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Pfizer Dashes Hopes For A PCSK9 Pill

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Pfizer has decided not to move forward with an oral PCSK9 blocker in early clinical development because the efficacy wouldn't stand up to injectable rivals.

Pfizer Inc. has decided not to move forward with the development of an oral PCSK9 inhibitor for the treatment of high cholesterol, president-worldwide R&D Mikael Dolsten revealed during the company's second quarter earnings call Aug. 2.

"We don't think the profile will be competitive," Dolsten said, pointing to the strong efficacy seen in Phase III clinical studies of the injectable PCSK9 blockers. Two injectable PCSK9 inhibitors are already on the market, Amgen Inc.'s *Repatha* (evo-

locumab) and Sanofi/Regeneron Pharmaceuticals Inc.'s *Praluent* (alirocumab), while Pfizer has one in late-stage development called bococizumab.

An oral pill would have had an interesting competitive position versus the injectable products, though its development was years off and the market dynamics for the PCSK9 blockers that have launched has so far been challenging, driven largely by payer pushback on price. The injectables cost roughly \$14,000 a year.

Pfizer is focusing on development of bococizumab, and is investing significantly in the program. The company is running six Phase III studies testing the drug's lipid lowering ability, including two cardiovascular outcomes

trials that Pfizer has been running in parallel. In June, Pfizer reported data from two studies, SPIRE-HR (high-risk) and SPIRE-FH (familial hypercholesterolemia), which both met their primary endpoint, demonstrating reductions in the percent change from baseline in LDL-C at 12 weeks versus placebo.

Bococizumab will be behind its rivals if and when it reaches the market, but Pfizer had been hoping to have cardiovascular outcomes data in hand around the same time as the competition, which would have helped to even the playing field. The company is running two cardiovascular outcomes studies, SPIRE-1 and SPIRE-2, which is testing the drug in high-risk patients. During the quarterly call, Pfizer said it expects to have cardiovascular outcomes data in the second half of 2017. Meanwhile, Amgen and Sanofi/Regeneron have moved up their timelines for reporting data. They both expect they could have data available before the end of 2016.

Pfizer may be scrapping the oral pill, but it still could wind up with different administration for its injectable. The firm is partnered with Halozyme Therapeutics Inc. on the company's ENHANZE technology platform for bococizumab, a drug delivery technology that can allow some biologics to be dosed subcutaneously. Halozyme announced in February that a Phase I trial has enrolled testing bococizumab with ENHANZE.

Pfizer has not revealed much information about the early stage oral program. During an interview at the J.P. Morgan Healthcare conference in 2015, Dolsten spoke enthusiastically about the opportunity and said it was based on "intriguing science" and that the drug lowered cholesterol substantially in animal studies. ▶

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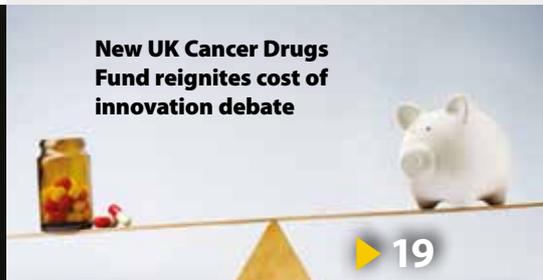
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from the editor

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Takeda's plans to transfer hundreds of R&D staff to an as-yet unnamed external company may offer some consolation to people set to lose their jobs at the Japanese major (see page 6).

Nevertheless, in the longer run it may prove to be more convenient for Takeda than for its divested workers. Externalizing R&D to CROs helps reduce big pharma's staff overheads and institutional inefficiency. Companies can also mitigate the immediate negative publicity around large-scale redundancy programs by pointing out that they are taking action to protect the interests of their workforce in finding new posts for them.

Merck Serono did it when it announced that at least 100 of 500 laid-off workers would get job offers from CRO partner Quintiles in 2013, while in 2014 GSK did it when it transferred 450 staff in Research Triangle Park to Parexel. However, affected employees face greater uncertainties. Less than a year after the Parexel transfer, a sizeable portion of those GSK workers lost their jobs once again. Sometimes the pharma company is just lobbing a ticking time bomb out of its own yard.



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Exelixis' Cabometyx Signals Changing Of Guard In Kidney Cancer

One of a trio of new drugs shaking up the kidney cancer market, Cabometyx (cabozantinib) does better than expected in its first nine weeks on the US market.

<http://bit.ly/2b5EpUB>

CHA, Sorrento JV Highlights Korean I-O Appetite

Sorrento and CHA Biotech's agreement to form a CAR-NK cell therapy joint venture is very much "on trend," being the latest in a recent series of immuno-oncology collaborations between Korean and foreign firms.

<http://bit.ly/2aJDkgJ>

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Does CheckMate 226 Take Bristol Out Of The End Game?

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Failure of Bristol-Myers Squibb's Opdivo in patients with lower expression of PD-L1 biomarker gives Merck & Co's Keytruda a huge advantage in first-line lung cancer, and leaves market-leading Bristol to wait for combination data.

Bristol-Myers Squibb Co. has enjoyed a long run as the golden child of immuno-oncology but the US pharma appears to have lost its shot at the biggest segment of all.

The firm's Aug. 5 announcement that its PD-1 inhibitor *Opdivo* missed the primary progression-free-survival endpoint in the much-anticipated CheckMate 026 study in first-line lung cancer prompted a dive that had the company closing down 15.99% and competitors up. Analysts reactions labeled it a "clear disappointment and overall surprise," the "worst case scenario" and "possibly the biggest surprise of my career."

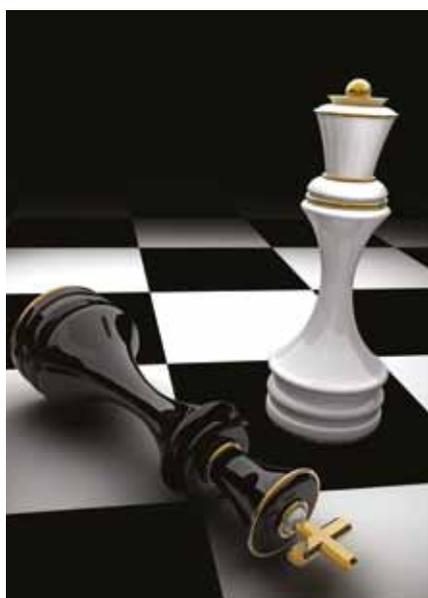
Opdivo (nivolumab) so far has been a spectacular success. Since its first approval in metastatic melanoma in December 2014, it has racked up other approvals in second-line squamous non-small cell lung cancer, non-squamous NSCLC, second-line renal cell carcinoma and classical Hodgkin lymphoma.

Bristol reported *Opdivo* held an 80% share of the PD-1 market and was the firm's top-seller during the second quarter, with \$840m in sales. It was thought to have an unassailable lead over Merck & Co. Inc.'s competing PD-1 inhibitor *Keytruda* (pembrolizumab), which trailed with \$314m in sales, most of which derived from melanoma.

Lung cancer is the largest market for the cancer immunotherapies, and Bristol has built its strong lead over Merck in the second-line setting in part because *Keytruda* was hampered by a requirement for PD-L1 expression testing. Bristol's approval is for all-comers.

The biggest prize, however, is first-line NSCLC, where PD-L1 expression testing is expected to be more the norm.

That's been Merck's big chance to capture market share, and it's been pushing hard to be first to market. It seemed to be in its grasp when it was the first to report data from a first-line lung cancer trial; in July, it revealed that *Keytruda* had improved PFS and



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also overall survival in the first-line KEYNOTE 024 study.

With the failure in the CheckMate 026, Merck seems to have a lock on that particular end game. It should swiftly get the first FDA approval for first-line lung cancer, and it also should soon get FDA approval to lower the threshold for PD-L1 expression for the second-line approval to just 1% or greater.

Merck said it has "begun to work with regulatory agencies to enable supplementary filing of these data to our existing *Keytruda* labels," the firm reiterated in a statement on Aug. 5.

Merck has already been touting that having the infrastructure in place for PD-L1 testing could give it an edge on the first-line market.

Pembrolizumab and nivolumab are very similar and have been viewed as the same by leading clinicians to date, but the companies have different development strategies, particularly for NSCLC. Bristol has used different cut-off levels for PD-L1 expression than Merck. In second-line trials, that strategy served Bristol well, as it gained labeling for all-comers regardless of PD-L1 expression. But in trying for the same result in the first-line setting, it may have reached too far.

A LOOK AT THE MARKET

Morningstar analyst Damien Conover has estimated that the market for PD-1/L1 inhibitors will be worth \$33bn in 2023, of which

\$20bn would derive from lung cancer.

The patient mix for the lung cancer market now is roughly 50/50 between first-line and second/third-line therapy, though Conover noted in an interview days before the CheckMate 026 news that it was unclear how that would change after immunotherapies started being used in the first-line. He suspected that patients would take a different I-O drug if they fail first line I-O treatment.

Bernstein analyst Tim Anderson expects to see in the next five years about \$1bn in lost *Opdivo* sales, about a 15% drop in EPS for Bristol, and a \$1bn gain in *Keytruda* sales – a 6% jump in EPS for Merck.

Consensus estimates put the first-line NSCLC market at around \$12bn, with *Opdivo* expected to take the lion's share and reach \$12bn across all indications by 2021, "with perhaps \$7-8bn of that coming from 1L NSCLC," Evercore ISI analyst Mark Schoenebaum said. "All told, perhaps \$4-4.5bn will be lost from the BMY model!" He sees about \$4bn of that going to Merck, which should have the market to itself until combinations come along in two or three years.

Bristol has taken a beating in trading. Its shares closed down 15.99%, with Merck up 10.41% and fellow immuno-oncology competitors AstraZeneca PLC up 1.32% and Roche up 1.87%.

WHAT'S THE NEXT MOVE?

There are no immediate clues about what happened in the CheckMate 026 trial – though the difference in the PD-L1 expression cut points used in Bristol's trial and Merck's Keynote 024 trial might be behind the failure. While Bristol has clarified that there did not appear to be enrollment anomalies or imbalances in the arms, and the chemo arm performed as expected, "we will be eagerly anticipating more details of the trial data in order to tell what exactly went wrong," Schoenebaum said in his Aug. 5 note to investors. ▶

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<http://bit.ly/2bb8luo>

Merck, Allergan Suggested As Suitors But Biogen's Attractiveness Questioned

Biogen's share price has risen on speculation that it is an acquisition target for Merck & Co. and Allergan Inc. But with a number of uncertainties hanging over the company, can Biogen negotiate a premium price?

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Biogen Inc's share price rose as much as 10% on Aug. 1, giving it a market cap of \$72.3bn, on media reports that the company had drawn takeover interest from Merck & Co. Inc. and Allergan Inc.

CEO George Scangos announced his resignation during Biogen's second quarter sales and earnings call on July 21, heightening uncertainty around the company's future prospects after a turbulent year and raising speculation that Biogen might be acquired.

Datamonitor Healthcare has forecast Biogen's top line to grow at a modest compound annual growth rate of 1.2% out to 2025, with headwinds affecting its lucrative multiple sclerosis franchise.

Analysts, however, have mixed opinions on whether the sale of Biogen is in the best interests of Biogen or potential acquirers. "We've been skeptical about Biogen as a target as the base business does not offer substantial growth and a positive ROI (return on investment) is going to be largely dependent on the success of aducanumab in Alzheimer's disease and would therefore be a big bet on the amyloid hypothesis," said Baird Equity Research analysts.

'CEO George Scangos' imminent departure is certainly consistent with the company mounting a temporary 'For Sale' sign to acquirers'

Alzheimer's drug aducanumab, a beta-amyloid antibody, is in Phase III testing after Biogen moved aggressively into advanced studies following positive Phase Ib data, but betting on success in Alzheimer's has historically only led to disappointment.

"We question the possibility of a premium valuation given current *Tecfidera* IP (intellectual property) risk, declining MS (multiple sclerosis) market share ahead of a substantial competitive launch and revenue growth gap, and the risk tied to the Alzheimer's program," added the Baird analysts.

Biogen's *Tecfidera* patent, which provides exclusivity to 2028, is currently being challenged. The product provides almost one third of Biogen's revenues (\$3.6bn in 2015 sales). If the patent is overturned, Biogen will be reliant on a patent that expires in 2020, with potential Hatch-Waxman exclusivity to 2023-2024 in the US. "Of course Merck doesn't really concern itself with IP risk and has been willing in the past to completely ignore binary patent decisions," noted Baird.

