scrip*, Daiichi Sankyo's global head of oncology R&D, Dr Antoine Yver, noted that Daiichi's previous indication was for a US BLA sometime in 2020. "This deal really reflects our focus on science as a company, and the very high quality of research that we have managed to perform" since initiating work in cancer just several years ago, he said.

Yver, himself a former global head of oncology R&D at AstraZeneca, has been spearheading the Japanese company's strategic pivot to oncology, and the new alliance represents a major validation of its efforts so far.

The shift comes amid the steady loss of exclusivity globally for former blockbuster olmesartan, an antihypertensive, and follows Daiichi's announcement that it was effectively putting back its key mid-term business targets.

The company is aiming for JPY500bn ($4.51bn) in oncology revenues in fiscal 2025, also helped by other pipeline assets such as the oral FLT3 inhibitor quizartinib, filed in the US last November for FLT3-ITD-positive relapsed/refractory acute myeloid leukemia.

As to whether the new deal signaled an emphasis on collaborations for Daiichi's oncology assets, Mackey told *Scrip* that "we have really been focused on DS-8201 so far and are really excited about the new deal. But it does now free up some focus on other assets, and if these show promise this may lead to case-by-case collaborations.

"We do not have a commercial presence in all markets, and we may look at specific or wider partnerships. But we may also consider independent development as well."

REGULATORY STATUS

The ADC combines trastuzumab, a humanized HER2-targeting antibody, with the deruxtecan topoisomerase I inhibitor payload, using a proprietary tetrapeptide-based linker. The targeted delivery inside malignant cells is designed to reduce systemic exposure and potential side-effects.

US Breakthrough Therapy Designation was granted in 2017 for HER2-positive, locally advanced or metastatic breast cancer patients treated with trastuzumab and pertuzumab (Roche's *Perjeta*) with disease progression after trastuzumab emtansine.

The therapy also has US Fast Track Designation for HER2-positive unresectable and/or metastatic breast cancer in patients progressing after prior treatment with HER2-targeted medicines, including trastuzumab emtansine.

In Japan, "sakigake" (pioneering therapy) status - which enables accelerated review and approval - has been granted for HER2-positive advanced gastric or gastroesophageal junction cancer.

In a statement on the deal, AstraZeneca CEO Pascal Soriot said that the therapy "could become a transformative new medicine" in breast and gastric cancers, and also "has the potential to redefine breast cancer treatment as the first therapy for HER2 low-expressing tumors."

For the UK company, the deal is seen as aligning with its science-led oncology strategy, one main pillar of which is the pursuit of ADC approaches.

PROMISING CLINICAL DATA

Clinical data so far for DS-8201 have been positive, showing good activity across several tumor types, with strong overall response rate and durability of response in HER2-positive breast cancer previously treated with Kadcyla.

In preliminary results reported in mid-2017 from a subgroup analysis of a dose-expansion arm in a Phase I trial in HER2+ patients with metastatic breast cancer who had been pretreated with Kadcyla and Perjeta, the overall response rate was 46.7%, with a 100% disease control rate. Five pivotal studies are underway, including three Phase III programs in HER2-positive breast cancer: DESTINY-Breast04 in previously treated HER2 low-expressing metastatic disease versus investigator's choice; DESTINY-Breast03 in metastatic disease versus trastuzumab emtansine; and DESTINY-Breast02 versus investigator's choice in post-trastuzumab emtansine.

In addition, there are two other ongoing pivotal Phase II trials: DESTINY-Breast01 in metastatic breast cancer resistant or refractory to trastuzumab emtansine; and for HER2-positive advanced gastric cancer resistant/refractory to trastuzumab (DESTINY-Gastric01).

Other Phase II studies are underway in HER2+ advanced colorectal cancer and metastatic non-squamous HER-overexpressing or HER2-mutated non-small cell lung cancer. At an earlier stage, the ADC is in Phase in combination with nivolumab for HER2-expressing metastatic and bladder cancer.

AstraZeneca said it expects the transaction to be neutral to core earnings in 2019, with growing core earnings per share accretion from 2020 and "a significant contribution" in 2023.

However, it will run a new equity placement of around $3.5bn to raise additional funds for the upfront and near-term milestone components, and more than half of this will be used to financially support the Daiichi Sankyo deal.

This will be accounted for as an intangible asset acquisition, and there will be no impact on existing 2019 guidance as published in mid-February.

Daiichi Sankyo expects no impact on its results for the current year ending this March 31, as the upfront portion will be booked over the period in which it has contractual performance obligations under the collaboration.

In a brief note on the deal, Morgan Stanley Japan analyst Shinichiro Muraoka described it as a "major positive" with significant financial benefits for Daiichi Sankyo.

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From the editors of PharmAsia News.

Lilly Opens Its Wallet For Early Immunology Tie-Up With ImmuNext

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Eli Lilly & Co. is bolstering its immunology portfolio through a deal with established pharma partner **ImmuNext Inc.** that pivots around a preclinical novel target the companies believe could lead to new treatments for autoimmune diseases by regulating immune cell metabolism.

Target validation studies have revealed the target operates independently and upstream of known immune checkpoint regulators, which brings an opportunity for the treatment of indications with limited options.

Lilly will pay ImmuNext $40m up front, with scope for a further $565m in development and commercialization milestones, as well as tiered royalties ranging from the mid-single to low-double digits on product sales. There will be no change to Lilly's 2019 earnings per share guidance as a result of the transaction.

ImmuNext will grant Lilly an exclusive, worldwide license to develop and commercialize the novel immunometabolism target. In addition, Lilly and ImmuNext will establish a three-year research collaboration to support the target's development.

