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Trump Drug Pricing Plan: Part D Surprises, PBM Challenges

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The Trump Administration's much-anticipated drug pricing plan proposes ideas for finding savings in Medicare Part D by modifying the protected classes policy.

The notion of changing the protected classes is among several policy proposals that had not been previously discussed by the Administration but are included in its "Blueprint to Lower Prices and Reduce Out-of-Pocket Costs."

The 44-page document, which includes more than 50 policy proposals, was released by President Trump and HHS Secretary Alex Azar during an event in the White House Rose Garden May 11. The breadth and number of policies included surprised many stakeholders and was greeted with concern by biopharma and pharmacy benefit managers.

"Today my administration is launching the most sweeping action in history to lower the price of prescription drugs for the American people," Trump said. "We will have tougher negotiations, more competition, and much lower prices at the pharmacy."

For example, the blueprint suggests, HHS may "support" better drug price negotiation in Medicare by "providing plans full flexibility to manage high cost drugs that do not provide Part D plans with rebates or negotiated fixed prices, including in the protected classes." Currently, "Part D plans are unable to negotiate lower prices for high-cost drugs without competition," the document says. "This change could allow Part D plans to use the tools available to private payers outside of the Medicare program to better negotiate for these drugs."

Part D plans are required to cover "all or substantially all" drugs in six protected classes, including antineoplastics, antidepressants, antipsychotics, immunosuppressants, anticonvulsants, and antiretrovirals.

The protected classes policy has hampered plans' ability to negotiate price concessions with manufacturers because they are not able to threaten manufacturers with non-coverage – every drug in a class must be on formulary. As a result, pricing for those drugs has not been subjected to the same pressure as non-protected classes.

The protected classes policy has long been the subject of criticism by insurers. The Centers for Medicare and Medicaid Services attempted to narrow the number of drugs that could benefit from the protected classes policy in a proposed rule released in early 2014. But fierce opposition from biopharma and patient groups led CMS to abandon the effort. *(Also see "CMS Drops Proposal To Change Part D Protected Drug Classes" - Pink Sheet, 10 Mar, 2014.)*

SHOULD DRUGS WITH PRICE INCREASES LOSE PROTECTED STATUS?

The blueprint also seeks stakeholder feedback on whether manufacturers of protected classes drugs that have increased prices or failed to provide rebates should have their protected status revoked.

"Should manufacturers of drugs who have increased their prices over a particular look-back period or have not provided a discount be allowed to be included in the protected classes?" the document asks.

CONTINUED ON PAGE 8

from the executive editor

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Last month, Pharma Intelligence hosted the Clinical and Research Excellence Awards in Boston, recognizing the top R&D achievements across the industry.

In the pages of *Scrip* we tend to focus on the clinical trial results and what they tell us about how a drug will fit into the commercial landscape – so it's a nice chance to step back and recognize the effort and innovation that goes into conducting the clinical trials and the companies that are taking the lead in key areas like rare disease development and real world evidence.

We were able to celebrate some recent accomplishments for some of the 2018 CARE Awards winners: Otsuka won Most Innovative Clinical Trial Design for the autosomal dominant polycystic kidney disease program for tolvaptan and won FDA approval the same day, while AveXis was lauded for Most Successful Early Phase Research for its gene replacement therapy AVXS-101 for spinal muscular atrophy a couple weeks after an $8.7bn buyout by Novartis.

The lifetime achievement award went to Josef von Rickenbach, co-founder and former CEO of Parexel, who over the past 35 years helped develop the entire field of clinical research organizations. The business he created has contributed to the development of more than 97% of the top-selling drugs today. (Stay tuned for an exclusive interview looking back at his career.)

Underneath all of the mergers and approvals and commercial successes (and failures) – the business of the biopharmaceutical industry – lies research. Basic science, discovery and development are the first steps toward later successes, and we're glad to highlight those accomplishments.

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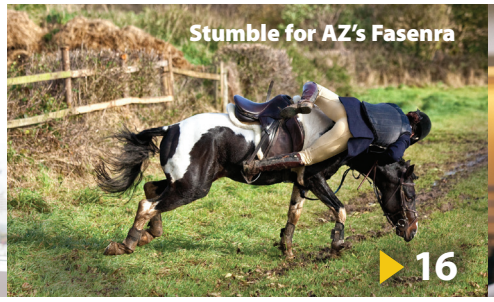

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Biopharma start-ups finally had an increase in financing activity, following three sequential quarters with a decrease. A review of biopharma start-up dealmaking and financing activity from January through March 2018, based on data from Strategic Transactions.

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$1.6bn Armo Buy Gives Lilly Its Most Advanced Immuno-Oncology Asset

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Eli Lilly & Co. is behind its big pharma peers in terms of investments in immuno-oncology, although cancer drugs already are an important part of its portfolio, but now it's catching up with the IO fervor via the $1.6bn acquisition of **Armo BioSciences Inc.**

The Armo deal gives Lilly its most advanced immuno-oncology (IO) asset – the pegylated Interleukin-10 (IL-10) known as pegilodecakin (AM0010), which is a next-generation IO drug that may work well alone and in combination with first-generation immunotherapies. Lilly Oncology Senior Vice President, Global Development and Medical Affairs, Levi Garraway spoke with *Scrip* on May 10, the day the deal was announced, about how pegilodecakin fits into the company's broader oncology portfolio.

> 'Our goal is to accelerate assets that are already in development, but also to augment the pipeline with multiple additional assets'

"Bringing in this particular asset, pegilodecakin, would bring one that is farthest along in clinical trials, but we do have several other IO assets in our pipeline," Garraway said.

"We brought it in because we felt that the mechanism of action was distinct and we saw that it had single-agent activity in some tumor types, but we do think that the biggest opportunity will likely be in combination," he added. "Combinations could include existing immune checkpoint inhibitors, but it will also include novel agents, and we do have some ideas about novel combinations using other [Lilly] portfolio drugs."

Lilly has its own PD-L1 inhibitor, LY3300054, in Phase I for the treatment of solid tumors, but the company lags behind leaders in the IO space, like **Merck & Co. Inc.** and **Bristol-Myers Squibb Co.**, which had the first PD-1 inhibitors approved in the US – *Keytruda* (pembrolizumab) and *Opdivo* (nivolumab), respectively.

Lilly also has early-stage immuno-oncology programs in the clinic targeting CSF-1R, TIM3 and IDO, and its preclinical alliances in the IO space include a collaboration involving Immunocore's T-cell receptor-based therapeutics and a cancer vaccine agreement with CureVac.

INVESTORS SUPPORT IO EXPANSION

However, Garraway notes that the company still is focused on oncology generally, not just IO, within its cancer drug portfolio.

"We are interested in building out our entire Lilly Oncology pipeline. Our goal is to accelerate assets that are already in development, but also to augment the pipeline with multiple additional assets. Some of them, of course, will come from our research labs, but others will come from external opportunities, such as the Armo Biosciences opportunity, and it's not limited only to IO," he said.

Lilly agreed to pay $50 per share for Armo – a 67.7% premium over the newly-public biotechnology firm's May 9 closing stock price of $29.82. Armo closed up 67% at $49.80 after the all-cash transaction was announced. Shareholders who've owned the stock since Armo's initial public offering in January at $17 per share will have nearly tripled their investment when the acquisition closes; the companies expect to complete the transaction during the current quarter. *(Also see "IPO Update: Seven In January As Big Returns, Solid's Slip-Up Contribute To Bubble Concerns" - , 2 Feb, 2018.)*

"Given the company's IPO occurred in January, this is one of the fastest post-IPO exits we've seen in a long time," Jefferies analyst Biren Amin said in a May 10 note. "We believe the terms are fair given Armo has presented Phase I/II data on pegilodecakin in pancreatic cancer, non-small cell lung cancer (NSCLC), renal cell cancer (RCC) and metastatic melanoma."

"Armo is currently running the Phase III SEQUIOA trial in second-line pancreatic cancer with the first efficacy interim analysis expected in 2020," Amin added. "The company also recently initiated [a] Phase IIb trial in combination with anti-PD-1 in first- and second-line NSCLC in the respective CYPRESS-1 and -2 studies, which are expected to complete in 2019. Furthermore, we think Lilly could potentially evaluate pegilodecakin in RCC and additional tumor types."

CYPRESS-1 combines pegilodecakin with Merck's Keytruda, while the IL-10 is being evaluated in combination with Bristol's Opdivo in CYPRESS-2.

"We believe [pegilodecakin] in NSCLC is the main motivator for the acquisition given the large market opportunity, modeling about $1bn risk-adjusted peak sales opportunity in the first-line setting alone by our estimate," BMO Capital Markets analyst Matthew Luchini wrote on May 10.

INVESTING IN LILLY'S LONGER-TERM STRATEGY

Lilly investors endorsed the Armo deal, sending the pharma's stock 2% higher to close at $80.86.

"Our initial impression of Lilly's Armo acquisition is incrementally positive as it meaningfully improves Lilly's oncology franchise and improves the probability of Lilly becoming a viable competitor in the increasingly fragmented IO market," BMO's Alex Arfaei said in a May 10 note.

"The acquisition also gives Lilly other IO assets, including a preclinical anti-PD-1 (AM0001) and a LAG-3, which create the interesting possibility of internal wholly owned IO combos," Arfaei wrote.

Pegilodecakin is Armo's only clinical asset, but the company lists AM0001 and the pegylated IL-15 AM0015 as being in the pre-investigational new drug (IND) application stage. The pegylated IL-12 AM0012 and the LAG-3 inhibitor AM0003 are preclinical.

"Our near-term focus is realizing the near-term opportunities for [pegilodecakin], but there are several preclinical assets that will deserve attention and testing in the clinic as well," Garraway said.

Morgan Stanley analyst David Risinger said in a May 10 note that Lilly has been taking steps recently to boost its immuno-oncology portfolio and its in-house expertise.

"Lilly's interest in IO was highlighted by its recent hiring of Leena Gandhi, director of thoracic medical oncology at NYU Perlmutter Cancer Center. Dr. Gandhi most recently served as the lead investigator on Merck's KEYNOTE-189 study," Risinger wrote.