Leerink analysts believe a potential acquisition of Biogen by Merck or Allergan "certainly makes sense."

Biogen is attractive for several reasons, they believe. "It offers the perfect portfolio for an acquirer – a large, highly profitable current

franchise to diversify its revenue base, a solid cash flow stream from a partnered asset with Roche [ocrelizumab] that could be sold or securitized to finance part of the purchase, [and] an exciting late stage asset in nusinersen."

Biogen decided to exercise its option on antisense candidate nusinersen following positive Phase III data from Ionis Pharmaceuticals' (formerly ISIS Pharmaceuticals) ENDEAR study.

Leerink are also looking on the positive side of the risky Alzheimer's program, calling it "one of the most exciting long-term opportunities in the industry" although with the caveat "albeit with considerable risk and years to pay-off."

Leerink and Baird also view the recent news of Biogen's CEO upcoming departure through different lenses. According to Leerink, "The unusual announcement of the imminent departure of CEO George Scangos is certainly consistent with the company mounting a temporary 'For Sale' sign to acquirers."

Baird analysts, however, argue that "as the CEO, Scangos would likely push to stay in the event of a near-term takeover." They note that others have argued that his leaving, "coupled with announcement of the hemophilia spinoff, and general restructuring efforts" are an attempt to package Biogen up for sale.

Credit Suisse analysts, meanwhile, have been weighing up who might have the most to gain by a merger with Biogen.

"From a financial perspective, Allergan would likely benefit from greater synergies in SG&A given the two companies overlap in neurology, while Merck would likely be able to generate more R&D synergies given their much broader R&D infrastructure. Allergan has the lower tax rate while Biogen's higher margins would make more of an impact on Merck than Allergan."

Credit Suisse would be "surprised if either company actually completes this deal" but sees more strategic rationale from an Allergan perspective given the joint presence Allergan and Biogen have in the neurology space.

Datamonitor Healthcare's PharmaVitae M&A Builder suggests a portfolio overlap of 12.2% for Allergan and Biogen chiefly in CNS and immunology and inflammation therapies. This compares to 8.9% for Merck as the suitor in sales predominantly for CNS and oncology therapies.

Lead analyst Ali Al-Bazergan believes less overlap is just one reason Biogen is a better fit with Merck: a merger could make the companies a force to be reckoned with in the CNS space. "In terms of pipeline, there's an obvious overlap in the central nervous system therapy area, with Merck and Biogen combined boasting nine unique drugs in development. Merck has a shared focus with Biogen in Alzheimer's disease with its lead BACE inhibitor MK-8931, which complements Biogen's adacanamab targeting amyloid-beta," he said. ▶

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A Split Won't 'Make Or Break' Pfizer, CEO Read Says

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Pfizer's chief executive assured investors there is no expiration date on optionality, suggesting the company could always reconsider splitting up the business even if decides against such action this year.

Pfizer Inc. CEO Ian Read wasn't giving away any clues during the company's second quarter sales and earnings call Aug. 2 on which way the big pharma is leaning on the issue of breaking up the business, but he did remind investors there is a possibility that it won't happen – and that such a decision wouldn't necessarily be a bad development for Pfizer.

"This is not a make or break decision for the company," Read assured investors. "I don't view there being a wrong answer here. The decision will be taken straight through the context of the best path forward for shareholders."

Investors are anxious for Pfizer to make a decision on breaking up the company, something management has been considering since 2011, with a decision promised to investors by the end of the year.

Nothing has changed in regards to the timeline. Read said the company is still on track to make a decision by the end of 2016, with the process being focused on determining if there is trapped value in the combined business and if the two separate businesses could operate more efficiently apart.

The company operates two distinct businesses: Innovative Health (previously Innovative Products), and Essential Health (previously Established Products), cash-generating mature products. But Read suggested that even if Pfizer decides against a break up now, that doesn't prohibit the company from reconsidering in the future.

"I don't think that optionality necessarily has an expiration date," Read said. "We continually look at our capital allocation, we continue to look at what is in the best interest of Pfizer, which businesses perform the best in Pfizer. ... We will set up the infrastructure to be able to look at this question at any point in the future."

A decision against a split could lead to some volatility in the stock, as many investors have been advocating for a division. More

recently, however, some analysts have been predicting that a Pfizer break up looks less likely, questioning the trapped value to be unlocked and given that the company's growth prospects have improved.

Read pointed out that a break up wouldn't improve the company's tax situation in the near-term, something that has been a key initiative for the chief executive.

"A separation doesn't, under current laws, facilitate a speedy ability to change the domiciles of either of the companies under the separation rules," he said. Both companies would be held to the standard of the combined company for three years post separation, he added. "I don't see a separation as being a quick route to improving the tax situation."

Pfizer turned in a steady second quarter performance. The company reported sales of \$13.15bn in the second quarter, up 11% driven by an additional \$1.14bn in revenues coming from the acquisition of Hospira Inc. Excluding Hospira, Pfizer's sales would have grown 1% to \$12bn, the firm reported. Net income declined 23% to \$2.02bn. ▶

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GSK, Google To Invest £540m In Bioelectronics JV

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GlaxoSmithKline plc is teaming up with the company formerly known as Google Life Sciences to create bioelectronic therapeutics, and hopes to have a product ready for market within seven years.

GlaxoSmithKline PLC is setting up a new company with Verily Life Sciences LLC (formerly Google Life Sciences) called Galvani Bioelectronics. Galvani, which will be 55% owned by GSK and 45% by Verily, will work to develop and commercialize bioelectronic medicines.

Moncef Slaoui (currently GSK's vaccines chief but the former head of R&D), will chair the board of the new company. "Many of the processes of the human body are controlled by electrical signals firing between the nervous system and the body's organs, which may become distorted in many chronic diseases," said Slaoui in a statement.

"Bioelectronic medicine's vision is to employ the latest advances in biology and technology to interpret this electrical conversation and to correct the irregular patterns found in disease states, using miniaturized devices attached to individual nerves. If successful, this approach offers the potential for a new therapeutic modality alongside traditional medicines and vaccines."

UK HQ

Galvani will be headquartered within GSK's global R&D center at Stevenage in the UK, with a second site at Verily's facilities in South San Francisco. It will initially employ around 30 researchers. The parent companies plan to invest £540m over the next seven years in the joint venture and contribute existing IP. The news comes a week after GSK said it was making £275m of new investments at three of its manufacturing sites in the UK.

GSK has been active in the field of bioelectronics since 2012. Kris Famm, head of its bioelectronics R&D, has been appointed president of the new company. "Neuromodulation has been around for decades and that is part of the strength of this collaboration" he told *Scrip*.

"Through the work GSK has done over the past few years we have seen a lot of potential in a range of diseases from metabolic, cardiovascular, immune-inflammatory, respiratory, and so on. The key to addressing those diseases successfully is to get close to the peripheral nerve and place small low power electronic devices there," Famm explained. ▶

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Refocus, Optimize, Externalize: Takeda Overhauls Global R&D

As it reported solid underlying growth in the fiscal first quarter, Takeda has unveiled a detailed implementation program for its stated strategic intent to refocus global R&D effort on selected disease areas, in a major overhaul that will make much wider use of external partners and affect "significant" numbers of people across the company.

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Under a sweeping new blueprint to refocus, optimize, and externalize its worldwide R&D activities, Takeda Pharmaceutical Co. Ltd. is to simplify its current network of internal sites, transfer an as yet unspecified but "significant" number of employees to new external partners, and fundamentally transform ways of working as it pursues improved focus, efficiency and appropriate capability in its operations.

As has already been indicated by the Japanese firm, it will reduce and concentrate its R&D presence on three core therapeutic growth areas – oncology, gastroenterology, and CNS, plus vaccines – with related activities to be geographically concentrated at its major Shonan site in Japan plus in the US, mainly in Boston but also at a smaller San Diego site. This simpler structure will be complemented by major regional centers in Deerfield, Osaka, and Zurich, and also smaller, leaner sites in London, Russia, China, Singapore, and Brazil.

"Our R&D organization now is greatly fragmented" and one important goal is simplification "to free up resources so we can do more work with partners externally," new chief medical and scientific officer Dr. Andy Plump told a session at Takeda's first quarter results briefing in Tokyo.

He conceded the changes will involve a reduction in Takeda's in-house workforce and that "it will be significant. There are a lot of people that will be affected...but we are not ready at this point to talk about a number, due to ongoing discussions with employees" and other stakeholders, he said. The company noted that the figures could also fluctuate "depending on the progress of implementing these programs and the transformation," although Plump did note that key regulatory interface staff would be retained in-house.

RATIONALE, SITE STRUCTURE

The fundamental restructuring is designed "to build a world-leading R&D organization and pipeline" and sustainable, long-term future growth, president and CEO Christophe Weber said in a statement. Other strategic aims are "to drive innovation, enhance partnerships, and improve R&D productivity," while increasing efficiency and putting the right capabilities in the right areas.

In general, the goal is to have "less capacity internally [for R&D] than what we need...and to use external capacity to deal with fluctuations" in a flexible way on top of that, according to actual pipeline requirements at any given time, Plump explained.

The narrowing of therapeutic focus also means that "we have made the decision...that specialty cardiovascular...will no longer be a strategic area for us, as we felt we didn't have the pipeline and resources," he said. Existing activities and staff in the field will be divested and transferred to an external partner, with which discussions are now at "an advanced stage."

More broadly, the intention is to shift a lot of R&D work now done

internally to an already selected – but as yet undisclosed – major external collaborator, Plump said. "We are in advanced discussions with a strategic development partner that will take on the vast majority of development work...that will be unlike any partnership formed between contract research organizations and pharma companies. Through this, we will have the opportunity to transition hundreds of our employees, preserving jobs."

The alliance will be truly global, including Japan, and encompass end-to-end trial management, but will also provide enough flexibility to work with other partners where necessary, he added.

MAIN RESEARCH SITES

Under the overhaul – which Plump preferred to characterize not as a cost-cutting measure but rather an attempt to rebuild Takeda's R&D organization – there will be three main internal R&D sites globally:

- **Shonan (Japan)** – a new research park will focus on CNS and regenerative medicine and also develop open innovation centers, along with pharmaceutical sciences functions relocated from Juso in Japan;
- **Boston (US)** – this East Coast site will act as a development center with a focus on oncology, GI, immunomodulation, biologics, and translational research, and be a center for external innovation;
- **San Diego (US)** – this West Coast site will specialize in supporting technologies for GI and CNS, and support research capabilities in pharmaceutical sciences.

In addition, development activities will be consolidated in Osaka (rather than Tokyo), while pharmaceutical sciences activities at sites in London, Juso, Singen (Germany) and Deerfield (US) will be halted.

The one-time implementation costs of the R&D overhaul will total around JPY75bn (\$733m) but are expected to lead to recurring annual cost savings of around JPY18bn, which will be reinvested back into the pipeline.

Q1 PERFORMANCE

The fundamental R&D shakeup somewhat overshadowed Takeda's results for the fiscal first quarter, when underlying group revenues grew 9%, although the reported figure slipped 3% to JPY434.0bn, affected by currency effects and the divestment of a mature product portfolio in Japan.

Underlying core earnings jumped 40%, falling 8% reported to JPY77.1bn, while reported operating profit was JPY152.9bn, more than triple the JPY49.6bn in the same period last year. Net profit attributable to shareholders surged to JPY99.5bn from JPY24.6bn, in both cases helped by a payment for the transfer of selected older products to the Teva Takeda Yakuhin Ltd. joint venture in Japan. ▶

From the editors of PharmAsia News.