Jay Rothstein, chief scientific officer at ImmuNext, said that the deal with Lilly would "bring forward a first-in-pathway antibody that specifically targets the metabolism of lymphocytes to reprogram rather than suppress the immune system."

EARLY PHASE PROMISES

Lilly is making good on its promises to look for deals that involve higher-risk early-stage molecules and new modalities. At Lilly's investor briefing in December 2018, chief scientific officer Dan Skovronsky told of the new appetite for preclinical and early phase assets.

"You'll see us engaging more and more on some of these target space deals," Skovronsky said. "That's new for us, but the goal is to have more first-in-class medicines, and that's the way we're going to do it."

The company has eight Phase I immunology assets in development, two in Phase II (baricitinb for alopecia areata and mirikizumab for Crohn's disease). In Phase III it is studying its JAK1/JAK2 inhibitor baricitinib for atopic dermatitis and systemic lupus erythematosus, its IL-17 ixekizumab for non-radiographic axial spondyloarthritis, and IL-23 antibody mirikizumab for psoriasis.

> "Immunology is an important area of research for Lilly, and we seek novel targets that could develop into new medicines for patients suffering with autoimmune diseases."

"Immunology is an important area of research for Lilly, and we seek novel targets that could develop into new medicines for patients suffering with autoimmune diseases," said Ajay Nirula, vice president of immunology at Lilly. "Regulating the metabolism of immune cells is a promising approach to treating these diseases, and we look forward to working with ImmuNext to advance their immunometabolism target."

INDUSTRY INTEREST

New Hampshire-based ImmuNext has become a staple discovery partner for the industry. Its anti-CD40L antibody was licensed by **Sanofi** in January 2017 for potential development in lupus and multiple sclerosis. It is thought the deal could earn ImmuNext up to $500m in milestones alongside tiered royalties if the antibody reaches the market.

In 2016, it inked a $400m deal with **Roche** that granted the Swiss major an exclusive license to develop and commercialize therapeutics that agonize the V-region immunoglobulin-containing suppressor of T-cell activation (VISTA) signalling pathway. VISTA is a negative checkpoint regulator.

And in 2012, it signed a $150m agreement with **Janssen Biotech Inc.** that focused on the development of novel therapeutics that modulate the immune system for the treatment of cancer.

Investors have also been looking with interest at the immunometabolism space for new and interesting companies developing therapies based on this approach.

In October 2018, **Sitryx Therapeutics**, a start-up backed by **GlaxoSmithKline PLC** among others, completed series A funding of $30m, and launched with six early-stage projects to target immunometabolic pathways with small-molecule candidates.

In April 2018, **Rheos Medicines Inc.** was launched with $30m in series A funding from venture capital firm Third Rock Ventures. The company wants to concurrently identify new targets and biomarkers, thus enabling a precision medicine approach for treating immune-mediated disorders. It has two preclinical programs: the first targets the CD4 T cell for treating inflammatory bowel disease, lupus and psoriasis; and the second targets CD8 as a potential treatment for autoimmune thyroiditis, immuno-oncology indications and vitiligo.

Lilly has paid to play catch up with the rest of industry in immuno-oncology. At the beginning of the year it spent $8bn on **Loxo Oncology Inc.**, paying $235 per share in cash, a premium of 68% to the latter's closing stock price on Jan. 4. And eight months previous to that, its $1.6bn buy of **Armo BioSciences Inc.** brought the company its most advanced IO asset – the pegylated Interleukin-10 (IL-10) known as pegilodecakin, a next-generation IO drug that may work well alone and in combination with first-generation immunotherapies.

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Allergan Acquiesces To Activist Appaloosa With CEO-Chairman Role Split, But Not Yet

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Allergan PLC finally gave in to activist investor Appaloosa LP's demand that the pharma's CEO and chairman roles be separated, but the decision to give those roles to two different people won't go into effect until current CEO and Chairman Brent Saunders leaves the company.

Allergan announced the decision on March 22 as it filed proxy materials with the US Securities and Exchange Commission (SEC) in support of matters subject to vote at a May 1 shareholder meeting, including a proposal by Appaloosa to immediately split the CEO and chairman roles. Appaloosa responded on March 25 with its own presentation pointing to Allergan's clinical and commercial setbacks in recent years – and the resulting stock price decline – as justification for immediately putting in place an independent chair of the company's board of directors.

Credit Suisse analyst Vamil Divan questioned in a March 25 note "if investors who have been frustrated with the team and the stock's performance will be satisfied with [the delayed separation of the chairman and CEO roles] as an outcome."

Considering Allergan's stock performance, it doesn't appear that Appaloosa is the only investor who disagreed with the company's decision to enact the CEO and chairman job separation upon the next leadership transition.

Its stock fell 2% to close at $146.34 on March 25 – less than half of Allergan's five-year high of $331.15 back in July 2015, when it agreed to sell its legacy generics business to **Teva Pharmaceutical Industries Ltd.** for $40.5bn. *(Also see "Teva to buy Allergan Generics; Mylan off the hook but Perrigo still wriggling" - Scrip, 27 Jul, 2015.)*

The company's stock also traded at that level as it announced its $560m acquisition of **Naurex Inc.**, but that deal recently went bust after the failure of the lead Naurex-originated drug candidate rapastinel in multiple Phase III depression studies. *(Also see "Allergan paying $560m for Naurex; stays quiet on rumored generics sale to Teva" - Scrip, 27 Jul, 2015.)*

Allergan's current stock price is 38.3% below where it closed two year ago and 8.2% below its year-ago level after various questionable strategic decisions, research and development setbacks, and commercial challenges.

ALLERGAN: NOW IS NOT THE TIME FOR LEADERSHIP CHANGE

Even so, the company argued in the proxy materials filed with the SEC after the market closed on March 22 that now is not the time to take Saunders out of the chairman seat. Allergan urged shareholders to vote against Appaloosa's proposal for an immediate separation of the CEO and chairman roles, and an appointment of an outsider to the chairman seat who has pharma industry leadership experience.