In general, the company has committed to bringing in more external programs, while still developing most of its assets based on in-house research and development.

Lilly Chairman and CEO David Ricks said during the company's first quarter earnings call on April 24 that "strategically, we understand we need to be active externally, and you can count on us to continue to look at all available choices to add to our pipeline, in particular, in oncology." Ricks has noted that Lilly expects to source about one-third of its assets from outside the company going forward.

In oncology, Garraway said the strategy is built around the idea of targeting mechanisms that are known to be essential to the survival of cancers cells or to their ability to evade attack by the immune system.

"We spend a lot of time prioritizing our own internal efforts to make rooms for things like [pegilodecakin], but also coming up with a decision framework that draws from our understanding of the science and how we might develop it. Are there ways to enrich patents molecularly or characteristics that might make them more likely to respond?" he explained. "All of these go into how we recognize what assets, either internally or externally, might have potential. This happens to be an interesting IO candidate, but our strategy is not limited to IO in that regard."

Garraway said Lilly liked the preclinical data for pegilodecakin, which showed that pegylated IL-10 as a single agent clearly activated CD8-positive T-cells and caused tumor regression, which is how an IO agent should work. "We thought that the biological rationale was strong for that reason and we also liked the clinical data that we've seen [including] single-agent activity in some tumors in patients," he said.

USING IL-10 TO BOOST CHECKPOINT INHIBITORS

Lilly also was encouraged by initial results for pegilodecakin in combination with existing immune checkpoint inhibitors. "Overall, the package looked like it had the potential to bring additional value to patients across multiple types of cancer. There was no single thing that put it over the hump, but it was the aggregate picture that made us feel like this was a potentially interesting asset," Garraway noted.

The aggregate picture that the Lilly Oncology executive described is in line with what Armo President and CEO Peter Van Vlasselaer envisioned when he spoke with *Scrip* in 2016 about the company's $50m Series C venture capital round.

"The first wave of immuno-oncology has taken place and the first generation molecule is PD-1," Van Vlasselaer said at the time.

"The generally accepted viewpoint is that we can combine immuno-oncology agents and improve the outcome. The question will be, what are those molecules and what will be the next wave in the space?" he continued. "You have a cornerstone molecule for checkpoint inhibitors and molecules that target the microenvironment and others that prime tumors to be responsive. We think [the latter] will be the cytokines [like IL-10, 12 and 15]. They are potent immune stimulators."

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Lilly Reacquires Aurora Kinase Inhibitor Via AurKa Buy For $110m

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Eli Lilly & Co. said on May 14 that it will pay $110m up front to buy **AurKa Pharma Inc.** in a deal that will bring the Aurora kinase inhibitor AK-01 back home to Lilly, which licensed the molecule to AurKa's founding investor TVM Capital Life Science after the cancer drug candidate was deprioritized.

AurKa's investors stand to earn up to $465m in regulatory and sales milestone fees if Lilly wins US FDA and other approvals, and if the drug's sales meet certain goals. The back-end payout reflects the risk and potential upside of developing an Aurora kinase inhibitor – a drug class that has seen many attempts, but no successes to date.

Nevertheless, the asset fits well into Lilly's oncology strategy, which recently was described to *Scrip* when the company agreed to pay $1.6bn for Armo Biosciences Inc.

Lilly Oncology Senior Vice President, Global Development and Medical Affairs, Levi Garraway said in a May 10 interview that the company's goal "is to accelerate assets that are already in development, but also to augment the pipeline with multiple additional assets. Some of them, of course, will come from our research labs, but others will come from external opportunities … and it's not limited only to [immuno-oncology (IO)].

Lilly is interested in cancer drug mechanisms that are known to be essential to the survival of cancers cells or to their ability to evade attack by the immune system, Garraway explained. The AurKa transactions fits into the company's interest in disrupting cancer cell survival, because Aurora kinases (Aurora A, Aurora B and Aurora C) contribute to genetic instability that leads to tumor formation.

Garraway noted in Lilly's May 14 AurKa deal announcement that the acquisition "expands our pipeline with a promising oncology compound targeting a distinct cell cycle pathway. The work done by AurKa will allow Lilly to leverage emerging data about cancers in which this molecule might be effective, and determine if it can be beneficial to people living with various forms of cancer."

HIGHLY SELECTIVE, POTENTIALLY SAFER

AK-01 is described as highly selective for Aurora A and Lilly decided to bring the drug back into its research and development pipeline based on "potential clinical benefit observed in Phase I studies." The company said it will run additional studies "to determine if the selectivity profile of AK-01 can improve efficacy while limiting toxicity risks to a manageable level."

Informa Pharma Intelligence's Biomedtracker database shows that **Casi Pharmaceuticals Inc.** has the Aurora A inhibitor ENMD-2076 in Phase II for breast and liver cancers, while **AstraZeneca PLC** initiated Phase I/II studies for the Aurora B inhibitor AZD2811 in acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS) in July 2017 (it ended development of a predecessor in this class, barasertib, in 2011). Also, **Nemucore Medical Innovations Inc.** has its Aurora B inhibitor in Phase I studies for solid tumors and hematological malignancies.

Meanwhile, **Otsuka Holdings Co. Ltd.** completed a Phase I/II study in AML at the end of 2014 for AT9283 – an inhibitor of multiple kinases, including Aurora A and B – but never reported results for the asset acquired in the purchase of **Astex Pharmaceuticals Inc.** in 2013.

Also, **Amgen Inc.** does not list its pan-Aurora inhibitor AMG 900 among current pipeline programs and the company last reported Phase I results in breast, ovarian and prostate cancers in November 2014, noting some tumor responses as well as Grade 3 adverse events in at least 70% of patients, including neutropenia, anemia, diarrhea and thrombocytopenia.

Takeda Pharmaceutical Co. Ltd. ended development of its Aurora inhibitor alisertib in 2016 after multiple failed studies in solid tumors and hematological malignancies, including a Phase III failure in lymphoma in 2015.

Cyclacel Pharmaceuticals Inc. has not progressed the development of its Aurora inhibitor CYC116 since at least 2013 and development of **MabVax Therapeutics Holdings Inc.**'s TLK60404 has been on hold since 2012 as it prioritized the use of its financial resources, according to Biomedtracker. The database shows **AbbVie Inc.**'s development of ABT-348 has been suspended since at least 2015 and **Rigel Pharmaceuticals Inc.** ended development of AS703569 in 2010 after **Merck Serono SA** backed out of a partnership involving the drug.

Development of the **Vertex Pharmaceuticals Inc.** Aurora kinase inhibitor MK-0457, partnered with **Merck & Co. Inc.**, ended in 2008 after a safety flag was raised in 2007 – a QTc prolongation noted in a Phase II leukemia study – and after it did not meet pharmacokinetic standards in a solid tumor study. Vertex subsequently ended development of the Aurora inhibitor VX-689. **Pfizer Inc.**, Shanghai Advanced Research Institute and **Sunesis Pharmaceuticals Inc.** also have shelved Aurora kinase inhibitors.

AURKA ONE OF LILLY'S MANY TVM DEALS

Despite past decisions to end Aurora kinase inhibitors, AurKa is not the only company that sees value in the drug target, and the two-year-old company seems to have generated results promising enough for AK-01 to attract the attention of Lilly once again.

AK-01 was discovered at Lilly, but was out-licensed to TVM after the big pharma completed a review of clinical pipeline priorities in 2016. The investment manager's TVM Life Science Ventures VII fund, which invests in early-stage drug candidates that can be developed in a capital-efficient manner, started AurKa to develop the Aurora kinase inhibitor.

The 2016 transaction between Lilly and TVM for AK-01 is one of multiple relationships between the big pharma and the investment firm, according to Informa Pharma's *Strategic Transactions* database. Lilly reacquired the migraine drug lasmiditan via the $960m acquisition of **CoLucid Pharmaceuticals Inc.**, whose venture capital investors included TVM, in January 2017.

Also, Lilly has an option to acquire an immuno-oncology drug from **Modulate Therapeutics Inc.**, which TVM funded and launched in 2016. And **Esperas Pharma Inc.**, in which TVM is an investor, was founded in 2015 to develop a Lilly-discovered cancer drug.

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You Work In The Pharmaceutical Industry: Here's Why You Should Care About The Novartis Payments

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Breaking news that a major pharmaceutical player – **Novartis AG** – is linked up in the Donald Trump/Michael Cohen paying-off-a-porn-star fiasco took the industry by, well, storm May 8. The merits and legalities of Novartis' decision to pay what appears to be $1.2m to Essential Consulting, a company owned by Trump's attorney Michael Cohen, in 2017 will be debated, but at the end of the day, the payments have a glimmer of paying for access, and the whole affair puts the pharmaceutical industry back in the red when it comes to the balance sheet of public perception.

The payments raise a lot of questions. First and foremost, why would Novartis make these payments and what were they hoping to get in return? On that front, the company isn't saying. They did say they weren't able to get the service they had anticipated related to US health care policy. Novartis said in a statement that after an initial meeting with Cohen in March 2017, it decided not to engage further, though they continued making monthly $100,000 payments because the one-year contract could not be terminated until it expired in February 2018.

Another question, though, is why does the industry keep finding itself muddled in scandals that reflect so negatively on a business area that does so much that is good. Just last year it was **Allergan PLC** that drew criticism for linking up with a Native American tribe to essentially try to block generic *Restasis* from entering the market. Before that, it was **Mylan NV** that was caught up in an investigation over price increases for *EpiPen*. Of course, there is Martin Shkreli, who ended up in jail. The industry likes to point fingers at "bad actors," but there seems to be more than enough negative publicity to go around.

Lobbying is hardly new when it comes to pharma and public policy, and lobbying is entirely legal, as is paying for health care consulting. No one is charging that Novartis did anything illegal. It is hardly the only pharmaceutical manufacturer who was anxious for insights into Trump after he was elected president in November 2016; many firms hired lobbyists to predict and better prepare for the new administration. The CEOs of several US-based drug companies visited the White House to meet with Trump just after his inauguration in January 2017, eager to have his ear on issues like tax reform and drug pricing. But this particular scenario has some strange considerations to it, most notably why would Novartis expect Michael Cohen to be able to offer health policy expertise?