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Biogen Snaps Up Ionis' Antisense Treatment

Shares in Carlsbad, CA-based Ionis Pharmaceuticals Inc. (formerly ISIS Pharmaceuticals) shot up by more than 30% to close at \$38.01 on Aug. 1 when it announced the initial data from its ENDEAR study of the antisense candidate nusinersen plus a \$75m license fee payment from Biogen Inc., which will now assume responsibility for the drug's development. Biogen's shares also received a 4% boost. A pre-specified interim analysis has shown that babies with infantile-onset (consistent with Type 1) spinal muscular atrophy receiving nusinersen experienced a significant improvement in achieving motor milestones compared with those who did not, with what the companies described as an acceptable safety profile. Biogen plans to start regulatory filings in the coming months.

alex.shimmings@informa.com, 2 August 2016

Lupin Buys Shionogi Brands

Lupin Ltd., India's third largest drug firm by sales, said on Aug. 2 that its Japanese arm Kyowa Pharmaceutical Industry Co. Ltd. is acquiring 21 long-listed products (off-patent branded medicines) from Shionogi & Co. Ltd. for JPY15.4bn (\$150m). The acquired products include sleep inducing drug Rhythmy, anxiolytic Resmit, psychoneurotic agent Novamin, antidepressant Surmontil, gastritis and gastric ulcer treatment Ulgut and oral hypoglycemic agent Dimelin. The transfer of marketing and manufacturing rights for the acquired products is effective Dec. 1, 2016. The Japanese market has witnessed similar deals involving long-listed products recently. One example would be Sun Pharmaceutical that earlier this year acquired a basket of 14 established prescription brands from Novartis AG's local subsidiary for \$293m; the products had combined annual revenues of around \$160m.

anju.ghangurde@informa.com, 2 August 2016

Novo Nordisk Cuts Forecast

US payer pressure resulted in a big contract loss for Novo Nordisk AS' blockbuster insulin NovoLog in the second quarter, prompting the Danish diabetes fighter to trim sales and profit forecasts for the full year. Novo Nordisk signaled intensifying pricing pressure from customers in the US, its biggest market, and warned that lower prices and escalating competition from biosimilars will remain a problem there. "In the US, the market environment is becoming increasingly challenging and contract negotiations for 2017 have reflected an intensifying price competition," chief executive Lars Rebien Sorensen said when updating investors on the group's second-quarter performance. The world's biggest maker of insulin presented a mixed quarterly earnings report Aug. 5 and cut its full-year sales and profit forecast, burdened by the loss of a key contract for its top-selling insulin NovoLog (insulin aspart). It did not identify the contractor. The group said 2016 profit likely will climb as much as 8% – but that's down from an earlier forecast of as much as 9% growth, while sales for the whole of 2016 are seen rising as much as 7%, but lower than an earlier outlook for as much as 9%. The Bagsvaerd, Denmark-based company said that after completing most of its 2017 negotiations with pharmacy benefits managers for insurance coverage in the US, average prices will be "low- to mid-single digit" percentage less than 2016 levels with rebates. US Health plans are looking to curb diabetes drug spending. Injectible diabetes drugs, namely basal insulins and GLP-1 agonists, are the main drivers of diabetes drug spending growth there. Diabetes represents 10% of overall US drug spending on average. Both basal insulins and glucagon-like peptide-1 (GLP-1) agonists are fast-growing categories of drugs within diabetes, powered by new launches and a push toward more aggressive treatment. More treatment options, however, also open the window for payers to implement cost management strategies. Many are moving increasingly toward closed formularies and drug exclusions as a negotiation tactic to extract steeper discounts from manufacturers.

sten.stovall@informa.com, 5 August 2016

How Incepta Is Shaping Bangladesh's Vaccines Future

Incepta Vaccine Ltd has operationalized an indigenous, fully integrated bulk facility that can manufacture both bacterial and viral bulk antigen independently. The facility expects to produce bulk antigens for a range of vaccines that include a 13-valent pneumococcal conjugate vaccine and 4-valent human papilloma virus (HPV) vaccine. Those for hepatitis B, cholera and typhoid have already been produced and some of them are in preclinical/clinical trials. Incepta's chair and managing director Abdul Muktedir told *Scrip* that the firm had prepared

the "clone" of the HPV vaccine and was now in the process of optimizing the antigen production. It expects to start testing the HPV vaccine in animals by the first quarter of 2017. "We are hopeful to commercially produce the HPV vaccine by the first quarter of 2018. It will be a tetravalent vaccine comparable with Gardasil," he said. Merck & Co. Inc. also has Gardasil 9, covering nine HPV types, five more than Gardasil which helps prevent infection caused by HPV types 6, 11, 16 and 18. Incepta, which is the first human vaccine manufacturing company in Bangladesh, has previously indicated that its vaccines are generally available at a discount of 40-50% to the reference product.

anju.ghangurde@informa.com, 2 August 2016

Shire Ups Synergies Forecast, Baxalta Integration On Track

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Shire PLC was “firing on all cylinders” in the second-quarter, according to its CEO Flemming Ornskov, while simultaneously absorbing rare disease specialist Baxalta, and now expects annual synergies from the deal of more than \$700m in three years – up from the \$500m forecast ahead of the acquisition’s closing in June.

Dublin-based Shire PLC lifted its outlook for 2016 and its predicted cost saving goal for the recent \$32bn purchase of US drug maker Baxalta Inc., as the newly formed rare disease giant beat market forecasts for sales and profits in the second quarter – and its CEO predicted the strong trend would continue.

Shire, which acquired Baxalta in early June, reported Aug 2 that it generated combined second-quarter revenue of \$2.43bn, while non-GAAP earnings per American Depositary Receipt, the earnings measure it prefers, rose 29% to \$3.38bn. The London-listed company said it now expects annual synergies from the deal of more than \$700m in three years, up from the \$500m forecast just before the acquisition closed in June.

Analysts say further cost optimization might still be achieved in the longer term. Datamonitor Healthcare expects that Shire will establish additional savings by moving Baxalta’s company headquarters to Ireland, where the corporate tax rate is 12.5% compared to America’s 35%.

Most of Shire’s brands beat analyst estimates during the second quarter, with legacy product sales jumping 19% from the year-ago quarter level. Legacy Baxalta product sales grew 12%. Shire provided full-year guidance including Baxalta for the first time, saying earnings per American depositary share excluding some costs will grow to between \$12.70 and \$13.10 for 2016. But the group said it has no plans so far to start breaking out individual drug sales from the products acquired from Baxalta.

Shire’s CEO Flemming Ornskov during the trading update reiterated his pledge to deliver double-digit compound annual top-line growth, with more than \$20bn in annual projected revenue by 2020 and about 65% of total annual revenues generated by its rare disease products, which offer huge growth potential. That pledge looks feasible, analysts say, due in part to the addition of Baxalta’s core therapies *Advate* (octocog alfa) and FEIBA (factor eight inhibitor bypassing activity) for hemophilia, and Gammagard Liquid (immune globulin intravenous human) and HyQvia for primary immunodeficiency.

Ornskov said the expanded group is innovating in a high value, high growth area with huge unmet medical need.

“There are over 7,000 rare diseases but only 5% of those have therapies available today. This number is increasing and that is evidenced by the increasing share of regulatory approvals they represent,” the CEO told an analysts call. “This wealth of scientific opportunity is well-suited to Shire’s business model, where we augment internal innovation with business development such as licensing or M&A, providing us with numerous attractive opportunities to expand our portfolio,” he added.

Management gave a brief pipeline update during the results presentation but said a more in depth presentation would be made in New York City on Nov. 10. The combined company now has more than 40 programs in clinical development.

Ornskov said Shire is on track to launch *Xiidra* (lifitegrast) in the third quarter for the treatment of both the signs and symptoms of dry eye disease after receiving recent FDA approval. The indication for both signs and symptoms of dry eye disease should give *Xiidra* a significant advantage over the only drug currently approved for dry eye, Allergan PLC’s *Restasis* (cyclosporine ophthalmic emulsion), which has yielded blockbuster sales despite marginal efficacy and a label that only cites its ability to increase tear production in patients with chronic dry eye. In investor presentations, Ornskov consistently has pointed to *Xiidra* as offering the potential to be a game-changer in dry eye disease and to be the fulcrum of the firm’s nascent ophthalmology franchise. Shire has decided to price *Xiidra* at around \$5,000 annually, putting it in direct competition with *Restasis*, analysts say.

Shire is on track to launch *Xiidra* in 3Q for the treatment of dry eye disease after receiving recent FDA approval

Ornskov noted that FDA on July 29 granted Fast Track Designation to SHP626 (volixibat) for the treatment of nonalcoholic steatohepatitis (NASH) with liver fibrosis, a serious condition with no approved therapies.

Shire said it plans by the end of the year to resubmit the New Drug Application (NDA) for SHP465, a treatment of attention deficit hyperactivity disorder following positive topline results of the SHP465 efficacy and safety study in adults with ADHD.

Shire also used its update to announce it reached an agreement with the U.S. Department of Justice and other authorities to end investigations into marketing practices at the Dermagraft business that Shire had sold in January 2014. The settlement, which could potentially result in a \$350m settlement, is subject to further approvals, the company said.

Asked by reporters how Shire – which is Dublin-based, London-listed but US-centric – might position itself for eventual UK departure from the EU, Ornskov replied the group was taking a wait-and-see attitude. “We do between 3% and 4% of our business in the UK and we conduct clinical trials with clients based in the UK. None of that has changed. We’re in the process of merging the two organizations – Shire and Baxalta – in the UK to a London-based location, putting it right at the heart of the country’s life sciences center so Brexit currently hasn’t had any impact on our plans.” ▶

Published online 2 August 2016

Mid-Sized European Companies Eager To Acquire During Growth Spurt

Among Europe's flourishing niche of mid-sized pharmaceutical companies, Italy's Recordati and Spain's Almirall have snapped up smaller local companies during the past six to nine months, while Switzerland's Actelion is concentrating on executing new product launches while considering M&A.

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The first half of 2016 saw two of Europe's mid-sized pharmaceutical companies snapping up compatriot companies while busily growing sales and profits. They're not just taking out assets from under the noses of Europe's Big Pharma firms, they're showing companies can still be built on the back of good ideas and rigorous business development planning, at relatively low price-tags.

Milan, Italy-based Recordati Industria Chimica & Farmaceutica SPA is a case in point, having acquired Milan-based Italchimici SPA in May 2016 for €130m (\$144m) for its gastroenterology and respiratory products, and the Swiss company Pro Farma in the middle of July for CHF16m (\$16.4m), in order to grow its business in Switzerland.

But is the motivation to sell their companies coming from the owners rather than the acquirers? "Have private European companies decided this is a good time to sell?" Recordati's CFO Fritz Squindo was asked during the company's first-half 2016 earnings call, held July 28. Squindo thought not, saying Recordati had "not seen any major changes in the M&A arena. M&A remains crowded and competitive, and we always have a list of proposals," he remarked.

That may be so, but another mid-sized European pharma, Spain's Almirall SA, has also been on the acquisition trail, buying the Lugano-Switzerland-based Poli Group Holding SRL in November 2015. It may be that smaller European firms are finding it increasingly difficult to cope with regulatory and investment demands geared towards much larger international companies.

For publicly-listed Recordati, the purchase of Italchimici was "an opportunity to accelerate growth in Italy, and to consolidate the product portfolio," Squindo noted, while providing some synergies on the cost side. Italchimici had revenues of €46m in 2015 from pharmaceuticals, food supplements and medical devices. In contrast, the

acquisition of the much smaller Pro Farma was seen by Recordati as an opportunity to develop its business in Switzerland, where Recordati has just started to market the lipid lowering agent, *Livazo* (pitavastatin).

The international ambitions of Recordati, which recorded growing first-half 2016 revenues of €588m (+9.1%) and net income of €122.7m (+18.9%), are well known. It has just licensed Western European and Algerian, Tunisian and Turkish commercialization rights to Gedeon Richter Ltd's novel atypical antipsychotic cariprazine, which was accepted for review by the European Medicines Agency in March 2016. The product is already marketed in the US by Gedeon Richter's licensee Allergan Inc. as *Vraylar*, also in March 2016.

ALMIRALL'S GROWING PIPELINE

For Spain's Almirall, the acquisition of Poli Holding Group (and its operating subsidiaries Taurus Pharma GmbH, Polichem SA and Polichem Srl) at the end of 2015 has allowed it to incorporate an R&D operation, a proprietary formulation technology, and three clinical-stage projects. The Spanish company also acquired in Feb. 2016 an aesthetics company, ThermiGen LLC, for \$82m that markets a heat-based skin surgery device.

The three Phase III products from Poli include P3058 (a terbinafine nail lacquer, according to Informa Pharma Intelligence's *Pharmaprojects* database) that is being evaluated in onychomycosis; patients are being recruited in Europe for the Phase III study and patient recruitment is due to start in the US in 2017, chief scientific officer Thomas Eichholtz told the company's first-half 2016 analyst's briefing.

A nail psoriasis project, P3073 (calcipotriol lacquer), is in a Phase III study that has completed EU enrolment, with US enrolment expected in the first quarter of 2017, and P3074 (topical finasteride), for androgenic alopecia, which has just started enrolment in an EU study, with a US study expected to

start in the second or third quarter next year, Eichholtz reported. Among Almirall's internal projects, dimethyl fumarate (DMF) for psoriasis has been submitted for approval, expected in the second quarter of next year, while ADP31415 is in Phase I.