An instantaneous change in the company's chairman "is an extremely disruptive manner in which to implement the separation of chairman and CEO and its also unnecessary in light of the board's adoption of an independent chairman policy, the strength of the company's board of directors and the company's overall strong governance position," Allergan argued.

The company adds in its proxy statement that separating the top leadership roles right now "could undermine Mr. Saunders' ability to lead and create an unnecessary crisis of confidence" as he and the rest of Allergan's leadership execute the new corporate strategy outlined last year.

The new strategy adopted in July calls for the company to focus on its medical aesthetics, central nervous system (CNS), ophthalmology and gastroenterology franchises while selling off its anti-infective and women's health businesses. *(Also see "No Fire Sale: Allergan May Sell Women's Health, Infectious Disease Units" - Scrip, 30 May, 2018.)* However, Allergan said when it reported fourth quarter and full-year 2018 earnings that while it was nearing a deal to sell its anti-infective products, it will hold on to its women's health assets. *(Also see "Allergan Thinks It's Ready To Withstand Restasis Generics" - Scrip, 29 Jan, 2019.)*

NEARLY YEAR-LONG BATTLE OVER LEADERSHIP

Appaloosa said in a statement about Allergan's decision to split the CEO and chairman roles when the company begins its next leadership transition that it and other new board-level changes "are no more than a meaningless series of gestures intended to preserve the current system of lax oversight and further entrench management."

The investment firm has been fighting for change at the top since April 2018 and hasn't backed down despite various board changes.

Allergan previously appointed Christopher Coughlin as lead independent director as a means of providing leadership and oversight by someone outside of the company's executive team.

"The board firmly believes that at the present time a combined chairman/CEO role coupled with a robust lead independent director role is the best structure to position the company for success as it executes its strategy to create a more focused, world-class biopharmaceutical business and develop its promising product pipeline," Coughlin wrote in a letter to shareholders included in the March 22 proxy statement.

"We heard during our engagement with our shareholders that many are supportive of the current combined chairman and CEO position with strong independent directors and robust board governance policies," he continued. "The board also heard from many of our shareholders during our engagement that they would value a policy requiring an independent chairman that the board could phase in with the next CEO transition. Accordingly, the Board has adopted a policy providing that the chairman of the board shall be an independent director, phased in with the next chief executive officer transition."

Along with the future splitting up of the chairman and CEO positions, Allergan also said in its March 22 disclosures that

the lead independent director role has been "enhanced" in response to shareholder input. In addition, the company's board of directors has now formed a mergers and acquisitions committee that is chaired by Bob Hugin, the former chairman and CEO of **Celgene Corp.**, who was appointed to the board in February.

Allergan also is down to 11 board directors, instead of 12, with the retirement of Catherine Klema. Her role as chair of the Compensation Committee will be filled by board member Thomas Freyman.

APPALOOSA COMMITTED TO LEADERSHIP SEPARATION FIGHT

Despite the concessions that the company has now made to its governance, Appaloosa is undeterred in its mission to shake up Allergan's leadership by taking the chairmanship of its board away from Saunders.

The investment firm noted in its March 25 statement that it is not the only shareholder unhappy with the company's direction – especially the direction of its stock price – noting that "the status quo is unacceptable and disruptive measures are necessary." Appaloosa said the company must fix what's broken or consider a sale or merger with an entity that can turn Allergan around.

The investor's presentation to shareholders notes management's "series of ill-considered initiatives and self-inflicted wounds," which include a failed attempt to shift ownership of patents for the dry eye drug *Restasis* (cyclosporine) to a Native American tribe in an effort to stave off generic competitors. *(Also see "Allergan May Rue Mohawk Tribe Deal As Court Invalidates Restasis Patents" - Scrip, 16 Oct, 2017.)*

Allergan's research and development setbacks as well as commercial disappointments have hit the company's stock especially hard, since Restasis generics are expected to impact the drug's blockbuster sales significantly this year. "There is no sign of a turnaround," Appaloosa asserted.

The investment firm noted that Allergan has written off $13.4bn worth of investments in acquisitions and R&D since the first quarter of 2015, including a $1.6bn write-off in the fourth quarter of last year related to the $1.9bn acquisition of **Kythera Biopharmaceuticals Inc.** in 2015 to access the double-chin reducer *Kythera* (deoxycholic acid). Kythera sales totaled just $38.1m in 2018.

Dermatologists have told *Scrip* that Kybella is a tough sell in their medical aesthetics practices, since the drug causes swelling before patients see its effects and it takes multiple treatments for satisfactory chin fat reduction. *(Also see "Medical Aesthetics: Sales Rise For Popular Products, But Unmet Needs Remain" - Scrip, 12 Sep, 2018.)*

Appaloosa pointed out in its shareholder presentation that while Allergan's stock performance is among the worst in its big pharma peer group, Saunders' compensation is among the highest of the CEOs of major drug companies. Saunders earned $58.5m in total compensation between 2015 and 2017 – $21.6m in 2015, $4.1m in 2016 and $32.8m in 2017 – putting his salary fourth-highest out of 14 companies, the investment firm pointed out.

Saunders' total compensation for 2018, upon shareholder approval at the meeting on May 1, is $6.6m. That includes $1.3m in base salary, $2.1m in stock awards and $3m in incentive plan compensation. The latter is based on 2018 company performance and is less than half of the $6.2m that the CEO could've earned under his compensation package.

Given mounting pressure from investors related to the company's performance, it remains to be seen how much longer Saunders will helm the company.