The legal filing from Aventatti & Associates, the attorney for the porn star Stormy Daniels, that first shed light on the payments by Novartis and other corporations says they were suspicious, coming just ahead of Trump agreeing to take a meeting with then incoming CEO Vas Narasimhan at the World Economic Forum in Davos, Switzerland in late January 2018. The insinuation is that Novartis paid for access to the president.

Narasimhan just talked during the company's first quarter earnings call April 19 about having dinner with President Trump in what, in hindsight, sounds like a public relations landmine. He was commenting on his positive outlook on any upcoming changes to the US drug pricing policy, pointing to encouraging conversations with FDA Commissioner Scott Gottlieb and CMS Administrator Seema Verma, as well as takeaways from dinners with President Trump himself.

Novartis insisted the agreement predated Narasimhan's ascent to CEO and that he had no involvement in the arrangement "whatsoever." The company seems to be pointing the finger, but at who? The former CEO Joseph Jimenez, who departed early this year after a relatively steady run and a smooth transition? Novartis is also facing political bribery allegations in Greece, which adds another layer of context to the issue.

Novartis has confirmed that it cooperated with Special Counsel Robert Mueller's investigation into the matter as part of his investigation into the Trump campaign and collusion with Russia, which sounds like a different kind of landmine to navigate altogether. Novartis provided the information and "considers this matter closed," the company said.

The bigger impact, however, may be fallout from embarrassing publicity. News of these payments comes at an important time for Novartis, when the company is pivoting increasingly toward highly innovative medicines and a message of developing breakthrough medicines for critical diseases that are worth their high costs. As the company's new CEO, Narasimhan has been an outspoken advocate in favor of the industry delivering value to patients and shaping the broader dialogue around a sustainable healthcare system. His tone has been refreshing, even as Novartis walks a difficult tightrope between delivering on innovation and pricing to value while launching a $475,000 a year cancer drug, the first-of-its-kind chimeric antigen receptor T-cell therapeutic *Kymriah*.

Now these payments cast a shadow over that message and put a sour note on any broader drug pricing points Novartis will make – and perhaps the industry more broadly. And this news breaks as President Trump is set to deliver a speech, already once delayed, on drug pricing May 11.

That raises another important point. US drug prices has become a fearsome topic for the industry to navigate and public perception of the industry continues to erode even as pharmaceutical manufacturers move closer to delivering potential cures for some of the most serious diseases.

Wells Fargo analyst David Maris warned in a May 2 report the US is on a long-term arc headed toward drug price controls. He said industry and investors do not see the trouble brewing. For all of industry's talk, it doesn't feel like pharma executives always accept the extent of the industry's public image problem. Maybe the people who work in pharma see so much of the science, the hard work, the investment and the slow, steady progress that benefits human health that they just can't see what the person picking up the unexpected prescription for an unwanted ailment at the pharmacy counter sees.

Maybe it is time to end the finger-pointing. No more it was them, not us. The problem is the industry's and it affects everyone.

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CONTINUED FROM FRONT COVER

"Should drugs for which a price increase has not been observed over a particular look-back period be treated differently when determining the exceptions criteria for protected class drugs?"

PART D NEGOTIATIONS HAVEN'T KEPT PACE WITH PRIVATE SECTOR

Medicare Part D has effectively used negotiating tools since it was launched but its approach needs an update, Azar later told a White House briefing with reporters.

"Over 15 years, as so often happens with government programs, it got frozen into place," he said. "And the private sector kept adapting and learning, especially after the economic crisis in 2007, how to control drug spend even better…We need now to bring the same tools that are available to the private sector to those Part D drug plans so they can negotiate even better."

Azar also highlighted a lack of price negotiation in the Medicare Part B program, which covers drugs administered by a physician. A plan to move at least some Part B drugs to the Part D program to subject them to more pricing pressure was included in the President's 2019 budget proposal. *(Also see "At Cross-Purposes? How Trump Budget's Part D Gap Discount Policy Aligns With New Law" - , 12 Feb, 2018.)*

"We've got to figure out ways to move those drugs, especially the high-cost ones, into the private Part D plan negotiations so that we can get a deal and start getting bargains on that for our seniors and for taxpayers," he said. The blueprint seeks comment on how that might be accomplished.

The Pharmaceutical Research and Manufacturers of America took issue with such policies in a statement on the blueprint. "The proposed changes to Medicare Part D could undermine the existing structure of the program that has successfully held down costs and provided seniors with access to comprehensive drug coverage," the group said.

"We must also avoid changes to Medicare Part B that could raise costs for seniors and limit their access to lifesaving treatments."

PBMS AND REBATING UNDER FIRE

Azar highlighted several other points in the blueprint during the briefing. Notably, he raised serious questions about how pharmacy benefit managers are compensated and of the rebating system altogether.

His comments about rebates echoed those made recently by FDA Commissioner Scott Gottlieb, who questioned whether the post-transaction price concessions should have a place in drug pricing anymore. *(Also see "A World Without Rebates: Is FDA's Gottlieb Offering New Vision?" - Pink Sheet, 9 May, 2018.)*

"We are calling into question today the entire structure of using rebates as the method of negotiating discounts in the pharmacy channel," Azar said. "What if instead we said: 'No rebates; flat price; fixed price in the contracts?'" The blueprint seeks comments on that approach to Part D contracting.

It also invites input on imposing a fiduciary duty on PBMs to act "solely in the interest of the entity for whom they are managing pharmaceutical benefits," without receiving payment or remuneration from manufacturers.

"We…have a real issue that we've got to look at, which is the role of compensation for pharmacy benefit managers," Azar maintained. "They're taking it now from both sides. They're getting compensated by their customers – the insurance companies – but they're also getting compensated by the drug companies they're supposed to be negotiating against."

In a statement on the blueprint, the Pharmaceutical Care Management Association argued that "getting rid of rebates and other price concessions would leave patients and payers, including Medicaid and Medicare, at the mercy of drug manufacturer pricing strategies…Simply put, the easiest way to lower costs would be for drug companies to lower prices."

NO FOLLOW-UP ON POS REBATES

Another important theme in the blueprint is out-of-pocket costs for patients. One policy proposal that has been strongly supported by pharmaceutical manufacturers is a requirement that plans redirect a portion of negotiated rebates to the point-of-sale to offset patient cost sharing.

The President's proposed budget includes a plan to implement point-of-sale rebates, the blueprint notes. However, the document does not solicit further comments on how such a program could be designed.

Asked how long it would take to implement the reforms in the blueprint, Azar said many of the proposals could be implemented relatively quickly through administrative action. Others would need legislation, which would be a more drawn out process.

Still, "it will take months for the kind of actions that we need here," he cautioned. "It took decades to erect his very complex, interwoven system. We're talking about entrenched market players, complex financial arrangements that would have to be redesigned. So I don't want to over promise that somehow on Monday there's a radical change. But there's a deep commitment" to pursue change.

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How Drug Promotion Might Change Under Trump's Rx Pricing Plan

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Any policy roll-out that features a Rose Garden announcement is destined to have some elements that are splashier than they are substantive, and the Trump administration's "Blueprint to Lower Prices and Reduce Out-of-Pocket Costs" is no exception.

During the May 11 event announcing the plan, HHS Secretary Alex Azar said, "Think about all the time everybody spends watching drug company ads, and how much information companies are required to put in them. If we want to have a real market for drugs, why not have them disclose their prices in the ads, too?"

The advantages of disclosure would be that "consumers would have much more balanced information, and companies would have a very different set of incentives for setting their prices," Azar said.

"We're immediately going to look into having the FDA require this," he said.

Like many of the "immediate" action items in the drug pricing plan, the new DTC requirement would actually take some time to implement, if the administration chose to proceed with it at all. *(Also see "'Immediate' Steps To Lower Drug Prices: The HHS Action Plan " - Pink Sheet, 13 May, 2018.)*

Later that afternoon, at a press briefing inside the White House itself, Azar expanded on the reasoning for the recommendation: "We believe it's an important part of fair balance that if you're telling a patient, activating a patient to have a discussion with their doctor about a drug, telling them all the good things that drug can do for them, it's material and relevant to know if it's a $50,000 drug or a $100 drug, because often that patient is going to have to bear a lot of that cost."

DTC advertising is a ubiquitous and often bizarre aspect of American life even for people who have no intention of asking their doctor about anything, so it makes sense that any plan to address drug pricing would address DTC advertising as well. The price-disclosure concept echoes a policy recommendation that the American Medical Association has made, but still feels like it's checking the box for "doing something" about advertising rather than offering meaningful reform.

To begin with, there's the question of what price would be disclosed. The administration's Blueprint says it could be the list price, but that would be misleading depending on the type of insurance a patient has. Also, what would be described by the list price? The price of a pill? A month's prescription? A typical course of treatment?

And given the shaky First Amendment ground that FDA finds its promotional enforcement powers on at the moment, it seems unlikely the agency would want to add a fight about compelled speech to its worries.

Tellingly, the DTC provision was not listed in separate statement issued by FDA Commissioner Scott Gottlieb about the pricing plan, suggesting that what makes a great talking point at the White House may not feel like great policy to those who would have to implement it.

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A POINT-OF-PRESCRIBING FORMULARY TOOL

While the DTC price disclosure concept probably won't gain much traction, another policy idea that Azar mentioned during the White House press briefing may have the potential to more significantly alter drug companies' promotional efforts.

"We also think it's a right that when you're sitting there with your doctor, you ought to be able to know what your out of pocket is for a drug you're going to be prescribed under your precise drug plan, and you ought to have that information, and you ought to have information on what competing drugs are that your doctor is not prescribing, and what you would pay out of pocket for that," Azar said. "And that ought to be across the Part B Plan and the Part D Plan."