Almirall has also just revealed a partnership with Woodcliff Lake, New Jersey-based Patagonia Pharmaceuticals LLC to jointly develop Patagonia's lead product, PAT-001, a first-of-its-kind topical isotretinoin product, for the treatment of congenital ichthyosis, that is expected to enter Phase II studies in the fourth quarter of 2016. Almirall has global marketing rights to PAT-001 in dermatological indications, in exchange for an initial upfront payment of \$3.5m and development and regulatory milestones of \$24m.

Almirall's executive vice-president of global commercial strategy, Alfonso Ugarte, noted that congenital ichthyosis affects around 100,000 to 160,000 patients in the US and the same in Europe, and PAT-001 could eventually have a sales potential of more than \$100m in the US alone. Congenital ichthyosis is a group of chronic skin disorders with persistently thick, dry, scaly or flaky skin, sometimes called "fish disease".

Dermatology has been earmarked as the business Almirall wants to be in, and the therapeutic category now accounts for 43% of total net sales, Ugarte reported during the analysts' call. Europe has become the company's largest sales region, accounting for 55% of sales, driven by the actinic keratosis products *Solaraze* (diclofenac gel) and *Actikerall* (fluorouracil plus salicylic acid). Almirall reported "solid" growth in the first half of 2016, with revenues up by 5% to €428.1m and net income up by 37% to €80.5 m, compared with the 2015 first half. ▶ Published online 4 August 2016



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Regeneron Emphasizes Pipeline Promise

Regeneron Pharmaceuticals Inc. executives emphasized the blockbuster potential of product candidates in the company's late-stage research and development pipeline on Aug. 4, while noting that the top-selling biologic *Eylea* (aflibercept) is facing increased reimbursement and competitive pressures. If two forthcoming US approval decisions go Regeneron Pharmaceuticals Inc.'s way – for the rheumatoid arthritis therapy sarilumab in October and the atopic dermatitis treatment dupilumab in the first half of 2017 – those products could offset a slowdown in *Eylea*'s sales growth. *Eylea* “is one of our most important approved products and continues to grow well globally. *Eylea* is now at an annual global net sales run rate that exceeds \$5bn,” president and CEO Leonard Schleifer said during Regeneron's earning call. “This has been driven both by the approval of *Eylea* in new indications as well as new data that have further increased the confidence of physicians in this product.”

mandy.jackson@informa.com, 4 August 2016

Adcetris Expands In Lymphoma

Partners Takeda Pharmaceutical Co. Ltd. and Seattle Genetics Inc. are pushing aggressively to expand the antibody-drug conjugate Adcetris (brentuximab vedotin) in new lymphoma indications. The first of three ongoing Phase III trials has read out positively, but late-stage studies are continuing in what are expected to be the larger commercial opportunities. The companies announced Aug. 1 that the Phase III ALCANZA trial, evaluating Adcetris in patients with CD30-expressing cutaneous T-cell lymphoma (CTCL) met its primary endpoint, demonstrating a highly statistically significant improvement in the rate of objective response lasting at least four months (ORR4), a novel endpoint negotiated with FDA under a special protocol assessment.

Araclon Sees Early Promise With Alzheimer's Vaccine

Phase I results for Araclon Biotech's Alzheimer's disease vaccine, ABvac40 – the only vaccine data presented at this year's Alzheimer's Association International Conference – warrant further exploration of this innovative approach to the disease. The Spanish biotech, in which pharma company Grifols SA is the majority shareholder, is now planning a Phase II trial for the vaccine on the back of the positive Phase I blinded study. A total of 24 patients with mild-to-moderate Alzheimer's disease participated in the Phase I study: 18 patients in the treatment group and six in the placebo/control group. Araclon said there were no significant differences with respect to adverse effects between participants in the group that received ABvac40 and those in the placebo group. Effectiveness of the vaccine was not assessed in the trial but the company noted that ABvac40 produced an immune response in more than 87% of patients who received the active product during the trial. ABvac40 is an innovative immunotherapy that acts specifically against amyloid beta protein 40 using the C-terminal part of the peptide. Datamonitor Healthcare analyst Maha Elsayed told *Scrip*, “This innovative approach is warranted in Alzheimer's disease considering the previous safety events that have emerged with active immunization against amyloid-beta.” Elsayed highlighted as an example Perrigo Co. PLC's AN-1792, the first active vaccine trial that was stopped in 2002 because of safety issues around patients developing encephalitis. Since this study, efforts have been made towards improving the safety of these immunotherapies in Alzheimer's, she noted.

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Seattle Genetics said it plans to file a supplemental Biologics License Application (sBLA) to expand the use of Adcetris in the indication in the first half of 2017 and will report the full data at the American Society of Hematology annual meeting in December.

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ReNeuron Presses On With Stroke Therapy Development

Further clinical testing of ReNeuron Group PLC's cell-based therapy CTX is warranted, experts say, after two-year follow-up data from its Phase I PISCES study published recently in *The Lancet* showed that single intracerebral doses were associated with improved neurological function with no major adverse events. The next important read-out for the product should come in the

fourth quarter from the three-month follow-up point in the ongoing Phase II PISCES II study; recruitment for this study is already complete. On the basis of these data, a pivotal Phase II/III study is planned in stroke disability, applications for which are slated for filing in the first quarter of 2017. In 2015, ReNeuron raised more than £68m to advance this and another of its pipeline programs for retinitis pigmentosa, in anticipation of the cell therapy field being revived as a R&D area. The full Phase I data are a boost for the field which has suffered setbacks despite promising animal data. Given the previous negative effects for similar transplanted fetal cells in Parkinson's disease patients which led to adverse events, the disappointments raised concerns that stem cell therapy for stroke could go the same way.

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MedImmune Gets Creative In Diabetes With PCSK9/GLP-1 Fusion Product

AstraZeneca PLC's MedImmune LLC will be the first drug developer to present data for a "fusion molecule" therapy combining a PCSK9 antibody with a GLP-1 peptide when a Phase I trial of its pioneering product MEDI-4166 in type 2 diabetics completes later this year. The company's head of diabetes innovative medicines, Cristina Rondinone, explains to Scrip the thought process behind the unique combination and what to expect for further development of the novel drug in 2017.

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MedImmune LLC, an AstraZeneca PLC company, will report Phase I data for its novel type 2 diabetes combination therapy, MEDI-4166, the first to fuse a PCSK9 inhibiting monoclonal antibody with a GLP-1 peptide, by the end of 2016; and Cristina Rondinone, vice president and head cardiovascular and metabolic diseases innovative medicines at MedImmune, told *Scrip* she expected to see the dual product in Phase II clinical trials next year.

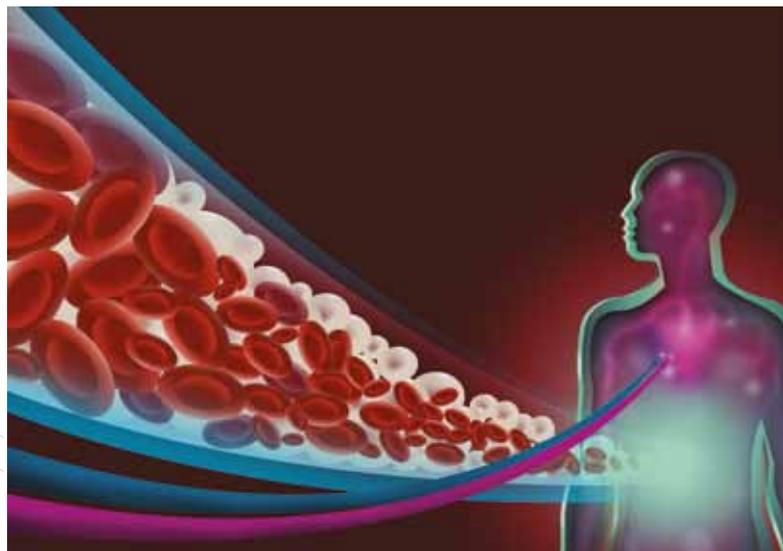
Both aspects of the fusion molecule, which is known as MEDI4166, are also being developed as separate pipeline products: the PCSK9 drug is currently in Phase II trials and the dual GLP-1/glucagon receptor agonist being used – MEDI-0382 – is currently at Phase I/II.

"This is a very novel concept and our first question was simple, 'Will it work?'" Rondinone said. "At MedImmune we have the capacity to do almost anything we want and I don't know that there is anyone else trying this idea." There are no other ongoing trials for combination therapies using a PCSK9 and a GLP-1 for the treatment of type 2 diabetes listed by clinicaltrials.gov or in a number of databases assessed by *Scrip*.

Both the PCSK9 (proprotein convertase subtilisin/kexin type 9) and GLP-1 (glucagon-like peptide-1) drug classes have gained a lot of attention in recent years, and on the back of positive data outcomes a number of products have been successful on the market for indications including hypercholesterolemia and type 2 diabetes. Meanwhile, diabetes patients have long benefited from combination formulations of older diabetes therapies, setting a strong precedent for two-in-one products in the area.

Diabetes may be an increasingly crowded market, but innovative products with the ability to show true differentiated effects and benefits over older treatments have been well received by regulators and physicians and patients. Rondinone believes MedImmune's pipeline products have potential in the future market space as the drug developer is seeking curative developments. "We are learning with these newer medications for diabetes that some have effects above just glucose control, and I believe we can have better drugs still that look at the whole physiology of the disease – products that can address chronic renal disease and cardiovascular events in diabetic patients," Rondinone said. "Previously, us drug researchers were going from the cell, to the animal, to the man; now we are observing what is going on in man then going backwards to design our therapies so they are fit for purpose. Our most exciting goal at MedImmune is to be able to cure diabetes."

MedImmune – which comprises nearly half of AstraZeneca's overall R&D portfolio – presented preclinical data for the PCSK9/GLP-1 product in June 2016 during the American Diabetes Association's annual meeting, but it is yet to report any data for the drug from human



trials. It launched a first time in human, Phase I, randomized, double-blind study to evaluate the safety and tolerability of MEDI4166 in October 2015 in the US – enrolling approximately 124 patients.

Rondinone said MedImmune's overarching strategy for diabetes R&D is to look at many possible combined mechanisms. "Our strategy is to use our protein engineers to create long-acting dual or triple agonists," she said. "We are looking at all sorts of combinations in this area and are very excited about opportunities here. Combination therapies are the only way to really treat diabetes; the whole disease and all the problems a patient has."

MORE INNOVATIVE METABOLIC RESEARCH

MedImmune's metabolic division also has an interest in cholesterol lowering drugs options outside of PCSK9s and it is currently developing MEDI-6012, a recombinant human LCAT (rhLCAT). An enzyme in the blood, LCAT converts cholesterol to cholesteryl ester, which is then sequestered in the core of the lipoprotein particle. MedImmune collected the drug via its acquisition on AlphaCore in April 2013. "The idea is to give this drug to patients after their first cardiovascular event in order to prevent a second CV event," Rondinone said. "This is very interesting to me and it's a new concept that not many researchers are trying."

Rondinone also noted that MedImmune would be seeking to work more closely with device and technology partners in the metabolic space in the future. "New digital technology can help us learn more about our patients and our patients need to know more about what effect the drugs they are taking are having on their body," she said. ▶

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Allergan, Gedeon Richter Unbowed By Cariprazine MDD Phase III Trial Failure

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Allergan PLC and Gedeon Richter Ltd. have hit a buffer in the development of their antipsychotic cariprazine in the additional indication of major depressive disorder, but they plan to proceed with a further pivotal trial, and mollified analysts with the announcement of a filing timeline to bolster the drug's label in schizophrenia.

Top-line Phase III data for Allergan PLC and Gedeon Richter Ltd.'s atypical antipsychotic Vraylar (cariprazine) show it failed to separate from placebo when used as an add-on therapy in patients with major depressive disorder (MDD) in a US study.

However, the companies are bloodied but unbowed by the blow, and plan to box on with another Phase III trial in adjunctive MDD, which they hope will lead to approval when added to previous positive study data they have garnered. Cariprazine was approved in the US last September for use in the treatment of manic or mixed episodes of bipolar I disorder and schizophrenia in adults, and is awaiting EU approval for schizophrenia. The drug is a potent dopa-

mine D(3)/D(2) receptor partial agonist with preferential binding to D(3) receptors.