"In the face of overwhelming evidence that the current strategy is failing, how could the board NOT insist on increased oversight of Allergan management?" Appaloosa argued in its shareholder presentation, noting that Saunders has threatened to resign as CEO if shareholders vote him out as chairman.

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Adios To Alcon In April As Novartis Confirms Spin-Off Date

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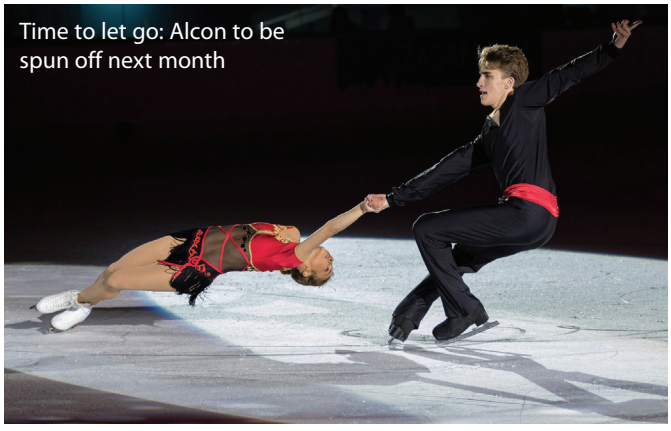
Novartis AG has confirmed April 9 as the date when it will spin off the ophthalmology unit **Alcon Inc.** and continue the Swiss giant's push to be a pure pharma-focused company.

Slightly ahead of some analyst predictions, shares in the eye-care business will start trading on Swiss market and the New York Stock Exchange next month, now that the necessary approvals have been obtained. The move will see each Novartis stockholder receive one Alcon share for every five shares or American depositary receipts they hold at the close of business on April 8.

Alcon has secured debt financing of $3.5bn and its credit rating has been confirmed as 'investment grade' by Moody's Investor Service and S&P Global in line with its medtech peer group. Novartis has splashed out recently to boost Alcon's growth pros-



Time to let go: Alcon to be spun off next month

pects and earlier this week, the $285m acquisition of **PowerVision Inc.**, which makes fluid-based lenses for cataract surgery patients, was announced.

Novartis has invested a lot in Alcon since splurging $52bn to buy it from **Nestle SA** back in 2011 but the group's fit within the parent company has proved problematic and the two main sub-divisions of surgical and vision care have struggled to grow. It was only from the second half of 2017, following heavy investment by its parent, that the Alcon business began its turnaround but Novartis is leaving the latter in pretty good condition.

In a recent investor note, analysts at Jefferies wrote that their "back of the envelope" valuation for Alcon on spinning off from Novartis, while way off the original purchase price, is $21-23bn. They expect to see "incremental buying of Alcon shares by some funds seeking to build a 'full size position', offset by others not wanting to own a non-pharma eye-care company, but also new investors keen on the Alcon story and ocular health sector, plus event-driven funds for the turnaround story."

The divestiture is key to CEO Vas Narasimhan's strategy of reshaping Novartis as an innovative research-based pharma company powered by digital technology. This means that there is no place for Alcon's surgical devices and contact lenses but Novartis has made it clear that it is not looking to exit ophthalmology but refocus its investments in that space.

Much of that focus is on brolucizumab, a humanized single-chain antibody fragment which Novartis is confident it can challenge **Bayer AG** and **Regeneron Pharmaceuticals Inc.**'s *Eylea* (aflibercept) as a leading treatment in tackling age-related macular degeneration. Two-year data was presented late last year which reaffirmed non-inferiority versus Eylea and superior reductions in retinal fluid, an important marker of disease activity in patients with neovascular AMD.

Earlier this year, head of pharmaceuticals Paul Hudson told *Scrip* that the company has used a priority review voucher to file brolucizumab "and we fully anticipate a launch in 2019." The drug, which is also being tested for diabetic macular edema, is likely to benefit from a less frequent dosing regimen to Eylea.

Novartis' older eye drug *Lucentis* (ranibizumab), which is also approved for AMD and a number of other indications, continues to sell well, with fourth quarter sales of the blockbuster jumping 7% to $520m. It also has high hopes for *Luxturna* (voretigene neparvovec), a one-time gene therapy for the rare eye disease biallelic RPE65 mutation-associated retinal dystrophy licensed from **Spark Therapeutics Inc.**; the latter is in the process of being acquired by **Roche** for $4.8bn.

Before brolucizumab, the next couple of months of 2019 are expected to see the launch of two other key innovative therapies from Novartis. The first is likely to be *Mayzent* (siponimod), a follow-up to the firm's blockbuster multiple sclerosis therapy *Gilenya* (fingolimod), which the company has said is the only drug proven to delay progression in patients with secondary progressive MS. Shortly after, the FDA is expected to give the green light to *Zolgensma*, Novartis's eagerly anticipated gene therapy for spinal muscular atrophy.

With this focus on innovation, observers are mulling over the possibility of Sandoz following Alcon out of Novartis. CEO Richard Francis will step down from the position at the end of this month, having said that he cannot commit to the "multi-year journey" that will see "a significant transformation" of Sandoz, while Narasimhan has stated that the next year and a half will see Sandoz become an autonomous unit within Novartis to enable it to compete in an increasingly challenging generics environment."

In their note, Jefferies analysts stated that "once Sandoz is transformed into a more autonomous unit over the next 18 months, we would not be surprised if that too may be spun-off, leaving an innovative pharma company."

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Shionogi Stays The Course As It Lays Out R&D Priorities

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While **Shionogi & Co. Ltd.** fell one short of its goal of progressing three drug candidates in fiscal 2018 (ending March 2019), the mid-sized Japanese pharma company is still hoping to take its launch tally globally to at least 10 compounds (including those out-licensed) by the end of the fiscal 2017-20 period.