As an example, Azar described a patient with a doctor and "this doctor has an infusion clinic as part of their office. So they write you a drug that might be an infused drug. You might have a $300 copay for that. Well, wouldn't you like to know that if the doctor instead wrote you a self-injectable drug, you'd have a $20 copay? And you could at least have an informed discussion. So we think that kind of informed consumer … will also help drive real savings in the system."

If HHS were to mandate some kind of point-of-prescribing formulary tool, it could significantly erode the power of sales rep interactions with physicians, since whatever preference they are able to impart on doctors could be undercut by a patient asking for cheaper alternatives before the scrip is even in hand.

Detailing would still help to drive volume more generally, and would continue to have an impact on uptake of products without clear in-class rivals, but expectations for what visits and reprints might be able to do for many drugs would have to be adjusted.

Of course, there are many steps between the single bullet point in the Blueprint and a world where sales reps can't move the needle because of patient formulary awareness, but companies should likely worry about this potential situation more than about having to disclose prices in their DTC ads.

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Takeda Feels Need For Speed In Approaching Shire Integration

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Takeda Pharmaceutical Co. Ltd.'s $62bn planned acquisition of **Shire PLC** may be moving ahead – pending shareholder approval – but in many ways the hard work is just beginning, even after a protracted pursuit that saw the Japanese firm raise its bid five times before final success.

While the acquisition of a late-stage pipeline and products in new niche areas are being seen as the main benefits by analysts in Japan, despite extensive elucidation of the key benefits of the deal by management, many investors in Takeda seemingly remain to be convinced of the fundamental rightness of the move.

The firm's shares closed down around 5% on May 9 after the acquisition agreement was announced the previous evening, apparently due to lingering worries over the huge purchase price – the largest overseas M&A deal ever in Japan – and funding arrangements (including a $31bn loan facility from a consortium of banks). This despite extensive company assurances over dividend policies and the rapid accretive affects of the transaction.

There also appear to be multiple "soft concerns" over the planned dual listing in New York and how this may detract from Takeda's Japanese identity, the longer term prospects for the price of the new shares, and the fact that current Takeda shareholders will be left with only 50% of the new company.

Takeda's CEO, Frenchman Christophe Weber, continued to give reassurances at media and analyst briefings that the merged company will be in a solid financial position and that the large debt load could be reduced quickly, through improved cash flow, cost savings, cash on hand, and potential asset divestments.

But one lesson from past mergers of this magnitude is that the integration process needs to be swift, decisive and well planned, to both assuage investor concerns and start to realize promised synergies and savings as soon as possible. Weber seems confident he is up to the job. He intimated to *Scrip* in an interview in 2016 that he is not one to shy away from a challenge, be it becoming the first non-Japanese head of Takeda (to which there was some investor and internal resistance) or being willing to "always look at acquisition opportunities" to reinforce the firm's geographic presence.

SPEED IS OF THE ESSENCE

But the level and complexity of integration required for bringing Ireland-based Shire into the fold is on a whole different level to Takeda's past much smaller acquisitions, while Shire itself is still digesting its own $32bn purchase of Baxalta in 2016.

Weber was eager to stress in a conference call that success factors for making the deal work have been taken on board, although details of the integration remain to be worked out over the time to the expected completion of the deal in the first half of next year.

In a line that will have pleased analysts looking for such action, "We want the integration to be very fast and very well done. We think that it's a key success factor," Weber declared.

"It will be a very fast integration into Takeda but really leveraging their [Shire's] know how and welcoming the majority of the employees. My belief is that many M&As fail because integration is not well done…the organization doesn't match the strategy or it's too slow."

Takeda in Tokyo told *Scrip* that the plan is for "full integration" of the two businesses off the bat, rather than potentially keeping Shire as a semi-autonomous rare diseases operation within the group, as happened after the 2008 acquisition of Millennium. This operated for some time as an oncology arm (given Takeda's then relatively limited activities in the area), although it is now fully integrated.

A Takeda spokesperson added that there would be no renaming of the merged entity and that "we will remain Takeda." Given that the firm has also just completed a major new global HQ building in Tokyo, any likelihood of the company moving outside its home base – despite half of the new company being held outside the country – also looks unlikely.

"We are committed to continue being headquartered in Japan and are in fact excited about our move into our new Global Headquarters next month."

On suggestions that the deal may be seen as a "stealth tax inversion", given Shire's Irish domicile that confers lower corporate tax rates, the company pointed *Scrip* to Weber's comments that the new Takeda's tax rate would be lower than Takeda's alone before the merger, but not down to the level of Shire's before the deal.

RESTRUCTURING PLANS

But while the intention is for rapid integration, what shape might this take? Takeda has said it is aiming for at least $1.4bn per year in savings three years after completion, and said in the call that initial one-off savings will be driven mainly by redundancies and consolidation of some locations, possibly in the US or even Ireland.

The indication so far is that the combined workforce of around 53,000 at the new Takeda could see overall cuts of 6-7%.

Chief Financial Officer Costa Saroukos said on the call that just over half of the projected savings will come from reduced selling general and administrative expenses, predominantly sales and marketing efficiencies, and overlapping office locations.

Takeda told *Scrip* it was still "too early to tell" what exact form these may take, and whether the operations of Shire - which Weber noted has a "much stronger position in the US" in its specialist areas - may be more or less affected.

Given the differences in commercial portfolios however, there would seem to be relatively little overlap in sales rep functions, and indeed Weber alluded in the call to increasing "voice" with prescribers through the merger.

Another 43% of the $1.4bn in savings is seen coming from R&D, predominantly rationalizing ongoing research and the early

stage pipeline, weeding out at an early stage those assets seen as non-core to the new company.

ASSET DISPOSALS?

Weber has hinted that some asset divestments might take place under the merger, without giving specifics, but stressed that no disposals are needed to retain investment grade. But if the company is not competitive, "sometimes it's better to sell than destroying value," he said.

Saroukos also emphasized that the post-acquisition net debt to EBITDA ratio (of 2.0x or less in the mid-term) does not include disposals, meaning that there there would be "considerable opportunity" to deleverage even further through this route. Given shareholder concerns over the level of debt, that Takeda's desire to pay this down quickly, this would seem to present a quick and easy opportunity.

Takeda has not hesitated in the past few years to hive off selected non-core assets and products, including a portfolio of older branded products in Japan facing generic competition to a local joint venture with Teva, along with selected facilities.

Shire's dry eye drug *Xiidra* (lifitegrast) is seen by some analysts as one divestment candidate, potentially along with Shire's hematology franchise.

While the company was non-committal on Xiidra, Weber was keen to stress in the investor call the "good synergies" in hemophilia, noting that Takeda is in fact already a leading supplier of plasma-derived products in Japan, that would add to Shire's very strong" business in the sector in a market where it has only a small presence. Although conceding that the competition in hemophilia is "very tight", Shire has already developed manufacturing advantages that are "very impressive", including a $2bn investment in a facility in Georgia, US, Weber pointed out.

Takeda will aim to leverage those along with Shire's skill set in developing constructs for gene therapy, the CEO added, also pointing to the high entry barriers for competitors, and "very high demand" globally for plasma products.

CULTURAL ISSUES

Despite all the talk of financial, research and commercial benefits, human factors can often be a key soft factor in making or breaking an acquisition. While this was not something touched on in the calls, Takeda already bills itself as a "modern global company rooted in Japan". With more than half of its business and workforce outside the country, and many non-Japanese top executives, it is probably the most internationalized of Japan's pharma companies.

While it has tried to remain cognizant of its 237-year history in Japan, and the core values of "Takeda-ism", the company has made a substantial shift to current international norms of staff management, hierarchy, promotion and diversity over the past few years.

As such, the combination with Shire should be relatively easy from the personnel aspect, with much likely confluence of approaches and systems, helped by both firms having their main business presence in the US and both abiding by the laws and practices there.

As for the top management, while it is planned that up to three Shire directors will join Takeda's board, the other senior leadership remains to be worked out. Five out of Takeda's 13 board members, and 11 out of 14 of the executive leadership are already non-Japanese.

Shire CEO Flemming Ørnskov will continue to lead Shire through the final stages of the Takeda acquisition (with the help of a substantial retention payment), but Takeda in Tokyo told *Scrip* that "we don't know yet" what, if any, his longer-term role in the new organization might be.

DEAL CATALYST?

One other big question arising from the Takeda/Shire combination is whether other major pharma firms in Japan might feel compelled to join in the M&A activity, either among themselves or with overseas targets, to remain competitive and build overseas presence.

While Takeda will not gain much in Japan from Shire's small business there, the same factors of a stagnant market and ever-more strict reimbursement pricing rules could force the internationally minded majors - which include Daiichi Sankyo, Astellas, and Eisai - to consider their options.

There have been some persistent rumors even before Shire relating to a possible combination of two of the country's top five firms, which would not be unprecedented given the merger of Yamanouchi and Fujisawa to form **Astellas Pharma Inc.** in 2005.

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Shire Poised To Move Into Pharma Top 10 With Takeda Combination

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With **Shire PLC** management finally recommending a $62.4bn offer from **Takeda Pharmaceutical Co. Ltd.**, the Japanese pharma is poised to move into the top 10 pharmaceutical companies club.

The combined company will have roughly $30bn in revenues, based on 2017 sales, leapfrogging Takeda into the top pharma rankings by revenue. Takeda/Shire would rank seventh based on pharmaceutical revenues, according to the *Scrip 100*, outpacing companies like **AbbVie Inc.**, **Teva Pharmaceutical Industries Ltd.**, **Amgen Inc.** and **AstraZeneca PLC**.

After turning down four previous offers, Shire's board has, as expected, backed the fifth – a 46% cash and 54% stock proposal – which means that Shire shareholders would own half of the combined group. The offer represents a premium of around 60% to Shire's share price before Takeda's interest was confirmed at the end of March and analysts at Jefferies Equity Research said "we believe the offer is not unreasonable" at a

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12% premium to Shire's £43.80 net present value share price estimate. *(Also see "Takeda Grabs Shire At Last After Long Pursuit" - Scrip, 8 May, 2018.)*

However, the sentiment on the London Stock Exchange, where the Irish-domiciled firm is quoted (Shire has a secondary listing on the Nasdaq in the US) was not hugely enthusiastic. The stock ended the day at £40.35, up 4.6%, but still short of the £49.01 value under the terms of the Takeda offer, which suggests that shareholders may still need some convincing about the virtues of the deal.