"It is not uncommon that clinical trials in MDD fail to show a separation from placebo even with effective drugs. Both companies remain committed to developing cariprazine as a potential treatment option for patients suffering from this serious illness and will continue to work on a subsequent Phase III trial," the companies said in a statement.

The double-blind MD-72 trial was evaluating flexible doses of cariprazine (1.5-4.5 mg) as an adjunctive treatment to antidepressant therapy in adults with MDD who failed to adequately respond to antidepressant monotherapy. The initial results show that none of the doses provided any difference from the placebo arm in the study, which according to the *clinicaltrials.gov* database planned to enrol 1,100 patients.

Unlike Vraylar, current antipsychotics have not shown efficacy in negative symptoms

This contrasts with the data from a previous trial, MD-75, in which flexible doses of cariprazine (2-4 mg) were significantly more effective than placebo in the same setting. This study enrolled about 820 patients and was conducted in both the US and Europe.

"We are disappointed with the results of this trial. However, we believe that our plan to move forward with another Phase III study in adjunctive MDD coupled with our previous positive clinical trial would provide the two studies needed for submission," said Allergan's chief R&D officer, David Nicholson.

NEGATIVE SYMPTOMS

Analysts were also relatively relaxed about the MDD failure. Umer Raffat at Evercore

ISI agreed that it was not uncommon for depression studies to fail to separate from placebo, and he was more interested in the update the companies gave for the product's hoped-for label boost, particularly for negative schizophrenia symptoms.

In January, Allergan and Gedeon Richter announced positive Phase III results for cariprazine in both the prevention of schizophrenia relapse and for the treatment of predominant negative symptoms (PNS) of schizophrenia, and they announced they were in discussions with the FDA over the submission of an efficacy supplement for each indication. For PNS, they were more specific, stating that this would come in the first half of next year.

The companies note that PNS, such as social withdrawal, lack of emotional display, is a serious unmet need for which there are no approved treatment options available, and this could prove a key differentiator for the product.

"Unlike Vraylar, current antipsychotics have not shown efficacy in negative symptoms," said Raffat, and he was pleased to get some clarity over the timings around a label expansion after it was not specified in the initial US label.

The key challenge for Vraylar is to differentiate itself on the crowded atypicals market, and negative symptoms provides it with its best chance. "Today, Allergan provided the first clear track towards how they intend to pursue this labeling indication... Negative symptoms remains perhaps the most important indication for Vraylar in my view," Raffat said.

BIPOLAR EXPANSION

The companies are also hoping to expand the label for Vraylar in bipolar patients, and have started enrolment in their Phase III clinical trial program for cariprazine as a treatment for bipolar depression in the US and Europe. This follows positive Phase IIb data for the drug in the treatment of bipolar depression published in November 2015 in the *Journal of American Psychiatry*. ▶

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Gonal-f 2Q Sales Allow German Merck To Up Forecast

Solid US demand for Gonal-f fertility and Rebif MS drugs in the second quarter – along with commissions from its Xalkori co-promotion partnership there with Pfizer Inc. – let Merck KGaA upgrade its guidance for the full year.

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Germany's Merck KGAA – which is trying to transform itself into a top oncology and immuno-oncology innovator – lifted its full-year earnings forecast Aug 4 in part on the back of stable US sales for its *Gonal-f* fertility treatment after the recall of a rival product there, and for demand for its *Rebif* (interferon beta-1a) treatment for relapsing forms of multiple sclerosis, which faces competition from oral treatments.

‘Dynamic market developments gave our healthcare and life science businesses additional tailwinds’

The company said its priorities going forward are now boosting its pharma pipeline, further integration of chemicals and biologicals maker Sigma-Aldrich, which it acquired recently for \$17bn, and reducing its new financial debt which stood at €12.5bn at the end of June and only slightly lower than the €12.7bn recorded at the end of 2015.

“We again achieved everything we aimed for in the second quarter. That applies to both the Sigma-Aldrich integration and the development of new medicines,” said Stefan Oschmann, chief executive of the family-controlled conglomerate which is also the largest maker of high-tech chemicals for display screens. “Strong demand for our products and dynamic market developments gave our healthcare and life science businesses additional tailwinds. Since particularly in healthcare our performance in the second quarter was so good, we have decided to lift our forecast for the full year,” he told an analysts call.

Merck therefore now expects group net sales to rise this year to between €14.9bn and €15.1bn from the previously forecast €14.8bn to €15.0bn, and raised its outlook for 2016 EBITDA before special items to between €4.25bn and €4.4bn, up from a

previous target range of €4.1bn and €4.3bn. Full-year EPS range is now €5.85 to €6.10 compared with €5.65- €6.00 previously. Around half of the guidance upgrade is due to the strong second-quarter with the remainder resulting from the sale of a minority interest held by the group's venture fund that generated €30m, and on R&D.

Merck, based in Darmstadt, Germany, has around 50,000 employees in around 70 countries. Over the past five years it has been rebuilding its pharma R&D organization and realigning its healthcare businesses to focus on neurology, oncology, immuno-oncology and immunology, while expanding its footprint in emerging markets. It also plans to bolster its biopharma R&D activities in Britain – despite Brexit – on grounds the

(follitropin alfa, r-hFSH) recombinant human follicle-stimulating hormone.

One of the big future hopes for Merck involves its multi-billion dollar collaboration with Pfizer Inc. on the development of immuno-oncology products, including the clinical-stage PD-L1 inhibitor avelumab. Through it, Pfizer will have access to Merck's Phase II PD-L1 inhibitor, but in return Merck has gained wider access to the US oncology market – and commissions – through a co-promotion deal for Pfizer's lung cancer drug Xalkori (crizotinib).

The FDA has given avelumab breakthrough designation, so the group plans to complete the drug's US filing submission in the early part of the second half of 2016.

Merck – which hasn't launched a new



UK is too key and dynamic a player in the life sciences sphere for it not to.

The company continues to reap benefits in the US for its infertility therapy Gonal-f (follitropin injection) for follicle stimulation after the loss of a competitor, Ferring Pharmaceuticals Inc., in the recombinant follicle-stimulating hormone (rFSH) market. Analysts think this benefit will flow into the second half of the year. But Gonal-f is seeing significant competition in certain EU markets from Teva Pharmaceutical Industries Ltd's rival *Ovaleap*

drug in a decade – is also banking on cladribine tablets, the oral multiple sclerosis medicine it suspended in late-stage trials five years ago but then resuscitated last September after having evaluated new data and done additional analyses of the product's benefit-risk profile. The company at the end of June submitted an application for marketing approval with the European Medicines Agency for cladribine and hopes to get EU approval by the middle of 2017. ▶

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How To Handle Off-Label Promotion: A Guide From PhRMA And BIO

Industry communication principles offer best practices for combating contrary evidence, refuting third-party comparative effectiveness analyses and sharing real-world evidence addressing health outcomes and costs.

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Off-label promotion has always been one of the mine fields of marketing, and with the shift toward more real-world and health economic data aimed at both prescribers and payers, two leading industry organizations have gotten together to offer a guide to best practices.

The *Principles on Responsible Sharing of Truthful and Non-Misleading Information About Medicines with Health Care Professionals and Payers*, released by the Pharmaceutical Research and Manufacturers of America and Biotechnology Innovation Organization July 27, are intended to prod the FDA to update its regulations on the subject.

The agency is in the process of writing guidances on using health care economic information for drug promotion and on communications on unapproved uses – though both have been in the works for years.

Neither guidances nor the PhRMA/BIO principles are binding on companies, however, and the boundaries of off-label promotion have largely been defined through First Amendment cases. The trade groups hope that the principles will lead to discussions on a safe harbor provision.

The principles are “intended to establish responsible, science-based parameters for accurate and trusted information sharing,” the document states. PhRMA and BIO

don’t expect companies to change their operations or change their compliance rules based on the principles. “This is really meant to inform the greater discussion right now,” Jeff Francer, vice president and senior counsel at PhRMA, told *Scrip*.

PhRMA and BIO seem to have adopted some of the same approaches FDA used for its social media strategy for their off-label principles. In several of the practical scenarios offered alongside the principles, companies are encouraged to give balanced accounts of the information, but were also encouraged to “refer the health care professionals to a website for more comprehensive information.” FDA’s proposed guidance for drug promotion on social media notes that ads and other communication must be balanced and include a link to a landing page with more comprehensive information.

“We are seeing a real revolution in health care and data and information sharing,” said Francer. “We believe that more robust information sharing between our companies and payers is critical to increasing the efficiencies of the marketplace.” But he stressed that information must be “science-based and based on established methodologies.”

Drug makers also must provide their information in the appropriate context, including the limitations of statistical methods and

study designs, and the data should be clearly communicated in a way that’s appropriate for the intended audience, Francer said.

While the FDA-approved labeling is “going to be and will remain the most authoritative data about an approved drug,” he argued “there’s an incredible proliferation of high-quality information that is not going to be reflected in the labeling.”

IMPATIENT PAYERS

One of the most critical situations involves discussions between sponsors and payers. Manufacturers increasingly find themselves in situations where payers want information about their products before they are commercialized, Francer explained.

Indeed, payers begin to plan their coverage and other related decisions 12 to 18 months before a medicine is on the US market, he pointed out. And, Francer said, payers don’t like to be surprised.

While companies have the ability to answer unsolicited questions, “that requires payers or anybody else to know the right questions to ask and to ask them at the right time, and that doesn’t lead to the most sufficient and timely information,” he argued.

FIGHTING AGAINST CONTRARY DATA

The principles offer companies a way of fighting comparative effectiveness studies conducted by pharmacy benefit managers that favor another treatment over one they market. Applying the principle that “additional science-based information from sources other than FDA-approved labeling helps health care professionals and payers make informed decisions,” if a company has data refuting the comparative effectiveness results, it “should be able to respond to the PBM’s public statements about the company’s drug with information from the company’s research,” PhRMA and BIO assert.

To be truthful and non-misleading, the company should include the results of the study for its and competitor products in its

PhRMA/BIO Information-Sharing Principles

1. Commitment to accurate, science-based communication.
2. FDA-approved labeling is primary source in sharing information with health care professionals.
3. Companies should provide scientific substantiation if shared information is not contained in FDA-approved labeling.
4. Science-based information from sources other than FDA-approved labeling helps health care professionals and payers make informed decisions for patients.
5. Communication should be tailored to the sophistication of the intended audience.
6. Science-based information about alternative use of medicines can improve health care decision-making.
7. Communicating with payers about new medicines and new uses of approved medicines facilitates quicker patient access upon approval.
8. Real-world evidence based on patient experience and pharmacoeconomic information can improve understanding of health outcomes and costs.
9. Commitment to sharing information published in scientific or medical journals.

response to the PBM statements, as well as their study's methodology and statistical analysis techniques, data limitations, pertinent safety results and bias risks. Oral and written communications can include summaries of the information and refer health care professionals to a website with more comprehensive study information, according to the document.

The practical scenario could become commonplace in the coming years, especially as more focus turns to comparative effectiveness research and product sponsors fight to retain market share.

The Institute for Clinical and Economic Review recently released a cost-effectiveness review of new multiple myeloma therapies, which raised concerns from groups cautioning against the possibility of restricting access to the products. ICER reviews have been cited by PBMs in the past.

Biologic sponsors also may employ the strategy upon facing biosimilar competition. Two of the leading PBMs, Express Scripts Holding Co. and CVS Health Corp., have already announced changes to their formularies to favor biosimilars.

Another scenario covers how a company could handle an external study presenting contrary evidence about a product's efficacy.

Say a supplemental NDA is pending for a new indication in children following approval in adults and FDA delays the label update. During the delay, another study surfaces from independent investigators with evidence against the product's efficacy in children.

In that case, for the product manufacturer to give information about its study to prescribers before FDA updates the label, it should disclose key elements of the study design, results of primary and secondary endpoints, safety results, regulatory status and other evidence necessary for a medical judgment.

PhRMA and BIO also advise that the company indicate the limitations of its study by disclosing "the existence of only one randomized, controlled trial supporting the information" and "lack of any reference study in the labeling."

PRESENTING PIPELINE INFORMATION

The principles also suggest how a company could present pipeline information to health plan pharmacy and therapeutics (P&T) com-

mittees or other highly sophisticated audiences. Such a presentation should include descriptions of the ongoing studies for the clinical stage products, such as a one-page description of each study, including the designs, primary and secondary endpoints, results of the primary and secondary endpoints, and statistical significance, which "do not make statements that any of the drugs has been determined to be safe or effective."