"Our challenge for 2019 will be to focus on high-priority projects, and maximize the value of in-licensed projects," president and CEO Dr Isao Teshirogi told a recent R&D briefing.

The company said it intends to continue to pursue external collaborations as part of its approach to accessing relevant assets and expertise, and in the fiscal year starting this April is looking to gain several approvals. In a note on the R&D update, Morgan Stanley Japan analysts said the briefing "confirmed steady progress on key projects."

Among the key assets for which launches are planned in fiscal 2019 is the injectable cephalosporin cefiderocol for multidrug-resistant Gram-negative bacterial infections (in US and EU). The US PDUFA goal is mid-August, for the specific indication of complicated urinary tract infections, including pyelonephritis.

In the HIV sector, where Shionogi's assets are licensed to the **ViiV Healthcare** joint venture, Teshirogi said potential FY19 launches include a combination of dolutegravir and lamivudine as the first two-drug regimen for treatment-naïve HIV patients, and cabotegravir plus rilpivirine as the first long-acting (monthly or bimonthly) injection for HIV.

Studies with this last regimen from the ATLAS and FLAIR trials met their primary endpoints of similar efficacy to the comparator group, along with a significantly greater increase in treatment satisfaction and preference versus previous oral therapy, the CEO noted.

There was also a low confirmed virologic failure rate (1%) across both treatment arms.

In Japan, approvals expected in the fiscal year about to start should include two in attention-deficit hyperactivity disorder

(ADHD): the alpha 2a agonist Intuniv (guanfacine; licensed from **Shire PLC/Takeda Pharmaceutical Co. Ltd.**) for the additional indication of adult ADHD, and the norepinephrine and dopamine reuptake inhibitor lisdexamfetamine for pediatric ADHD.

FIVE KEY PROJECTS

Executives told the briefing that Shionogi will focus on five high-priority, clinical development stage projects this fiscal year. The earliest of these is S-004992, an oral inhibitor of mycolic acid synthesis still at the pre-Phase I stage for tuberculosis.

Further advanced is S-600918, a once-daily, oral P2X3 receptor antagonist for neuropathic pain and refractory chronic cough (RCC), now being prepared for a global Phase II dose-finding study in the RCC setting.

The P2X3 receptors involved in the cough reflex are expressed in the peripheral nervous system and are associated with the cough reflex. "There are no approved drugs for RCC, for which the long-term use of centrally-acting antitussives is not recommended and CNS side-effects are observed," development division senior vide-president Dr Toshinobu Iwasaki told the meeting.

The company estimates the number of RCC sufferers in the US alone at around six million, and the placebo-controlled proof of concept study will enroll around 30 patients.

Some analysts have noted that the drug may be associated with milder taste disturbance than **Merck & Co. Inc.**'s (twice-daily) gefapixant (MK-7264), a same-class molecule now in Phase III for RCC.

Shionogi disclosed at the meeting that S-637880, a molecule of undisclosed modality, is set to enter a global Phase II trial for neuropathic pain in fiscal 2019.

As for the remaining key projects, the GABA-A receptor positive allosteric modulator S-812217 (licensed from **Sage Therapeutics Inc.**) for major depressive disorder should move into Phase III in Japan sometime in FY19, adding to the ongoing US program in this indication and a completed US study in postpartum depression.

Japan currently has around five million depression patients, making this the largest non-fatal disease population in the country, Iwasaki noted. The debilitating disorder results in an aggregate of around 40 million days' absence from work annually, with related productivity losses estimated at JPY40bn ($361m).

S-770108, an inhaled formulation of the anti-fibrotic pirfenidone, is set to enter a UK trial to evaluate lung penetration in idiopathic pulmonary fibrosis patients. The hope is that the new route of delivery could reduce systemic exposure and dose-escalation side-effects associated with current oral formulations, while also improving compliance.

The intention is to file for approval based on a single Phase II/III study, and Shionogi is designing a commercial inhaler with external partners that will be effective even in patients with lowered lung capacity.

OTHER HIGHLIGHTS

Otherwise, executives stressed at the briefing that the company's general intention is to expand peptide drug research, invest to acquire new technologies and pursue imaging biomarker research to improve clinical success.

Shionogi's strategic focus on infectious diseases and CNS disorders will continued unchanged, and the company intends to acquire novel drug targets though open innovation initiatives, and continue to build on its structure-activity relationship expertise as an engine for discovery in the small molecule space.

Dr Takeshi Shiota, senior vice president of the Pharmaceutical Research Division, told the R&D briefing that the company will seek various indications and formulations in Japan for BPN14770 (with **Tetra Discovery Partners LLC**).

The preclinical, PDED-targeting negative allosteric modulator, which improves neuronal plasticity in Alzheimer's models, is being positioned for improvement of cognitive and memory deficits, potentially including Alzheimer's and Parkinson's, depression and brain injury. The non-alcoholic steatohepatitis (NASH) candidate S-723595 (also preclinical), a repurposed idiopathic pulmonary fibrosis drug, has a "unique mechanism" in the indication to decrease muscle ectopic fat and improve insulin resistance, the latter being a problem in many NASH patients.

"The molecule could be a strong partner for other NASH development compounds," Shiota told the meeting

XOFLUZA ACTIVITY

The flu drug *Xofluza* (baloxavir marboxil), which is already on the market in Japan and the US, is seen as a key mid-term growth driver, although Shionogi did note the emergence in trials of I38 mutation flu A variants with less susceptibility to the novel antiviral.

The company said it will monitor the situation closely, and is investigating a possible combination with an (unidentified) oral neuraminidase inhibitor in a trial in severely ill and hospitalized patients. Early studies show a decreased risk of emergence of i38 variants for the combo in this setting.