Jefferies expects the Shire share price to be spread out for a while, given that the acquisition is not expected to become effective until the first half of 2019, possibly a year away. "Plus owning around half of the enlarged Takeda with a Japanese and US listing could be unattractive/problematic for some shareholders," the analysts wrote.

Shire's management sounded convinced of the benefits in prepared statements with CEO Flemming Ornskov saying that the last five years has seen its transformation into the leading rare disease biotech and "with a truly innovative portfolio and pipeline, I believe that the combination of the two companies is in the best interests of shareholders and offers an opportunity to improve the lives of even more patients globally with rare and highly specialized conditions."

Chairman Susan Kilsby added that the deal "helps create an even stronger biopharmaceutical company, with a robust R&D pipeline and expanded global footprint [and] recognizes the strong growth potential of our leading products."

There was no Shire representation on the two conference calls held to announce the proposed deal, during which Takeda CEO Christophe Weber explained the rationale for a deal that represents the largest overseas acquisition by a Japanese company. Unsurprisingly, he focused on the addition of Shire's rare disease portfolio and specifically therapies for three sub-areas: lysosomal disorder products such as *Elaprase* (idursulfase) for Hunter syndrome, *Vpriv* (velaglucerase alfa) for type 1 Gaucher disease and *Replagal* (agalsidase alfa) for Fabry disease; hereditary angioedema products including *Cinryze* (C1 esterase inhibitor) and *Firazyr* (icatibant); and hematology, notably Shire's hemophilia franchise consisting of *Advate*, *Adynovate*, *Vonvendi* and *Feiba*.

Weber said rare diseases, oncology, gastrointestinal disorders and neuroscience will comprise the four core areas for the new Takeda and 75% of its sales. The other 25% will come from plasma-derived therapies, coming mainly from Shire, as well as vaccines, general medicines and ophthalmology.

Weber's comments about core areas should resolve Shire's dilemma about what to do with its neuroscience business. The company had been mulling over the possibility of a potential spin-off before announcing in January that it was creating two distinct divisions – one focused on rare diseases, the other on neuroscience.In April, Shire unveiled plans to sell its oncology business to **Servier SA** for $2.4bn.

DIVESTMENT POSSIBILITIES

When asked whether that 25% includes assets that Takeda would consider divesting, Weber said it was very early days. Then, he added that Takeda has offloaded some assets in the last three years from "some businesses [where] we were either not competitive or that were not core," including its respiratory portfolio which was sold to **AstraZeneca PLC**. *(Also see "AstraZeneca Builds Another Respiratory Extension With Takeda Deal" - Scrip, 16 Dec, 2015.)*

However, as Edward Thomason, company analyst at PharmaVitae, pointed out to *Scrip*, Takeda decided to out-license its ophthalmology assets to **Scohia Pharma Inc.**, a biotech venture the drug maker set up in March last year with Innovation Network Corporation of Japan and **Medipal Holdings Corp.**. This suggests that the end could be nigh for Shire's dry eye drug *Xiidra* (lifitegrast), he believes, as the drug and Shire's ophthalmology pipeline candidates do not fit with Takeda's current strategy and focus, and likely could be divested.

First-quarter sales for Xiidra reached $62.1m, up 61% year-over-year, but well short of consensus, which was $90m. Shire still expresses high hopes for Xiidra, with CEO Ornskov previously noting that prescription growth remains strong and the drug's overall performance has been held back in the US due to lack of Medicare access.

The company believes approval of Xiidra this year in Europe will be one of its near-term growth drivers, and Weber probably will be keeping a close eye on its progress. The Takeda CEO told the call that of the non-core assets, "some are doing well and others not so well." PharmaVitae's Thomason also suggested that "with no therapy area overlap, it's possible that Takeda may divest Shire's hematology franchise, selling out before headwinds strengthen with the launch of **Roche**'s *Hemlibra* (emicizumab)." The latter, which is restricted to patients with factor VII inhibitors, is expected by many observers to become the dominant treatment in the hemophilia market. However, Weber noted that Takeda has done its homework and taken into account the likely levels – and speed – of erosion for Shire's hematology franchise.

As to shaping the future direction for Takeda, up to three Shire directors will join the board upon completion of the acquisition (the Japanese firm's website notes that it has 13 board members). As part of "executive retention arrangements," Ornskov and Shire CFO Thomas Dittrich will each be entitled to receive a cash payment equivalent to 200% of their respective annual salaries and target bonuses for 2018; the total value of these arrangements is $9.1m, Takeda noted.

As for Ornskov's longer-term future, Thomason does not believe he will be on the board, "given his commitment to move away from neuroscience and small-molecule medicines that Takeda heavily relies on." He feels it is more likely that Andreas Busch, Shire's head of R&D, "will play a larger role in the combined firm, using his expertise in cardiovascular, oncology and hematology therapy areas to support the new company's rare disease therapy focus and platform." *(Also see "Shire Tempts Busch From Bayer As It Eyes Top Spot In Rare Diseases" - Scrip, 1 Dec, 2017.)*

Takeda, which predicts annual cost synergies of at least $1.4bn three years after completion, noted that its combined 53,000-strong workforce is likely to be reduced by 6%-7%, due to commercial, research and manufacturing overlaps, especially in the US. Takeda confirmed that its leadership team will be primarily located in Tokyo or the Boston area and will evaluate the consolidation of Shire's operations in Boston, Switzerland and Singapore, and the possibility of retaining its offices in these locations.

However, the merger could mean curtains for Shire's Dublin base. The companies said that a review of the functions at its current headquarters in the Irish capital, which has 400 employees, will be undertaken within the first year following completion of the acquisition.

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Exelixis' Cotellic Fails To IMblaze A Trail In Colorectal Cancer

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Exelixis Inc.'s hopes of expanding the label for *Cotellic* (cobimetinib) have been dealt a severe blow with the failure of a closely watched late-stage trial evaluating the MEK inhibitor in combination with **Roche**'s checkpoint inhibitor *Tecentriq* (atezolizumab) for colorectal cancer (CRC).

Exelixis got the bad news from Roche's Genentech unit, which was running the IMblaze370 trial, that the Cotellic/Tecentriq combo missed its primary endpoint and did not deliver an improvement in overall survival (OS) versus **Bayer AG**'s standard of care therapy *Stivarga* (regorafenib). No specific data have been published from the 363-patient study which evaluated the combination in patients with metastatic CRC whose disease had progressed or who were intolerant to at least two chemotherapy regimens.

Michael Morrissey, Exelixis CEO, said in a statement, "We are disappointed that the IMblaze370 trial did not reach a positive conclusion," noting that metastatic CRC "is an aggressive and difficult-to-treat disease." Cotellic is currently approved on both sides of the Atlantic in combination with Roche's *Zelboraf* (vemurafenib) for unresectable or metastatic melanoma in patients with a BRAF V600E or V600K mutation.

Morrissey added, "We will continue to work with Genentech on the evaluation of cobimetinib's potential in other tumor types," and there are two ongoing late-stage trials, both for the aforementioned skin cancer – IMspire150 TRILOGY is looking at a triple combination of Cotellic, Tecentriq and Zelboraf in previously untreated patients with BRAF V600-positive metastatic melanoma, while IMspire170 is evaluating the Cotellic/Tecentriq combo in BRAF V600-wild type metastatic melanoma.

The failure of IMblaze370 suggests that Exelixis faces a struggle in getting anything other than melanoma on the label for Cotellic, which is also being evaluated in trials as part of combination therapy for triple-negative breast cancer (TNBC). The results also highlight the company's reliance on cabozantinib, marketed in the relatively small medullary thyroid cancer market as *Cometriq* and as *Cabometyx* in the larger renal cell carcinoma (RCC) space.

Cabometyx received US approval at the end of December last year as a first-line therapy for RRC, having got an initial thumbs-up for the disease in 2016. That decision resulted in first-quarter 2018 sales of $128.9m, a 44% leap on the previous quarter and approval in Europe for first-line RRC is expected shortly, following a positive opinion from the Committee for Medicinal Products for Human Use (CHMP) received in March by partner **Ipsen**. *(Also see "CHMP Nod For Ipsen's Mainstay Cancer Drug Cabometyx In First-Line RCC" - Scrip, 23 Mar, 2018.)*

Morrissey stressed that Exelixis remained focused on maximizing the potential of the cabozantinib franchise, evaluating the compound alone or in combination with checkpoint inhibitors across numerous tumor types. In March, the firm completed the submission of a supplemental New Drug Application to the FDA for Cabometyx as a treatment for patients with previously-treated advanced liver cancer with data from the CELESTIAL Phase III trial which evaluated the drug in patients who had previously received treatment with Bayer's standard-of-care *Nexavar* (sorafenib).

Datamonitor Healthcare oncology lead analyst Hardik Patel told *Scrip* that while most of the company's development had indeed been focused on Cabometyx/Cometriq, when it comes to Cotellic, "there is still hope for the combinations" in the IMspire trials. The potential for a Tecentriq combination is higher in melanoma than in CRC to begin with, he said, as the efficacy of MEK inhibitors in melanoma was well established.

In TNBC, Patel said the data are still fairly early, but Cotellic did provide modest improvements in PFS in the Phase II COLET trial. However, due to the unmet needs in TNBC, those modest gains may be enough to support Cotellic's approval should the efficacy demonstrated in this trial be replicated in larger studies. Nevertheless, the results are clearly a blow and Exelixis shares took a bashing, down 10.6% to $19.35 at 12.35pm ET.

'NOT WHAT WE HOPED FOR' – ROCHE CMO

As for Roche, the results from IMblaze370 "are not what we hoped for," said chief medical officer Sandra Horning. The company noted that more than 95% of patients in the study had microsatellite stable (MSS) tumours where checkpoint inhibitor monotherapy has not demonstrated clinically meaningful efficacy in mCRC and now the combo has failed as well.