Jeff Francer

PhRMA and BIO suggest that when companies communicate top-level pipeline information, they disclose the lack of FDA approval and the possibility that some products may not be approved, as well as any "material safety risks" that have been found in the clinical studies to date.

Interestingly, among the proposed reasons for reviewing pipeline information is to allow a P&T committee time to plan for potential product costs. It references a principle that "communicating with payers about new medicines and new uses of approved medicines facilitates patient access upon approval."

The principles state that drug manufacturers should be allowed to talk to P&T committees about their pipeline not only to allow time for them to make reimbursement decisions as well as "account for the potential cost of the new medicine."

Should pricing information from a P&T committee presentation leak out of the meeting room, especially if the drug is expected to be impactful, any backlash could be problematic for the sponsor. Several federal institutions are highly interested in the growing drug pricing issue, including Congress, which has jumped into the pricing fight in recent months, including pushing for a priority review pathway

for generics. Both presidential candidates also have made dealing with escalating drug prices a priority.

INFORMING THE DISCUSSION

Another scenario looks at what happens when a company with a marketed Parkinson's disease drug conducts a post-hoc analysis of data from its pivotal trials to measure the effect of the medication on pain, which was among the symptoms measured as part of a composite primary endpoint, but whose individual symptom scores were not pre-specified as a secondary or tertiary endpoint and there were no published studies available with contradictory evidence.

So, PhRMA and BIO said, to communicate the analysis' results to prescribers in a truthful and non-misleading manner, the manufacturer should disclose the omission of the effect of the drug on pain as a pre-specified primary, secondary or exploratory endpoint; the post hoc nature of the analysis and its consequent failure to meet the FDA's standard for an adequate and well-controlled study; the pre-specified primary endpoints and the results; the methodology for the analysis, including whether it was designed to test a pre-specified endpoint in accordance with a pre-specified analysis plan and how the study controlled for confounding factors; the results of the analysis, including the statistical significance and confidence intervals; the pertinent safety results; any other risks of bias not already specified with a retrospective data analysis; and the fact that the analysis was not included in the product's labeling and regulators did not consider it in approving the product.

Under that situation, PhRMA and BIO said the firm should summarize all of those disclosures in oral or written communications and also could refer the health care professional to a website for more comprehensive information about the study.

"There can be many ways of sharing information about medicines, and it may not be feasible to provide comprehensive contextual information orally," Francer said in an Aug. 4 email. "Thus, we believe that in different circumstances, combinations of oral, written, and online communication may be appropriate." ▶

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CVS Excludes Lantus, Neupogen For 2017

CVS Health Corp. is moving to promote the use of biosimilar and follow-on competition to Amgen Inc.'s granulocyte-colony stimulating factor drug *Neupogen* (filgrastim) and Sanofi's glargine insulin *Lantus* by excluding those drugs from coverage in its standard national formulary in 2017. The standard formula covers approximately 25 million individuals and is among the formulary options CVS offers to its payer clients. Neupogen and Lantus were not excluded from coverage in 2016. "Biosimilar and follow-on biologics will be included as a key component of our 2017 standard formulary strategy, replacing higher cost drugs within the categories," CVS said in announcing its exclusion list Aug. 2. "This will include the biosimilar *Zarxio*, replacing Neupogen, to decrease the risk of infection in patients receiving treatment for certain forms of cancer, and the follow-on product *Basaglar* – approved in Europe as a biosimilar – replacing the insulin Lantus for treatment of diabetes." Pharmacy benefit manager Express Scripts Holding Co. does not exclude Lantus or Neupogen in the current version of its 2017 formulary exclusions list, which was released Aug. 1. However, the company is not ruling out a change for Lantus when Basaglar enters the market. "We will reassess this category when Basaglar becomes available," a spokesperson for the company said. Basaglar was approved by FDA in December 2015 after Lilly reached a patent settlement agreement with Sanofi. Under the agreement, Lilly can launch Basaglar in the US on Dec. 15, 2016 in exchange for undisclosed royalties on sales. Lantus sales have been declining in the US as a reflection of price concessions to payers and competition, including from Sanofi's own longer-acting insulin glargine, Toujeo. CVS also excludes *Toujeo* from its standard formulary in 2017. US sales for Lantus declined 15.7% to approximately \$1bn in the second quarter, according to Sanofi, while US sales for Toujeo totaled about \$119m.

catherine.kelly@informa.com, 3 August 2016

Can Torrent Sustain Brazilian Mojo?

Torrent Pharmaceuticals Ltd. reported a 20.6% decline in revenues to INR15.45bn (\$230.6m), with net profits down to INR2.92bn (-55%) for the first quarter ended June, largely on account of a slump in the US business. First quarter US revenues declined to INR4.34bn from INR8.88bn in the same period last year. The first quarter of the previous fiscal included exceptional revenues primarily on account of the launch of generic Abilify (aripiprazole) with limited competition in the US. Ex-aripiprazole, the business grew at "low double-digits." But the sharp decline in 1Q earnings came laced with some interesting commentary on one of Torrent's key markets – Brazil – currently grappling with political and economic turmoil. Revenues from Brazil rose 21% to INR1.67bn; the growth in Brazilian real is 31%. Torrent Brazil has "turned the corner" during the first quarter in terms of underlying business growth as well as the impact of the foreign exchange fluctuations in Brazil, Torrent's top brass said at a post results earnings call. "The authorities in Brazil allowed us to take a 12.5% price increase in April, and Torrent, like most of the industry peers, has taken all the allowable price increases," Sanjay Gupta, Torrent's executive director (international business), said. Most of the firm's competitors in Brazil had also taken the "maximum price hike." Gupta indicated that Torrent was focusing "very narrowly" on a clutch of 10 brands (within its basket of about 35 products there), each with sales greater than BRL15m and the three areas – CNS, cardio, and diabetes – that the company operates in were growing higher than the pharmaceutical market there. "As result of which, focused brand building efforts on some of the larger products and with the dedicated CNS and a dedicated cardio, diabetic field force, we're seeing good traction in Brazil. So I think this trend hopefully should continue in the future."

anju.ghangurde@informa.com, 1 August 2016

Will Generic Epclusa Shake Up Bangladesh HCV Market?

Bangladesh's HCV market report card currently reads along these lines: generic versions of *Sovaldi* and *Daklinza* have made significant gains leaving interferon by the wayside, while generic *Harvoni* has had a quiet run. But, the arrival of cut-price *Epclusa* generics could bring change, besides putting the spotlight on the growing prowess of the South Asian nation's pharmaceutical sector. Industry leaders there said that generic versions of Gilead Sciences Inc.'s *Sovaldi* (sofosbuvir) and Bristol-Myers Squibb Co.'s *Daklinza* (daclatasvir) fared "very well" and rendered interferon "almost obsolete" in Bangladesh. "This is because of the high price of interferon in the local market compared to oral drugs," Abdul Muktadir, chair and managing direc-

tor of Incepta Pharmaceuticals Ltd told *Scrip*. Generic versions of *Harvoni* (the fixed-dose combination of ledipasvir and sofosbuvir) have not been too successful in Bangladesh, because genotype 1 and 4 is less prevalent in the country compared with other genotypes. Significantly, Incepta indicated that its generic version of Gilead's *Epclusa* is "almost ready" for launch and the firm expects some realignment in market shares in the hepatitis C segment with the product's potential entry. Muktadir said that the price of generic *Epclusa* had not been fixed yet but added that it would be "similar to [Incepta's] *Twinvir* (sofosbuvir + ledipasvir) – Taka800 or 1,000 per tablet." Gilead had earlier announced a wholesale acquisition cost of \$74,000 for a 12-week course of *Epclusa* therapy, making it cheaper than sofosbuvir, which had an initial pricing of \$84,000 for 12 weeks.

anju.ghangurde@informa.com, 5 August 2016

Teva Advancing Two Advair Generics With Late 2017 Target

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Teva will move forward an internal generic Advair candidate and one acquired from Allergan to improve its chances of getting an interchangeable version of the market-leading asthma drug approved by FDA.

Teva Pharmaceutical Industries Ltd. is doubling down on its efforts to develop an interchangeable generic Advair. The company will advance an internal candidate and a second acquired with the acquisition of Allergan PLC's generic drug business, Teva Global Generic Medicines Group President and CEO Sigurdur Olafsson said during the company's second quarter sales and earnings call Aug. 4.



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The financial update fell just days after the Federal Trade Commission cleared Teva's \$40.5bn acquisition of Allergan's generic drug business July 27 and 48 hours after the closing of the deal Aug. 2.

"Our intention is to continue with both programs so we have a better chance of introducing a generic interchangeable AB-rated Advair to the market," Olafsson said. Neither program has completed Phase III testing yet, he added. Teva is aiming to be in a position to file an abbreviated new drug application (ANDA) for a fluticasone/salmeterol drug in late 2017 or early 2018, he said.

The launch of an interchangeable ge-

neric version of GlaxoSmithKline PLC's blockbuster drug for asthma and chronic obstructive pulmonary disease is viewed as a lucrative commercial opportunity because of the drug's widespread use, pressure from payers to reduce costs in the category and high barriers to entry in the respiratory field that are expected to limit the amount of generic competition.

Two other generic drug companies have already confirmed they have filed ANDAs for generic versions of Advair in the US: Mylan NV and Hikma Pharmaceuticals PLC. Both applications have user fee dates in the first half of 2017, although there is no guarantee of a first round approval given FDA's concerns about the complicated delivery of respiratory drugs.

Teva's merger with Allergan's generic business positions the Israeli company as the dominant player in the generic industry. The company provided investors with a financial update for the combined company in July, estimating net revenues in 2019 would be \$26.7bn to \$27.8bn in 2019 and EBITDA would be \$10.7bn to \$11.5bn. The firm also plans to host an investor meeting in September to overview the combined business.

Teva announced Aug. 3 that it would also buy Allergan's Andia Inc., the fourth largest distributor of generic pharmaceuticals in the US and a business Allergan previously said it would keep. Teva will pay \$500m to buy Andia, gaining three distribution centers with a total of 650 employees.

Andia came to Allergan through legacy Actavis, like the generic drug business, and Olafsson, who previously worked at Actavis, knows both businesses well. "It really gives us an opportunity to service our customers better, not only on the generics side but also in terms of our specialty business," he said.

Andia provides access to 60,000 pharmacies, Olafsson said, but is much smaller than the top three drug distributors in the US and has a reputation for delivering a high level of service.

Teva reported lower generic drug revenues in the second quarter, down 7%

compared to the second quarter of 2015 to \$2.3bn. US generic drug revenues declined 33% to \$892m due to lower sales of aripiprazole (*Abilify*), esomeprazole (*Nexium*) and budesonide (*Pulmicort*) due to loss of exclusivity. Profit of \$1.1bn was down 11%.

The company's specialty drug business had a better quarter, with sales of \$2.3bn up 9% in the quarter, fueled by sales of its top-selling brand drug *Copaxone* (glatiramer) and respiratory products.

VIGODMAN PLEDGES COPAXONE 40MG EXCLUSIVITY UNTIL 2H2018

One overhang for Teva remains the exclusivity for Copaxone, with some investors concerned about how long the company will be able to fend off generic competition to its newer 40mg dose. Novartis AG's Sandoz already launched a generic version of the original Copaxone, administered daily, in June 2015, but Teva has been able to defend against it by switching patients to the 40mg dose, administered three times a week.

Now the company is facing generic threats to the new dose on multiple fronts. Generic rivals including Mylan and Sandoz have filed ANDAs for the 40mg version. Mylan announced the US Patent and Trademark Office instituted an inter partes review (IPR) proceeding against three of five patents protecting the 40mg version last year.

CEO Erez Vigodman insisted during the conference call that the 40mg version of Copaxone will be safe until the second half of 2018 because any generic launch prior to a final non-appealable court ruling on all five patents would be at-risk.

The company expects a decision on the IPR proceedings by Aug. 25. IPR decisions can be appealed by either side to the federal circuit, Vigodman noted, a process that should take about a year.

Teva has also filed a patent infringement lawsuit against several generic drug manufacturers in Delaware district court, with proceedings expected to begin in September, Vigodman said. ▶

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Roche Aborts But Regeneron, Amgen and Pfizer Sign Up

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Deal activity over the past seven days sees Roche knock back Inovio a second time, Regeneron plan for its future via an alliance with Adicet Bio, Amgen supplement its preclinical pipeline with a candidate from Advaxis, and Pfizer shore up its gene therapy ambitions with an acquisition.