In other activity around the drug, a US sNDA has been completed in the high-risk flu patient indication, based in a study showing a significant reduction in time to symptom improvement in influenza B patients compared with oseltamivir (**Roche**'s *Tamiflu*), with a lower incidence of related complications.

Approval is expected in Japan in FY19 of a granule formulation for children under 20kg, and also planned is a Japan NDA for prophylaxis use.

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From the editors of PharmAsia News.

Basaglar Saved Medicaid Millions, Highlighting Benefits Of Competition, JAMA Analysis Shows

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The launch of **Eli Lilly & Co.**'s long-acting insulin glargine copy *Basaglar* saved the US Medicaid system $72.9m in less than two years, according to an analysis published online in the *Journal of the American Medical Association* (JAMA) March 25.

The analysis by Inmaculada Hernandez, University of Pittsburgh School of Pharmacy, et al. sought to explore how competition impacted reimbursement and market share in the long-acting insulin category and how the use of copycat Basaglar over the branded product, **Sanofi**'s *Lantus*, resulted in savings. *(See table.)*

"New product entry was associated with a halt in increases in reimbursement levels for incumbent products," the researchers determined. "The first biosimilar insulin had a large uptake and was associated with modest reductions in insulin expenditures for Medicaid." High insulin prices have been getting a lot of attention amid the public outcry over the high cost of medicines. Drug makers, including Lilly, argue that they are offering higher rebates that offset list price increases.

Nonetheless, many insulins are older medicines that have lost patent protection, but still don't face biosimilar competition. In addition to Basaglar, Lilly also markets a portfolio of branded short-acting insulins, including insulin lispro products *Humalog* and *Humulin*.

Basaglar was approved by FDA in December 2015 as a new drug, not an official biosimilar, because of FDA's classification for insulins, which are considered complex small molecules, but are in the midst of being reclassified as biologics. Basaglar is nonetheless the first and only follow-on version of Sanofi's Lantus on the market in the US. It launched in December 2016 after Lilly worked out a patent settlement agreement with Sanofi.

Around the same time, several other branded long-acting insulins also entered the marketing, including Sanofi's next-generation insulin glargine *Toujeo*, Novo Nordisk's next-generation *Tresiba* (insulin degludec) and a combination of insulin glargine and lixisenatide from Sanofi called *Soliqua*.

Through 2014, long-acting insulin prices grew substantially, partly because there were only two products on the market, Lantus and Novo Nordisk's *Levemir* (insulin determir). Insulin prices increased by 320% from 2001 to 2014, according to the JAMA analysis. Lantus dominated the Medicaid market, with 80% of international units (IU) reimbursed for long-acting insulins, while Levemir accounted for the

Changes In Spending Associated With Use Of Basaglar Instead Of Lantus In Medicaid (a)

	NO. OF ML (100 IU REIMBURSED)			MEAN AMOUNT REIMBURSED PER ML (100 IU) AFTER MINIMUM STATUTORY REBATES, $(B)			SAVINGS FROM BIOSIMILAR USE (C)	
Quarter	**Lantus**	**Basaglar**	**% Of mL (100 IU) Basaglar**	**Lantus**	**Basaglar**	**Spending If 100% Brand-Name Use, $**	**$**	**%**
Q4 2016	15,388,234	1,062	0	18.90	16.37	290,854,469	2,688	0.0
Q1 2017	14,854,227	528,227	3	18.89	16.31	290,533,522	1,359,898	0.5
Q2 2017	13,160,463	2,708,533	17	19.01	16.29	301,641,334	7,349,793	2.4
Q3 2017	10,782,516	4,297,872	28	19.01	16.29	286,682,620	11,711,823	4.1
Q4 2017	8,924,676	5,656,298	39	19.31	16.33	281,555,989	16,873,763	6.0
Q1 2018	8,635,776	6,526,285	43	19.28	16.60	292,340,602	17,489,712	6.0
Q2 2018	6,993,888	5,593,548	44	19.97	16.72	251,333,434	18,140,025	7.2
Total, Q4 2016 To Q2 2018						**1,704,087,501**	**72,925,015**	**4.3**

(a) Lantus is insulin glargine and Basaglar is the "biosimilar" for insulin glargine.

(b) Under the Medicaid Drug Rebate Program, innovator products are subject to a minimum statutory rebate of 23.1% of average manufacturer price. In analyses, the 23.1% rebate base was applied to the mean reimbursement amount per milliliter (100 international units [IU]) before rebates, which was the estimate available in the data. Because Basaglar was approved through a new drug application, it is treated as an innovator drug by Medicaid and therefore subject to the 23.1% rebate rate. These estimates do not account for additional rebates due to price increases above inflation or other supplemental rebates negotiated between manufacturers and Medicaid.

(c) Number of milliliters (100IU) reimbursed for Basaglar x (postrebate mean amount reimbursed for Lantus minus postrebate mean amount reimbursed for Basaglar).

Source: JAMA Network

other 20%. The market share for the two drugs declined, however, after the entry of new products, with Lantus falling to 42% of IU reimbursed and Levemir falling to 14% in the first quarter 2018.

By the first quarter of 2018, the market share for Basaglar was 34% of all IU for long-acting insulins reimbursed and 44% of all IU for insulin glargine. Newer branded insulins like Toujeo and Tresiba each took about 5% of the market, while Soliqua had an insignificant market share impact.

Basaglar, though it does not carry regulatory designation as a biosimilar, has had success gaining traction in the US market, whereas some more traditional biosimilar launches have not. *(Also see "Lilly/BI's Basaglar: A Rosier Outlook For US Biosimilars?" - Scrip, 31 Jan, 2018.)* Basaglar generated $801.2m in 2018, Lilly reported, making it one of the company's more successful recent launches behind products like the diabetes drug *Trulicity* (dulaglutide) and *Taltz* (ixekizumab) for psoriasis and psoriatic arthritis.