Still, analysts at Jefferies wrote in an investor note May 10 that early data had raised expectations for the combo. "Preclinical models had suggested targeted inhibition of MEK would lead to upregulation of MHC I on tumor cells, inducing intratumoral T-cell infiltration and enhancing anti-PDL1 activity," they noted.

The failure of IMblaze370 does not come as a huge surprise given that last month, recruitment was suspended for a Phase II study called MODUL which has an arm looking at the Cotellic/Tecentriq combo as first-line treatment of mCRC. The halt was called following four deaths, one of which was linked to treatment.

While disappointing for Roche and its hopes of getting another indication for Tecentriq, which is currently approved for bladder and non-small-cell lung cancer (NSCLC),Vincent Meunier at Morgan Stanley issued a same-day note saying that the failure of IMblaze370 "is a small negative [as] we note that other checkpoint inhibitors used in monotherapy have already failed in this difficult-to-treat indication hence expectations were low."

The Jefferies analysts are focusing on Tecentriq's potential in lung cancer, noting that at ASCO on June 4 Roche will present the OS analysis from the IMpower150 study of Tecentriq plus *Avastin* (bevacizumab) and chemotherapy in first-line non-squamous NSCLC and the primary progression-free survival and safety results from the IMpower 131 of Tecentriq plus chemotherapy, in first-line squamous NSCLC. *(Also see "Roche's IMpower150 Gets AACR Applause But Merck's KEYNOTE-189 Big Winner " - Scrip, 17 Apr, 2018.)*

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This Isn't The Big One: Darzalex Wins US Approval In First-Line Multiple Myeloma

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Following a priority review, Johnson & Johnson's **Janssen Biotech Inc.** has gained supplemental approval in the US for *Darzalex* (daratumumab) to treat newly diagnosed multiple myeloma patients who are ineligible for autologous stem cell transplant. However, the approval was for a combination of Darzalex with a three-drug regimen known as VMP that is used more commonly in Europe and Japan than the US.

VMP is *Velcade* (bortezomib), marketed by **Takeda Pharmaceutical Co. Ltd.** exclusively in the US and partnered in Europe and Japan with **Johnson & Johnson**), melphalan and prednisone. The preferred first-line treatment approach in the US is VRD – Velcade, **Celgene Corp.**'s *Revlimid* (lenalidomide) and dexamethasone – or KRD, which includes **Amgen Inc.**'s *Kyprolis* (carfilzomib), Revlimid and dexamethasone, for high-risk patients.

Expansion into first-line treatment has been expected to boost Darzalex sales, and Datamonitor Healthcare has estimated that of total forecast peak sales of $3.6bn in the major markets of the US, Japan, France, Germany, Italy, Spain and the UK by 2026, $1.5bn will come from usage in previously untreated patients who are ineligible for stem cell transplantation.

The latest supplemental approval was based on Phase III data from the ALCYONE trial of Darzalex with VMP versus VMP alone, but there are two other ongoing Phase III trials of the drug in first-line multiple myeloma. CASSIOPEIA is comparing VTD (Velcade, thalidomide and dexamethasone) plus Darzalex with VTD alone, and has an estimated primary completion date of August 2022; MAIA compares Revlimid and dexamethasone plus Darzalex with Revlimid and dexamethasone alone, with a primary completion date estimated in December 2019.

FURTHER FIRST-LINE LABEL EXPANSION EXPECTED

"We anticipate an interim data readout on our Phase III MAIA trial with daratumumab and Revlimid during 2018," a spokesperson for Danish biotech **Genmab AS**, from which Janssen licensed Darzalex, told *Scrip*. "If the data is positive, J&J are likely to see a label expansion with this front line treatment option."

The spokesperson said that "the VMP front line indication will not be a main driver of Darzalex sales in 2018" because "this is more of a European regimen and the decision on the approval in EMA is not likely to come until later in the year due to the timelines of the regulatory process in EMA."

They added that sales growth in 2018 would come from the "further roll-out in the rest of world of second-line treatment, further building of second line in US and roll-out in Japan in second line" following approval in November 2017. Genmab executives said on the company's May 8 first-quarter earnings call that a filing for first-line use of Darzalex with VMP would be made imminently in Japan with approval expected before the end of 2018.

Genmab does not receive a milestone in connection with the latest supplemental approval, although its deal with Janssen includes around $1bn in total potential milestone fees, split fairly evenly between R&D and commercial. Genmab has received $481m to date.

Darzalex was approved by the FDA for use in the second line in November 2016 following third-line approval in June 2016 and original approval in November 2015 as a fourth-line therapy. *(Also see "Janssen/Genmab Win 1st Anti-CD38 In Multiple Myeloma" - Scrip, 17 Nov, 2015.)*

In the first quarter of 2018, Darzalex net sales totaled $432m, of which $268m were booked in the US. Janssen licensed the drug in 2012 from Genmab, which books royalties on worldwide sales and which is forecasting 2018 full-year sales of $2bn-$2.3bn for the product. First-quarter sales of the anti-CD38 antibody were up $61m on the previous quarter.

On how the expansion into earlier lines of treatment might affect the product's overall sales, Genmab said: "Patients are likely to stay on drug longer in earlier lines of treatment. So you are moving treatment of patients into earlier settings, but not necessarily losing sales. In second line, in combination with Revlimid, the median [progression-free survival (PFS)] was not reached in the analysis of the POLLUX trial data as reported at ASH. Therefore, it could be that patients can remain on Darzalex for multiple years. Maintenance may also potentially be a contributor to sales growth."

THREATS TO EXPANSION?

However, aside from the fact that use of the regimen that has just been approved for the first line is far from widespread in the US, expectations for the drug's commercial expansion prospects also are tempered by the prospects of CAR-T therapy targeting B cell maturation antigen (BCMA) to treat multiple myeloma. Partners **bluebird bio Inc.** and Celgene have shown good results in heavily pre-treated patients with bb2121, for example, and other CAR-T developers like **Poseida Therapeutics Inc.** also are working in the field. *(Also see "Next-Generation CAR-Ts Tackle First-Generation Safety, Solid Tumor Challenges" - Scrip, 21 Apr, 2018.)*

Still, it looks unlikely that such therapies would rapidly replace drug therapy: according to Bernstein analyst Wimal Kapadia writing in a Jan. 30, 2018 note, BMCA CAR-T "will not penetrate [first/second-line] multiple myeloma and if it does (post-2025), Darzalex will be well-established in the treatment paradigm." CAR-T therapy is still too new to have shown sufficient longer-term treatment data, and its administration and manufacturing complexity may hinder its uptake, particularly in earlier lines of treatment.

In an interview with *Scrip* in November 2017, Genmab's CEO Jan van der Winkel was skeptical about the potential for CAR-T to capture a large part of the multiple myeloma market. "The reality is that most of the patients with a disease like multiple myeloma are fragile, elderly patients with an age over 70; they are not a patient treated in the CAR-T trials," he said. "So, I think CAR-T technology is a very good technology, very promising, but only for patients for which

no other options actually work. So, more or less the fourth-line patients, or fifth-line treatment patients."

With other drugs in the pipeline, such as **GlaxoSmithKline PLC**'s anti-BCMA antibody-drug conjugate GSK 2857916, van der Winkel pointed out that GSK's program includes studies of the candidate in combination with Darzalex, as does **Karyopharm Therapeutics Inc.**'s development program for selinexor in multiple myeloma. *(Also see "New Mechanism And Oral Activity Underline Selinexor's Role In Multiple Myeloma " - Scrip, 1 May, 2018.)* "The strength of dara is daratumumab is an ideal combination drug for a lot of these other drugs with other mechanisms of action," he commented. "So that will likely grow the total market for daratumumab."

OPPORTUNITIES PENDING

In March 2017, trials of Darzalex in non-Hodgkin's lymphoma were suspended after disappointing overall response rate results, but expansion beyond multiple myeloma still is a possibility. The drug also is being tested in solid tumors. Results are expected later this year in non-small cell lung cancer in combination with **Roche**'s PD-L1 inhibitor *Tecentriq* (atezolizumab), while Phase I/II data on Darzalex combined with **Bristol-Myers Squibb Co.**'s PD-1 inhibitor *Opdivo* (nivolumab) in a number of solid tumors are due in 2019.

Additional opportunity for Darzalex comes from the development of a more convenient subcutaneous version (the marketed drug is administered intravenously), for which a Phase II trial in multiple myeloma is expected to start imminently, with primary completion slated for the second half of 2019. **Halozyme Therapeutics Inc.**'s Enhanze drug delivery technology was licensed to create the subcutaneous formulation.

In the longer term, however, Darzalex may come under pricing pressure in the US, with **Sanofi** and **MorphoSys AG** both potentially launching competing anti-CD38 therapies for multiple myeloma. The former's isatuximab (SAR650984) is in Phase III, with interim data from the ICARIA-MM trial in later lines of treatment in combination with *Pomalyst* (pomalidomide) and dexamethasone expected in 2018. MorphoSys' MOR202 is in Phase I/IIa, with final data due this year.

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Faron's Traumakine Flops In Phase III

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Faron Pharmaceuticals is in turmoil after its lead drug *Traumakine* (interferon-beta 1a) failed in a pivotal Phase III trial; the company awaits full data from the INTEREST study but the future looks bleak for further development of the drug.

Traumakine is being developed as a treatment for in acute respiratory distress syndrome (ARDS). However, the drug failed to meet its primary endpoint in the Phase III INTEREST trial. In the study, the Traumakine and placebo groups reported similar all-cause mortality rates at day 28 and at day 90, with no difference in the number of ventilator free days.

Faron's CEO Markku Jalkanen said the company would wait for full data from the trial before deciding how to proceed with the Traumakine program. However, after reporting top-line data on May 8 that showed the trial missed its key endpoint, Faron saw its stock price (traded on the London Stock Exchange) plummet more than 80%.

Jalkanen was keen to point out during a May 8 analyst call that safety was continually monitored throughout the Phase III study and no clinical concerns were noted following the repeated administration of Traumakine.