Below is a roundup of some of the most noteworthy transactions that occurred between July 31 and August 5.

ROCHE KNOCKS INOVIO, AGAIN

Roche has decided to break off its deal with Inovio Pharmaceuticals Inc. for the development of hepatitis B DNA immunotherapy INO-1800, which is in Phase I testing.

Inovio's president and CEO Joseph Kim put Roche's move down to a "strategic decision in the area of hepatitis B." The news comes less than two years after Roche's "surprise" decision to return rights to the prostate cancer immunotherapy INO-5150. Both products were licensed by Roche in 2013 for a \$10m signing fee, with potential milestone payments to Inovio of \$412.5m.

Inovio plans to continue development of INO-1800 independently. A Phase I trial is currently enrolling patients in 30 sites in the US and Asia-Pacific. Inovio hopes to complete enrollment in the first half of 2017 with results due in the second half.

REGENERON LOOKS TO THE FUTURE

Regeneron Pharmaceuticals Inc. has entered a collaboration and licensing agreement with "off-the-shelf" cell therapies developer Adicet Bio Inc.

Adicet was founded by OrbiMed and Aya Jakobovits, a venture partner at the VC firm who was president and founding CEO of Kite Pharma Inc., a developer of autologous, or personalized, cell therapies. Adicet raised \$51m in a series A round at the start of this year. The relative ease of manufacturing and distributing off the shelf therapies may pose a threat to companies in the field of autologous chimeric antigen receptor T-cell (CAR-T) therapies, including Kite and its competitors Juno Therapeutics Inc. and Novartis AG.

According to Regeneron, its collaboration with Adicet is intended to generate multiple clinical product candidates for various hematological and solid tumor cancers. Under their agreement, Adicet will receive a \$25m upfront payment, as well as research funding over the next five years.

AMGEN UNLOCKS RUNWAY FOR ADVAXIS

Amgen Inc. has lowered stress levels at Advaxis Inc. by signing a global agreement for the development and commercialization of the small biotech's preclinical cancer immunotherapy ADXS-NEO that sees it make a \$40m upfront payment and purchase \$25m of Advaxis stock.

The financial support from Amgen "puts Advaxis on very solid footing to continue to aggressively advance lead product candidate axalimogene filolisbac, also known as AXAL," said Advaxis CEO Daniel O'Connor on a conference call accompanying the announcement.

Advaxis has had a turbulent time with AXAL, which is in Phase III testing. It had briefly been the subject of an FDA clinical hold last year. The hold was lifted in December.

Advaxis will lead the clinical development of ADXS-NEO through proof-of-concept, retain manufacturing responsibilities, and receive potential milestone payments of up to \$475m plus royalties.

PFIZER EXPANDS GENE THERAPY PRESENCE

Pfizer Inc. has expanded its commitment to gene therapy with the acquisition of Bamboo Therapeutics Inc. The privately held firm is developing gene therapies for rare diseases related to neuromuscular conditions and those affecting the central nervous system.

Earlier in the year Pfizer bought a 22% stake in Bamboo for \$43m. The latest transaction sees Pfizer buy the rest of the company for \$150m, with its shareholders being eligible for potential payments of up to \$495m contingent upon certain milestones. The deal significantly expands Pfizer's presence in gene therapy by providing it with

a clinical and several pre-clinical assets that complement its rare disease portfolio, an advanced recombinant Adeno-Associated Virus (rAAV) vector design and production technology, and a fully functional Phase I/II gene therapy manufacturing facility that Bamboo acquired from the University of North Carolina earlier this year.

JAZZ AND PFENEX TEAM UP

Pfenex Inc. has granted Jazz Pharmaceuticals PLC worldwide rights to develop and commercialize multiple early stage hematology product candidates. The agreement also includes an option for Jazz Pharmaceuticals to negotiate a license for a recombinant pegaspargase product candidate with Pfenex. Under the agreement, Pfenex will receive upfront and option payments totaling \$15m and potential milestones of up to \$166m and royalties. Both parties will be contributing to development efforts.

JANSSEN BREAKS IT OFF WITH CARNA

Just nine months after teaming up, Janssen Biotech Inc. (a J&J subsidiary) has called off its deal with Japanese biotech Carna Biosciences Inc. covering a small molecule kinase inhibitor program. Details are sketchy on what went wrong, but Carna is attributing it to discontinuation on the part of Janssen owing to "strategic reasons." However, "this program is considered promising," said Carna, and it intends to continue developing it.

MAYNE CLOSES TEVA/ALLERGAN DIVESTITURE

Mayne Pharma has completed its \$652-million transaction with Teva and Allergan, taking ownership of 37 approved and five filed generic pharmaceutical products. The transaction is part of the largest generic pharmaceutical divestiture overseen by the Federal Trade Commission and the result of Teva's \$40.5bn acquisition of Allergan's generic drug business, which closed last week. Mayne Pharma secured the greatest number of products of the 11 buyers. ▶

New UK Cancer Drugs Fund Dismays Pharma, Charities

The re-launch of the controversial Cancer Drugs Fund in the UK has offered another point for debate about cancer drug pricing, budgetary pressures and the cost of innovation. Pharma companies believe they will have to shoulder additional financial risks while patients will still not get full access to the medicines they need.

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Pharma and charities in the UK expressed concerns following the formal launch of the revamped Cancer Drugs Fund, saying the new entity – controlled by the National Institute For Health and Clinical Excellence (NICE) – will not solve underlying problems of drug reimbursement which, in turn, restrict access to novel oncology therapies.

Firms claim the NHS failed to listen to industry on how best to manage potential over-spending, while some patient groups believe the underlying problems of how cancer drug value is assessed have not been addressed, which they believe will leave people still without access to drugs available in other countries.

NHS England earlier in July issued new guidelines on how cancer drugs will be appraised and funded in the UK, including the operation of the controversial Cancer Drugs Fund (CDF), which had been established in 2011 as a separate silo fund for cancer drugs that NICE assessed as being too costly for the publicly funded National Health Service (NHS). It was closed in March after heavily overspending.

Announcing the revamped fund is “open for business,” Jonathan Fielden, deputy national medical director at NHS England, on July 29 said: “Today marks the culmination of extensive work to ensure the new CDF will benefit the cancer patients, taxpayers and industry. The new approach developed by NHS England and NICE is faster and less rigid than before, meaning patients will be able to access promising new and innovative treatments much earlier.”

The new CDF is a “managed access” fund, with a fixed annual budget of £340m. Publishing of the reforms, unveiled late on July 8, followed a 12-week consultation that ended in February.

Under the new process, all new cancer drugs will be referred to NICE, which is independent of government, for appraisal, a process which will start much earlier than previously with the aim of publishing draft guidance prior to a drug receiving its marketing authorization and then final guidance within 90 days of marketing authorization wherever possible.

Any drugs receiving either a draft recommendation for routine commissioning or, where uncertainty exists, a recommendation for use within the CDF will receive interim funding from the CDF from the point of marketing authorization.

The new Cancer Drugs Fund will now have clear entry and exit criteria allowing medicines to move in and out over time, whereas the old fund only had entry points. There is also a much needed system for getting some promising new cancer medicines to National Health Service patients more rapidly, while gathering evidence about their effectiveness.

All new drugs will enter the NICE appraisal process before licensure, and products referred to NICE by government ministers will get draft recommendations at the time of a positive opinion from the European Medicines Agency and final guidance will be published within 90 days of marketing authorization. “This is

faster than any other European country and will benefit NHS patients and companies alike,” a spokesperson said. NICE has already started looking at the drugs in the old CDF to see whether they can be recommended for routine funding, he added.



CDF OVERSPEND WORRIES PHARMA

A major sore point for the pharma sector will be how overspending by the fund is financed.

To avoid the CDF overspending – and thus being closed to potential new entrants – a proportional rebate will be applied to all pharmaceutical companies receiving any funding from the new CDF budget in the event of an overspend. Agreement to this mechanism will be a condition for all pharmaceutical companies receiving funding from the CDF budget, according to NHS England.

That arrangement worries the pharma industry operating in the UK.

“Given the fact that the old fund consistently overspent significantly on its allocated budget, and that industry already underwrites the majority of expenditure on branded medicines over and above agreed levels, a fairer and more equitable system of financial risk must be prioritized,” said Paul Catchpole, value and access director at the Association of the British Pharmaceutical Industry (ABPI), referring to the negotiated voluntary five-year Pharmaceutical Price Regulation Scheme (PPRS) currently in effect in Britain.

David Montgomery, Pfizer UK’s oncology medical director, said that “while we’ve indicated our agreement to proceed with the new arrangements for the fund, we remain concerned that many cancer medicines still won’t get to patients through either NICE or the new CDF.”

“The new CDF won’t work for many modern cancer medicines.

NHS England has not listened to concerns expressed by industry around the expenditure control mechanisms, in which companies are expected to underwrite 100% of all risk in managing the CDF budget," Montgomery said, adding "we believe that this creates uncertainty for industry and does not accurately reflect the significant contribution that industry makes already in improving patient access to the medicines they need.

Lisa Anson, country president for AstraZeneca UK and Ireland, said the fundamental issues with how NICE assesses cancer medicines remain. "Unless these are addressed, patients will continue to face the same access challenges that led to the CDF being set up in the first place. Also, the new operating procedure for the CDF introduces a complex commercial process for companies to navigate, on top of discussions that have already taken place with NICE."

Some patient groups are alarmed by the changes.

"The new CDF will do next-to-nothing to solve the wider problems that are preventing NHS patients from accessing the best cancer drugs," said Baroness Morgan, the chief executive of the charity Breast Cancer Now.

"The CDF was set up because NICE's methodology was not working for cancer drugs, and this new process offers little change. With the Fund's drug assessment now being handed back to NICE, we worry that patients in England will miss out on effective drugs being made available in other countries," she said.

But the NICE spokesperson threw the issue back at the drug makers, saying "it's now up to those companies to show that they recognize the challenges as well as the opportunities their new drugs present to patients and the NHS by showing the same flexibility on cost as they have in their recent negotiations with NHS England for drugs already in the CDF."

Anticipating that stance, AstraZeneca's Anson said "we recognize NHS budget challenges, however it is also important to recognize the value of novel breakthrough cancer medicines that extend and improve the quality of patients' lives."

Pfizer's Montgomery noted that pharma "is a high-risk industry and it's not as simple as, or sustainable to, continuously ask companies to drop the price of these specialist medicines. It will impact our ability to make further medical progress if we do so."

Roche UK's general manager Richard Erwin echoed that frustration, adding: "now that the assessment of new cancer medicines for reimbursement has been returned to NICE, we must, as a matter of urgency, address the challenge they have in assessing the real clinical value of cancer treatments – which necessitated the creation of the original CDF. We are calling on government today to review NICE's assessment methodology to stop patients facing ongoing anxiety around the availability of existing and new cancer medicines."

Breast Cancer Now's Morgan said the pharmaceutical industry should also take responsibility and begin offering "more sensible prices." She said the UK government should also get more actively involved to find a workable balance.

"Absolutely nobody benefits if effective new drugs are not made available on the NHS. We believe that enabling the British government to negotiate on price – as happens elsewhere in Europe – could significantly improve access for cancer patients," she said. ▶

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Astellas Dips Into Digital Health

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New venture DigiTx will give Astellas a leg up in its quest to access novel digital health technologies, in a move unveiled as the Japanese firm reported continued strong growth for top product Xtandi.

Astellas Pharma Inc. is aiming to board the digital health train through a new US investment venture it has set up with the major healthcare-focused venture capital group MPM Capital.

California-based DigiTx Partners will invest in broad initiatives across the digital health area, with a "special focus on companies which create solutions that improve patient outcomes and provide substantial synergy with a broader pharma business," the companies said.

The investments will concentrate on earlier stage companies but will include both start-ups and those at the growth stage. Astellas in Japan declined to disclose further details of the investment split or amounts in DigiTx, or the total fund that the new company would have available for investment.

The Japanese major and MPM already have some links through the US immuno-oncology venture Potenza Therapeutics Inc., in which MPM is a founding investor and Astellas last year took out an option to acquire as part of a development alliance.

While MPM is already an investor in the digital health space through the personal genetics and DNA analysis company 23andMe Inc., Astellas is taking its first decisive steps, apparently hoping through DigiTx to tap into technologies that it might use in its own business. "We will explore business opportunities... and extend our knowledge in the area," chief strategy officer Dr. Kenji Yasukawa said in a statement.