Reimbursement rates for Lantus and insulin detemir increased in parallel in 2006-2014 by an average of 13% annually, but stabilized after the new products entered the market. Reimbursement rates for Basaglar have been 15%-16% lower than the rates for Lantus since it launched, without accounting for inflationary or supplemental rebates. Thus, the authors calculated that Basaglar saved Medicaid $72.9m from December 2016 through second quarter 2018, about 4.4% of Medicaid spending on insulin glargine 100 IU/ML.

The analysis relied on state Medicaid drug utilization data and managed care reimbursement records for long-acting insulins from 2005 through second quarter 2018. For each product and quarter, the authors calculated the mean amount reimbursed per 100 IU and the market share, defined as the proportion of all long-acting IU reimbursed for the particular product.

Savings associated with Basaglar were estimated by multiplying the number of milliliters (100 IU) reimbursed for Basaglar each quarter by the lower reimbursement rate of Basaglar versus Lantus. Because Basaglar was approved as a new drug, it receives the base rebate of 23.1% under Medicaid. No additional supplemental rebates were counted, as the information is proprietary.

As Hernandez et. al point out, Medicaid savings from Basaglar could be lower if Sanofi offered larger supplemental rebates for Lantus than Lilly did for Basaglar. The authors also acknowledged that it is not possible to determine whether the slowing price increases for incumbent products was a result of Basaglar specifically or related to the approval of several branded competitors.

"Nonetheless, these findings suggest that increased competition in the long-acting insulin market was associated with lower per milliliter reimbursements in Medicaid, lending support to policies that expedite biosimilar approval and market entry," the authors concluded.

Savings could be even greater if biosimilars were to become interchangeable in the future and automatically substituted at the pharmacy.

Interestingly, despite the commercial success of Basaglar and the savings to the US health care system, Merck announced last year it will not commercialize its own version of insulin glargine, even though it was already tentatively approved by FDA in 2017. *Published online 22 March 2019*

Signs Of Change? Lilly, Merck, Janssen Report Slowing List Price Growth In 2018

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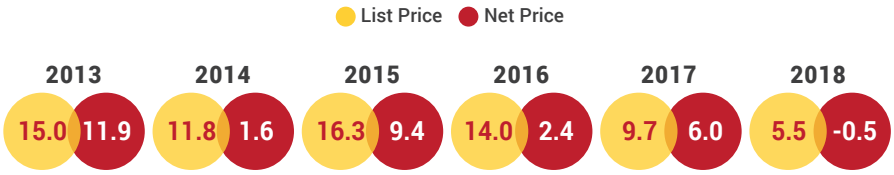
In response to ongoing pressure from the public and policymakers, three big pharmas scaled back average list price increases across their US drug portfolios in 2018, according to recently released data.

Eli Lilly & Co., **Merck & Co. Inc.** and **Janssen Pharmaceutical Cos.** are all reporting that list prices rose in the mid-single digit range in 2018, continuing the slowdown seen in recent years.

The change in Lilly's pricing seems particularly noteworthy. List prices across the company's US products rose 5.5% in 2018 compared with an increase of 9.7% the year before, according to Lilly's Integrated Summary Report, released March 24.

The company does not break out price changes for specific products, but the report indicates that a slowdown in insulin prices was a factor. The last list price increase for Lilly's *Humalog* or *Humulin* insulins was in May 2017, a spokesperson said.

Comparison Of Lilly List And Net Price Changes For U.S. Product Portfolio
(% Change Versus The Prior Year)



The company has argued that burgeoning rebate demands have fueled its list price increases, particularly for insulins. Between 2014 and 2018, the average list price for Humalog U100 rose 51.9%, but its average net price declined by 8.1%, the report says.

Nevertheless, criticism over insulin list price increases from the Administration and Congress has continued to build.

As a result, and in addition to suspending price increases for its insulins last year, Lilly also recently announced it would effectively lower Humalog's price 50% by introducing an authorized generic for the product at a much cheaper price.

TURN TO PAGE 23

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

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

PIPELINE WATCH, 22–27 MARCH 2019

Event Stage	Lead Company/Partner	Drug Name	Indication	Comments	Change To LOA (%)	LOA (%)
Phase III Published Results	Intercept Pharmaceuticals, Inc.	Ocaliva (obeticholic acid)	Primary Biliary Cholangitis	POISE; The Lancet Gastroenterology & Hepatology, March 25, 2019	0	100
Phase III Published Results	Novartis AG	Mekinist (trametinib)/Tafinlar (dabrafenib)	Melanoma	COMBI-AD; The Lancet, March 27, 2019	0	100
Phase III Published Results	AstraZeneca PLC	Faslodex (fulvestrant)/anastrozole	Breast Cancer, Metastatic	S0226; NEJM, March 28, 2019	0	100
Phase III Updated Results	Strongbridge Biopharma plc	Recorlev (levoketoconazole)	Cushing's Syndrome	SONICS; Encouraging Results	0	62
Phase III Updated Results	Novo Nordisk A/S	semaglutide, oral	Diabetes Mellitus, Type II	PIONEER 3 (vs. sitagliptin); Superior Effects	0	99
Phase III Updated Results	Ascendis Pharma A/S	TransCon growth hormone	Short Stature	heiGHt; Superior Efficacy	0	68
Phase III Updated Results	BioLineRx Ltd.	BL-8040	Bone Marrow Transplant	GENESIS (w/G-CSF); Improved Cell Mobilization	0	35
Phase III Updated Results	Boehringer Ingelheim/Lilly	Jardiance (empagliflozin)	Diabetes Mellitus, Type II	EMPRISE Vs DPP-4 Inhibitors; Real-World Study Positive	0	100
Phase IIb/III Updated Results	CytoDyn, Inc.	leronlimab	HIV/AIDS	Sustained Benefits	0	91
Phase III Suspension	Proteon Therapeutics, Inc	vonapanitase	End-Stage Renal Disease	PATENCY-2; Missed Co-Primary Endpoints	-62	0
Phase III Top-Line Results	Nippon Shinyaku/Pharmacosmos	Monofer (iron isomaltoside)	Iron-Deficiency Anemia	Potential Benefits Vs ferric carboxymaltose	0	63
Phase III Top-Line Results	Aimmune Therapeutics, Inc.	AR101	Peanut Allergy	ARTEMIS; Induced Tolerance	0	99
Phase III Top-Line Results	Otsuka Holdings Co., Ltd.	AVP-786	Agitation In Alzheimer's Disease	TRIAD-1; Encouraging Results	0	52