In the INTEREST trial, the median number of ventilator free days at Day 28 was 10 days in patients treated with Traumakine and 8.5 days in the placebo group. Furthermore, all-cause mortality at Day 28 was 26.4% for Traumakine and 23.0% for the placebo group; and at Day 90, all-cause mortality in the Traumakine group was 32.6% compared with 31.6% in the placebo group.

Faron's CEO said the company was disappointed and surprised by these results. "We need to further analyze the data in order to understand how this study differs from our previous positive results with ARDS patients, both in terms of Traumakine's efficacy, and in the unusually low mortality rate observed in the placebo arm," he noted.

The double-blind, randomized Phase III INTEREST trial recruited 300 patients across eight European countries. Its failure in ARDS is a huge setback for Faron, which had begun to prepare for its transition from a clinical- to a commercial-stage business.

Phase III data from an ongoing trial in Japan for Traumakine in ARDS are expected in the third quarter of this year. Jalkanen said the company was looking forward to these results. Traumakine is licenced to **Maruishi Pharmaceutical Co. Ltd.** in Japan.

During the analyst call, Faron's chief executive noted that if positive efficacy data can be gleamed from a deeper analysis of the INTEREST trial the company hopes to seek a partner to take Traumakine forward. Positive Phase III data from the Japanese study would help Faron secure a deal for Traumakine in the near future. While it investigates what went wrong in the INTEREST trial, Faron has also decided to delay plans to pursue Traumakine in other indications. Some research had been ongoing for Traumakine in aortic aneurysm.

Meanwhile, Faron will focus on its only other pipeline asset, *Clevegen*, which is being pursued as a treatment option for various cancers. Clevegen is a novel anti-Clever-1 antibody that causes changes in the immune environment of solid tumors by switching immune suppressive M2 macrophages to immune active M1 macrophages.

However, making this asset a priority sets Faron back several years on its journey to become a commercial company.

Jalkanen said Faron would start an open-label clinical study for Clevegen this year, with initial data expected for the drug candidate in the first half of 2019. He added that the company would consider partnering options for this program.

Faron's stock lost 83% of its value on the morning of May 8, following the news the INTEREST study had failed to meet its primary endpoint. Its share price sat around GBp124 by mid-morning that day, a drop from its close price of GBp725 on May 7.

Jalkanen said the company was well financed and able to take Clevegen into clinical studies, with a budget already set aside of around £3.5m for first clinical trials of the drug. He expects Faron to end the year with around £6-7m in cash.

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AZ's Fasenra Hits First Hurdle Hard In COPD Study

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Shutterstock: Steve Horsley

AstraZeneca PLC's hopes of turning its asthma biologic *Fasenra* (benralizumab) into a franchise from a single-indication product has hit a stumbling block after its failure in a chronic obstructive pulmonary disease (COPD) Phase III study, the first of two eagerly awaited readouts.

The company has announced top-line results from the GALATHEA trial which reveal that Fasenra did not meet the primary endpoint of a statistically significant reduction of exacerbations in patients with moderate to very severe COPD. The study is part of VOYAGER which is currently the largest COPD biologics development program in the world with close to 4,000 patients.

The safety and tolerability findings in GALATHEA were consistent with those observed in previous trials with Fasenra, AstraZeneca said, but the pressure is now on for positive results from the second VOYAGER study, the TERRANOVA trial. The latter, which like GALATHEA is also evaluating the interleukin-5 inhibitor as an add-on to dual or triple inhaled therapy compared with placebo in patients with a history of exacerbations across a range of baseline blood eosinophils, is due to read out before the end of the quarter.

AstraZeneca chief medical officer Sean Bohen said in a statement that the company would "now await the results of TERRANOVA and a full evaluation of both trials to determine next steps for Fasenra in COPD."

Analysts at Morgan Stanley issued a note on May 11 saying that the COPD failure was "a significant negative as the expectations were building up for this indication," but all hope is not lost. They noted that **GlaxoSmithKline PLC**'s rival severe asthma drug *Nucala* (mepolizumab) also had mixed data in its first COPD study – METREO - which did not meet statistical significance in reduction of exacerbation although the results were suggesting a positive trend. *(Also see "Glaxo Set To File Nucala In COPD, Despite Mixed Phase III Results" - Pink Sheet, 12 Sep, 2017.)*

However, the second study, called METREX, was positive and GSK filed Nucala in the US in November 2017. "A similar scenario for AstraZeneca is not impossible if TERRANOVA yields positive results and if the combined data are encouraging," the analysts added, but the information coming out from the company so far does not indicate that the GALATHEA results were close to significance.

Datamonitor Healthcare analyst Chris Mulligan told *Scrip* that, "Fasenra's future as a treatment for COPD is looking doubtful, " especially as AstraZeneca's press release on the top-line results "lacked any numerical data." He added: "The conspicuous absence of any positive spin relating to the analysis of patients with an elevated eosinophil count – as has been seen before for IL therapies in respiratory disease – implies there is little to be salvaged from this trial."

Mulligan added that more would be known when the full data are released and TERRANOVA reads out, "but as that study has the same primary endpoint (annual exacerbation rate) and patient inclusion criteria, it is unlikely to provide a different result." He concluded by saying that "while this is obviously disappointing for AstraZeneca, for Fasenra the COPD market was always secondary to the asthma market. As such, the drug still has a promising future in respiratory disease."

Fasenra, the company's first respiratory biologic, is approved in the major markets for severe eosinophilic asthma. It got the green light in the US in November last year, and even though it is the third IL-5 treatment for this indication to hit the market – after Nucala and **Teva Pharmaceutical Industries Ltd.**'s *Cinqair* (respizumab), its take-up has been impressive. *(Also see "AZ Looks To Lead Severe Asthma Market After US Fasenra OK" - Scrip, 15 Nov, 2017.)*

Speaking to *Scrip* a couple of weeks before the GALATHEA announcement, Tom Keith-Roach, head of AstraZeneca's respiratory business, said that the launch of Fasenra had been "extremely encouraging, ahead of where we expected to be at this point." Actual sales figures will be disclosed when the company unveils its first-quarter results on May 18.

As for COPD, Keith-Roach said that VOYAGER was focusing on a population with severe uncontrolled COPD who have eosinophilic inflammation and who are "on all the inhaler combinations medical science can throw at them and they are still having two or more exacerbations per year." It is notoriously hard to treat these refractory patients but the need for new options for them cannot be overstated; he said that 25% of patients are dead within a year of having a severe exacerbation. "It is a more catastrophic event than a heart attack."

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AstraZeneca's Imfinzi, Lynparza On Track To India Debut: **https://bit.ly/2Im42xP**

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Daiichi's Quizartinib Looks To Join Novartis' Rydapt In AML

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Daiichi Sankyo Co. Ltd.'s top-line announcement that its investigational, oral FLT-3 targeting quizartinib demonstrated an overall survival benefit in a Phase III acute myeloid leukemia (AML) study gives the company a leg up in oncology, but it remains to be seen whether the drug will be able to compete in this niche space.

AML is a small indication with 21,000 new diagnoses in the US in 2017, and about one-third of these cases are FLT3-positive, yet AML has been an active area for big pharmas developing a range of drugs with different mechanisms for the disease. *(Also see "AML Pipeline Update: Pharmas Pursue Big Breakthroughs In Niche Spaces" - Scrip, 6 Jan, 2017.)*

For those patients who can tolerate it, standard treatment for newly diagnosed AML entails induction therapy with the "7+3" chemotherapy regimen (seven days of standard-dose cytarabine and three days of an anthracycline) followed by stem cell transplant, and relapse is common. Older patients, who are less able to tolerate the 7+3 regimen, may get single-agent chemotherapy or a hypomethylating agent.

Approval of **Novartis AG**'s *Rydapt* (midostaurin) for patients with FLT3 mutations in 2017 represented a breakthrough in this disease type. *(Also see "Novartis' Rydapt: Two Indications, Two Prices" - Scrip, 1 May, 2017.)*

COMPETITION ON THE WAY?

Daiichi announced May 8 that quizartinib demonstrated an overall survival benefit in the Phase III QuANTUM-R study of 367 AML patients with a FTL3-ITD mutation, who were refractory or in relapse after first-line therapy. Safety was in line with expectations, the company said.

Rydapt is the only FLT3-targeting drug available for this segment of the already small AML market, but FLT3 inhibitors as a whole will make the largest contribution to the overall growth of the AML market, Datamonitor Healthcare analyst Dominique Fontanilla told *Scrip*.

In addition to quizartinib, **Astellas Pharma Inc.**'s gilteritinib is under review with the FDA for relapsed AML, with a review date of March 29, 2019. *(Also see "Pipeline Watch: Phase III Starts With Gilteritinib, Lumateperone, Pro 140" - Scrip, 25 Aug, 2017.)* Daiichi said it was going to begin regulatory filings for quizartinib based on the QuANTAM-R results.

Quizartinib has a chance to influence a market that has been slow to move – the five-year survival rate in AML is only 27% and the standard of care has been the same for decades, Fontanilla said. This is a niche market and new products will target very specific patient populations based on age and mutations, so competition is likely to be minimal. Rydapt was approved for younger patients – under 60 years old – with FLT3 mutation-positive AML in combination with 7+3, so these patients will be more clinically fit and have a relatively better prognosis, she noted.

Quizartinib, on the other hand, is targeting relapsed/refractory patients with the FLT3-ITD mutation, which results in very poor outcomes in AML and represents an area of high unmet need, Fontanilla said. As for quizartinib's efficacy, historically, the FDA has required a statistically significant overall survival benefit with a good safety profile, so the announcement that the drug met its primary endpoint is encouraging and important, she noted.

However, the agency's approval of **Celgene Corp./Agios Pharmaceuticals Inc.**'s *Idhifa* (enasidenib) in 2017 for relapsed/refractory AML shows that the FDA will accept complete remission data over overall response rate data for the relapsed setting, though positive overall survival data is the gold standard, Fontanilla said.