Digital health encompasses everything from novel devices to improve drug delivery to mobile apps, and technology to improve physician-patient interactions, digitize medical records, disseminate diagnoses, allow online booking of appointments, and to monitor individual health parameters.

Big pharma has been taking steps into the field for a while, and other Japanese companies are now doing the same, with Eisai for instance recently unveiling an online portal to help link dementia patients with carers and medical staff

XTANDI DOMINATES Q1

News of the venture came as Astellas reported fiscal first quarter results dominated by the performance of prostate cancer drug Xtandi (enzalutamide; licensed from Medivation Inc). Global sales of the anti-androgen rose 9% to JPY64.2bn (\$633.2m) in the three months, dominated by the US, with Astellas saying it is looking to promote further penetration in the chemotherapy-naive metastatic castration-resistant prostate cancer setting.

The drug has already been launched in around 60 countries in various indications, including more than 40 in the chemo-naive setting. Astellas is forecasting that worldwide sales for the full fiscal year will rise by around 17% to JPY296bn. ▶

From the editors of *PharmAsia News*

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Stockwatch: The Art Of Strategic News Placement

Earnings announcements from Teva and clinical trial results from Biogen, Ionis and Sage have turned out to have quite different interpretations in retrospect. Exciting news can sometimes look more like a vehicle for strategically timed stock promotion than a genuine material event.

ANDY SMITH

Teva Pharmaceutical Industries Ltd. recently pre-announced its second-quarter results along with rosy long-term financial guidance that extended to the end of the decade. Teva's forecasts incorporated a number of assumptions that included the acquisition of Allergan PLC's generics business with associated cost savings, and the announcement resulted in about a 4% jump in Teva's share price. The analysts from Mizuho suggested that Teva's investors were "reassured with above-consensus longer term guidance and a bullish stance on the Allergan deal."

When Teva officially announced its second-quarter report on August 4, the results were "roughly in line with expectations" according to the analysts from JP Morgan but the US generics business was below expectations. Increasing the US generic footprint was *the raison d'être* for the Allergan transaction so it was just lucky that Teva's \$15bn debt issue came a few days after its rosy advertisement for its future and before last week's earnings report.

Adding to Teva's commentary on US generic drug price deflation were the pre-announced sales and profits warning from Hikma Pharmaceuticals PLC as the lowered profitability of its US generics business resulted in a full-year guidance cut.

With last week's raised tempo on the utilization of biosimilars by companies where their use will generate more profits than the originator molecule – pharmacy benefit managers such as CVS Health Corp. and dialysis clinics like Fresenius Medical Care AG – a strategic focus on US generic small molecules rather than biosimilars now looks less than strategically optimal. No wonder Allergan retained its biosimilar business.

BIOGEN ACQUISITION SPECULATION

Early access to the results of a positive interim analysis of Ionis Pharmaceuticals Inc.'s intrathecally-administered antisense drug

nusinersen in the phase III infantile-onset spinal muscular atrophy ENDEAR study enabled partner Biogen Inc. to announce the exercise of its \$75m option to acquire the commercialization and development rights for nusinersen. Despite no public disclosure on the detail of the safety, efficacy, how many patients had been treated before the study had been stopped or the status of the other primary or secondary endpoints, the share prices of both companies were propelled up about 30% and 8%, respectively. The analysts from Leerink assigned \$2bn in sales by 2022 for nusinersen while those from Citigroup described the result as "good news comes early." However, without a single p-value in sight I was left wondering about the real purpose of all the enthusiasm.

Later in that same week, press reports of Allergan's and Merck & Co. Inc.'s interest in acquiring Biogen prompted a further 10% share price spike and I started to wonder whether the nusinersen interim analysis announcement had been stage managed in order to push up the price for Biogen.

Both the interim ENDEAR analysis and any M&A interest would have been known by Biogen well before any of last week's announcements. In the event, a ticker-tape parade of sell-side analyst notes fluttered down from the internet assigning take-out valuations for Biogen – that now included nusinersen – as high as \$414 per share (compared to the \$316 where they finished the week). Within 18 hours, these must have felt like the black flies in Alanis Morissette's Chardonnay as firstly Allergan was suggested not to be interested and then Biogen itself was reported as not receiving any formal expressions of interest.

SAGE DATA

With a p-value of 0.008 for the primary endpoint, there appeared to be no scope for ambiguity in the announcement of SAGE Therapeutics Inc.'s Phase II trial results for SAGE-547 in post-partum depression (PPD).

Almost immediately after the announcement there were questions from social media commentators on why, when the study was designed to enrol 32 patients, only ten were enrolled on SAGE-547 and 11 on placebo. In addition, since the drug is parenterally administered and has limited patent protection, there were further doubts on the commercial potential for SAGE-547. With such a small number of patients but data on the mean reductions from baseline for SAGE-547 and placebo in the primary endpoint of Hamilton Rating Scale for Depression (HAM-D) at 60 hours, the number of patients in each arm achieving remission (HAM-D <7) and the percentage remission in each arm, a simulated dataset can be constructed that fits all Sage's reported averages and results in the same p-value.

Analysts from Cowen described Sage's study, as having "very robust positive results" which of course they are not, while Sage suggested that a Phase III study may not be required, which of course it will be.

In the cool light of retrospect, recent pre-announced earnings and clinical trial results seemed to have the real purpose of either raising money, or helping to sell the company involved. Is it too cynical to wonder if many announcements of this type are really intended just to result in a transaction rather than to disclose material events?

The Magna Biopharma Income fund holdings include Allergan and Fresenius.

Andy Smith is chief investment officer of Mann Bioinvest. Mann Bioinvest is the investment adviser for the Magna BioPharma Income fund which has no position in the stocks mentioned, unless stated above. Dr Smith gives an investment fund manager's view on life science companies. He has been lead fund manager for four life science-specific funds, including International Biotechnology Trust and the AXA Framlington Biotech Fund, and was awarded the Technology Fund Manager of the year for 2007. ▶

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Late-stage clinical developments for the week 29 July – 4 August 2016

LEAD COMPANY	PARTNER COMPANY	DRUG	INDICATION	MARKET
REGULATORY APPROVAL				
Neurim Pharmaceuticals Ltd.	-	<i>Circadin</i> (melatonin) prolonged-release tablets	insomnia	Honduras
SUPPLEMENTAL REGULATORY APPROVAL				
Merck & Co. Inc.	-	<i>Keytruda</i> (pembrolizumab)	advanced non-small cell lung cancer	EU
Ipsen	-	<i>Dysport</i> (abobotulinumtoxinA)	lower limb spasticity in children	US
REGULATORY FILING ACCEPTED				
Sanofi	Regeneron Pharmaceuticals Inc.	sarilumab	rheumatoid arthritis	EU
SUPPLEMENTAL REGULATORY FILING ACCEPTED				
Taiho Pharmaceutical Co. Ltd.	Taisho Toyama Pharmaceutical Co. Ltd.	<i>Zosyn</i> (tazobactam plus piperacillin)	complicated skin and soft tissue infections	Japan
ORPHAN DRUG DESIGNATION				
Roche	-	<i>Zelboraf</i> (vemurafenib)	Erdheim-Chester disease	US
Vicore Pharma AB	-	C21	idiopathic pulmonary fibrosis	EU
FAST-TRACK STATUS				
Microbion Corp.	-	MBN-101	diabetic foot ulcers	US
Vaccinex Inc.	-	VX15 MAb	Huntington's disease	US
Shire PLC	-	volixibat (SHP626)	non-alcoholic steatohepatitis (NASH)	US
BREAKTHROUGH THERAPY DESIGNATION				
Novartis AG	-	ribociclib (LEE011)	HR-positive HER2-negative breast cancer	US
MEI Pharma Inc.	-	pracinostat	acute myeloid leukemia	US
COMPLETE RESPONSE LETTER				
ADMA Biologics Inc.	-	RI-002 (intravenous immunoglobulin)	primary humoral immunodeficiency disease	US
REGULATORY FILING				
Sunovion Pharmaceuticals Inc. (Sumitomo Dainippon Pharma Co. Ltd.)	-	SUN-101 (glycopyrrolate)	chronic obstructive pulmonary disease	US
SPECIAL PROTOCOL ASSESSMENT AGREEMENT				
Amarin Corp. PLC	-	<i>Vascepa</i> (eicosapentaenoate)	dyslipidemia	US
PHASE III TRIAL INITIATION				
PharmaMar SA	-	lurbinectedin (PM01183)	small cell lung cancer	-
DBV Technologies SA	-	<i>Viaskin Peanut</i>	pediatric peanut allergy	-
Edge Therapeutics Inc.	-	EG-1962 (nimodipine microparticles)	subarachnoid hemorrhage	-
PRODUCT LAUNCH				
Vanda Pharmaceuticals Inc.	-	<i>Hetlioz</i> (tasimelteon)	non-24 hour sleep-wake disorder	Germany
PRODUCT RELAUNCH				
MannKind Corp.	-	<i>Afrezza</i> (human insulin) inhaled powder	type 1 and 2 diabetes	US

Source: Informa Pharma Intelligence's Biomedtracker

Cambridge, Massachusetts-based **Proteostasis Therapeutics Inc.** has named **James M. DeTore** chief financial officer, **Dr. Geoffrey S. Gilmartin** chief development officer, **Dr. Marija Zecevic** vice president of business development and **Eric B. Rabinowitz** a new member of the company's board of directors. DeTore joins the company from bluebird bio, Inc., where he was CFO from 2014 through 2016, leading the company's financings and investor relations strategies, and helping to raise over \$720m in capital. Most recently, Gilmartin was senior medical lead for global medicines development at AstraZeneca PLC. Zecevic, the founder and managing director of consulting firm Zebra Ventures, has collaborated with Proteostasis Therapeutics on multiple projects since July 2014. Finally, Rabinowitz – who is currently vice president of global corporate development at Perrigo Company PLC – will replace Conor Walshe as a member of Proteostasis' board.

Chronos Therapeutics Ltd., a private biotech company focused on ageing diseases, brain and nervous system disorders, has named **Drs. Fraser Murray** and **Timothy Schulz-Utermoehl** vice presidents of pre-clinical development. The pair joins Chronos from Polleo Pharma, a UK biotech start-up company they co-founded, and will be re-

sponsible for three pre-clinical research programs Chronos recently acquired from Shire plc – these include a dopamine active transporter inhibitor program in multiple sclerosis fatigue and the company's orexin 1 antagonist program in addictive behaviors. Both Murray and Schulz-Utermoehl have previously held leadership roles at Shire, AstraZeneca PLC and Merck & Co.

Apellis Pharmaceuticals Inc. has appointed **Dr. Robert Kim** chief medical officer. Kim will help the company optimize its drug development strategy as its clinical programs progress toward late-stage clinical testing. Most recently Kim was CMO and head of R&D at startup Vision Medicines. He is currently an associate clinical professor of ophthalmology at the University of California, San Francisco.

Intrexon Corporation has named **Dr. Andrew J. Last** chief operating officer, effective August 29, 2016. Last, who will oversee operations across the company's multiple technology divisions and operating subsidiaries, will report to Intrexon's president Geno Germano. Most recently Last was executive vice president and COO of Affymetrix where he was responsible for directing five business units – overseeing strategic marketing, product management, R&D, clinical opera-

tions, regulatory affairs, quality assurance and overall manufacturing operations.

Ascendis Pharma A/S, a clinical stage biopharmaceutical company, has appointed **Scott T. Smith** senior vice president and chief financial officer. Smith was most recently director of the healthcare investment banking group at Wedbush Securities, from 2012 to 2016, where he led the healthcare team and oversaw a substantial increase in revenue and transaction volume. Ascendis Pharma is developing an internal pipeline of therapeutics using its TransCon technology to address unmet medical needs in rare disease indications. TransCon technology can be applied to a broad range of drug therapies, including proteins, peptides and small molecules, to create "prodrugs" that provide predictable and sustained release of an unmodified parent drug.

Araim Pharmaceuticals, has appointed **Ferdinand Breedveld**, chair of its board of directors. Breedveld will succeed **Dr. Tony Cerami**, who has been chair of the board since founding the company in 2006. Cerami will remain involved with Araim Pharmaceuticals as chair of the scientific advisory committee, focusing his efforts on the scientific advancement of the company's innate repair receptor (IRR) platform.

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