Source: Biomedtracker | Informa, 2019

CONTINUED FROM PAGE 21

Slower growth in Lilly's average list prices contributed to a decline (0.5%) in net prices for the first time in five years. Average net prices as a percent of list prices have fallen from 59% in 2014 to 46% in 2018, as price concessions grew, the report notes.

JANSSEN NET PRICES FELL 6.8% IN 2018

Janssen's US list price increases slowed from 8.1% in 2017 to 6.3% in 2018, Johnson & Johnson Executive VP and Worldwide Chairman, Pharmaceuticals Jennifer Taubert told the Senate Finance Committee in written testimony submitted for a Feb. 26 hearing.

Average net prices dropped 6.8%, Taubert reported. That followed a 4.6% net price decline the previous year. "For the second year in a row, discounts and rebate outweighed [list price increases], and aggregate net price – in other words, the real price – decreased," she pointed out.

Taubert appeared with several other big pharma executives at the highly anticipated hearing on drug pricing. She previewed the company's US price transparency report in her testimony; the official report will be released later this week. During 2018, Janssen gave up approximately $21bn in discounts and rebates, representing a 47% concession rate, Taubert said. Discounts and rebates totaled approximately $15bn., or 42%, in 2017.

Merck's US list prices were up an average of 5.5% in 2018 after increasing by 6.6% in 2017, according to the company's recently released 2018 Pricing Transparency Report. Unlike Lilly and Janssen, Merck recorded an increase in net prices (2.99%). The trend line in the company's net prices have bounced around in recent years based on changes in product mix and generic competition. For example, net prices declined 1.9% in 2017, after growing by 5.5% annually in 2015 and 2016.

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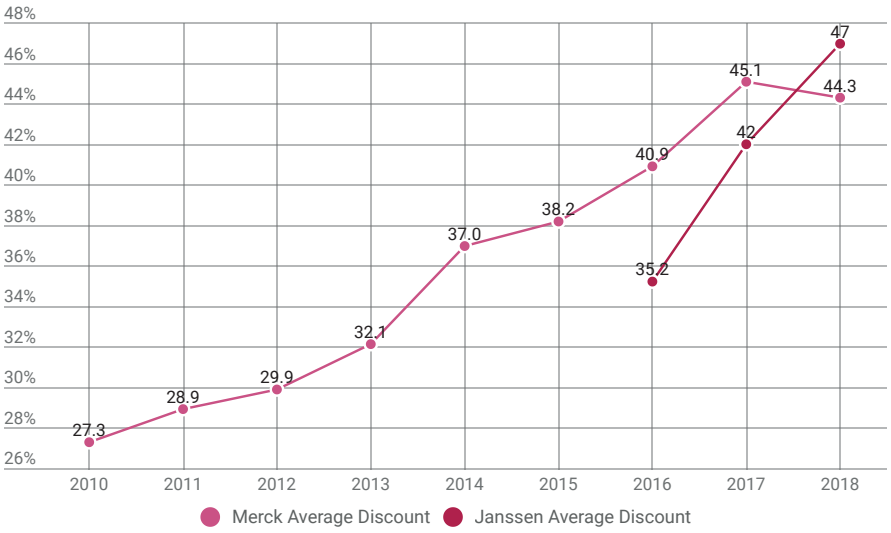
Janssen Discount Rate Passes Merck's



Note: Data from annual price transparency reports. Janssen information only available for past three years.

APPOINTMENTS

Executive	To Company	New Role	From Company	Previous Role	Effective Date
Eyal C. Attar	Aprea AB	Chief Medical Officer and Senior Vice President	Agios Pharmaceuticals	Senior Medical Director and IDH Hematology Medical Lead	25-Mar-19
Shreeram Aradhye	Axcella Health Inc	Chief Development Officer and Executive Vice President	Novartis Pharmaceuticals	Chief Medical Officer (CMO) and Global Head, Medical Affairs	25-Mar-19
Frank D. Lee	FORMA Therapeutics	Chief Executive Officer	Genentech	Senior Vice President, Global Product Strategy and Therapeutic Area	27-Mar-19
Willem H. Scheele	Imara Inc	Chief Medical Officer	Pfizer	Executive Director, Clinician Group Lead, Rare Diseases	27-Mar-19
John A. Bardi	Intra-Cellular Therapies Inc	Senior Vice President, Market Access, Policy and Government Affairs	Otsuka America Pharmaceuticals	Vice President, Market Access, Policy Advocacy, and Government Affairs	26-Mar-19
Joanne Jenkins Lager	iTeos Therapeutics SA	Chief Medical Officer	Sanofi	Vice President, Head, Global Oncology Development	1-Apr-19
Greg Whitehead	Rubius Therapeutics Inc	Chief Quality Officer and Senior Vice President	bluebird bio Inc	Vice President, Quality	25-Mar-19

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

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