JOB CUTS IN THE US

The good trial news for quizartinib comes at an awkward time for the Japan-based company. Daiichi said in its first quarter earnings report that it cut 280 employees from various sites in the US as it streamlined and tightened the company's focus to improve its long-term success. *(Also see "More US Positions Go As Daiichi Sankyo Refocuses" - Scrip, 5 Mar, 2018.)* It's unclear how the change in human resources plans will affect the launch of quizartinib in the US.

Previously, Daiichi suspended the development of its investigational HER3-inhibiting antibody patritumab in non-small cell lung cancer (NSCLC) after disappointing results in the first part of a global Phase III study.

The company's US business has struggled as sales of the angiotensin II receptor antagonist olmesartan eroded following the launch of generics, and minimal growth for *Lixiana/Savaysa* (edoxaban)and *Movantik* (naloxegol) failed to offset any losses, Datamonitor analysts note.

It has taken a strategic decision to build up in oncology to help overcome the expiry and tap into a fast-growing segment with outstanding unmet needs.

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Sanofi R&D Chief Elias Zerhouni On Partnerships, Drug Targets, And Market Dynamics

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As president of global research and development at **Sanofi**, Elias Zerhouni instituted two major changes: shifting the company's focus to biologics and forging partnerships with other companies.

He said the big change he made was turning to biologics and he increased Sanofi's focus on partnerships. "You have to be humble. If you don't know something, partner with somebody who does," Zerhouni said.

Elias Zerhouni

Zerhouni gave an overview of his nine-year stint at Sanofi in a keynote address at the Financial Times US Healthcare & Life Sciences Summit in New York on May 10, where he was asked about the lessons he learned at Sanofi. Zerhouni is to step down in July and turn over the reins to John Reed, the former global head of Pharma Research & Early Development (pRED) at **Roche**.

Zerhouni, who was director of the National Institutes of Health before joining Sanofi and at Johns Hopkins University prior to that, said his first lesson was that there was not enough bridging between academia, government and industry.

"I realized the culture was wrong, the science was not there," he said. "The tradition of big pharma, 100 years of it, was standing in the way of new science," he added.

Zerhouni said the challenge he faced was "how to transform a mainline big pharma, small molecule-oriented company with an R&D model that was exactly what IBM had in the 1950s or '60s" into an externally oriented organization that would link up with people doing science around the world.

He pointed to Sanofi's partnerships with **Regeneron Pharmaceuticals Inc.** and **Alnylam Pharmaceuticals Inc.**, saying they had been very successful.

Sanofi's antibody discovery collaboration with Regeneron has resulted in three drug approvals from the US FDA: the PCSK9 inhibitor *Praluent* (alirocumab), the interleukin-13/IL-4 blocker *Dupixent* (dupilumab) for atopic dermatitis, and the IL-6 inhibitor *Kevzara* (sarilumab) for rheumatoid arthritis. That collaboration wound down last year although the companies are continuing to develop immuno-oncology drugs under a new alliance signed in July 2015.

DRUGS WITH MANY TARGETS

Zerhouni also said it is important to build an organization that understands molecular networks and that no single disease can be treated by a single drug. "There is not a single condition that I know of that is dependent on a single intervention," he said, adding that rare disease is the only exception.

He said having a strategy that focuses on macromolecules that you can develop once and apply to many targets is the best way to achieve what you need. It reduces the cost of development, not by 10% but by orders of magnitude, he said.

"We are going from a single missile with one warhead to missiles with four to five warheads," Zerhouni stated. "That way you can reduce your cost and improve your success rate."

Zerhouni also pointed to changes in the marketplace. He said price is going down and health care costs are being pressured by governments while there is a long cycle time for R&D. As the head of R&D "you try to reduce the cost of trials, you try to have a high success rate" and still there's the challenge of finding drugs that payers are not going to basically say, yes, it reduces mortality and morbidity by 30%, but not embrace it.

"Ten years ago, that would have been a miracle drug. Today it's a complete commercial dud. So, what is an R&D head to do?"

FIVE-YEAR STRATEGY

As for what he would do next, Zerhouni joked, "I miss boredom." He said he would look forward to having a long night's sleep without having to travel the next day.

He said he did not plan on going back to government, as seven years is a good length of time and any more than that would be an overdose. "You shouldn't overdose on government," he added.

Zerhouni noted that he took the job at NIH because he felt he owed it to the country. "I am an immigrant. I came out of nowhere. I was given this chance at NIH and I thought it was the right thing to do," he said.

As for advice for his successor, Zerhouni said R&D requires a five- to seven-year timeframe. "You have to look at this strategically as a phase and you have to commit to it," he said. "You cannot be the leader that comes in and leaves. A company that changes a lot in R&D heads is a company in trouble."

"I didn't see myself doing this next phase of R&D after having done what I did," he said, adding "I think I left it in a better place."

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From Drinks To Drugs: DyDo Charts Its Pharma Course

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Japan has long been a source of unlikely entrants into the pharmaceutical industry, with materials companies such as **Teijin Ltd.**, major drinks firms like **Suntory Ltd.** and **Kirin Holdings Co. Ltd.**, and diversified groups including **Kowa Co. Ltd.** all building a presence of varying size and success over the past decades, usually with the help of mainstream partners.

As such, Osaka-based drinks group **DyDo Group Holdings** – whose main business is in canned coffee found in the ubiquitous vending machines across Japan – is not blazing a pioneering trail, although it is taking a more focused approach than some of its predecessors.

One of the pillars of its current mid-term corporate plan is to establish new business foundations, given price pressures and a static market for its mainstay lines, to help reach a group sales target of JPY200bn ($1.83bn) and a 4% operating margin in the current fiscal year ending next January 20. While the planned pharma business will not be making any financial contributions this term, the hope is to steadily build these up over the next few years.

Explaining the broad strategic thinking behind DyDo's recent decision to enter into the prescription sector, group president Tomiya Takamatsu was quite clear. "Our core [drinks] business is stable, but it is a mature market with lower growth. We want to develop new markets.

BUILDING ON FOUNDATIONS

"We had a choice of moving in two directions – expanding our existing business or moving into new areas. Remember that 60 years ago we also had no experience in our [now mainstay] business," Takamatsu told *Scrip* in an exclusive interview at the group's Tokyo offices.

"Actually, we don't see it as that distinct from our core business, which is also health-related, and our origins were in home health product sales [in the 1950s], so in some respect we are going back to our roots," he said. DyDo – established under its current name in 1975 – already markets a series of health drinks and has a consumer health business focused on over-the-counter mini tonic drinks and food.

The company first disclosed in March that it was planning to enter the drug business in July 2019 as part of its mid- and long-term growth strategy, with a clear initial focus on orphan drugs in Japan. DyDo sees a total rare disease domain market of several billion yen in the country, where official orphan status is conferred to therapies for disorders with fewer than 50,000 patients and where there is high outstanding medical need.

"We needed to narrow our focus as there is a lot of competition in the wider areas," Takamatsu explained, "and Japan's rapidly ageing population and demand for longer healthy lives were other key factors" behind the decision.

Japan in addition provides a range of government policy support to drugs with limited markets, including priority regulatory consultations, expedited reviews, research grants, and tax incentives, all of which are seen by DyDo as positive entry factors.

The DyDo president freely admitted that the company currently has few relevant skills in-house among its roughly 3,800 employees and that it will need to recruit talent, which will be a gradual process. Some functions will be outsourced, and the main initial focus will be on exploring research seeds for candidate drugs and building an initial pipeline. The split of internal and external functions has yet to be decided, but concentrating on niche indications means that full in-house capabilities across all areas are not necessarily required. Patient registries in Japan meanwhile mean that only a relatively small sales force targeting selected specialists would be needed.

One other benefit of focusing on unmet needs is that the most recent revisions to Japan's reimbursement pricing system set stricter qualifying criteria for new drugs to be eligible for pricing premiums, setting the bar higher for innovation but also providing rewards for those novel products that have demonstrated clear benefits.

"The pharma industry needs a long-term perspective, and being a latecomer can actually be a strength, as we can learn from others and adapt to changing systems," Takamatsu observed.

FUND INVESTMENT

The company has already set up a new strategic investment group in its corporate strategy department to study the sector, and has recently invested JPY2bn (about $18.3m) in a fund partnership under Asajes Ventures, a new Japan-based fund co-founded by **Innate Pharma SA** chairman Dr. Hervé Brailly and Dr. Chika Yoshinaga.

Asajes provides consulting services, information and assistance in finding/licensing assets and potential partners in the US and Europe for companies in Asia, and will be assisting DyDo in getting its pharma interests off the ground.

Asajes declined to disclose the total size of the fund and its investors, but Yoshinaga (formerly with Quintiles) told *Scrip* that "we are not a normal VC [venture capital] group. We can provide business development and clinical trials and development expertise, along with capital. We do not invest in established companies, but can help shorten the time and cost to market."

Brailly added that there are still plenty of good opportunities to bring new specialist products with patient benefits to Japan, where "many smaller companies are still not present, and where we can help make a bridge."

While the two firms did not reveal further details of their relationship, it appears likely that Asajes will help research and identify potential licensing candidates to help kick-start DyDo's pharma activities.

LOOKING AHEAD

DyDo's Takamatsu told *Scrip* that the firm would like to have its first commercial drug products "as soon as possible" and that the overall goal is to bring one asset a year to the market. No pharma business financial targets have so far been disclosed but the hope is to have sales of around JPY1bn for each planned product, he disclosed.

Clearly there is a long way to go, but in terms of what success might look like in 10 years, Takamatsu said: "We would hope to be of a certain size in pharma, with a self-supporting business [in the sector] meeting its targets and being a core activity alongside beverages and food.

"We want the perception of DyDo to change."

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From the editors of PharmAsia News.

Greener Pastures? Long-Time Pfizer China GM Starts New Era

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First came the wave in which local pharma heavyweights started recruiting R&D executives. Now a new crop of biotech startups in China are hiring away talent from multinational drug firms in the country.

Pfizer Inc.'s **Wu Xiaobin** is the latest multinational executive to jump to a start-up, signaling an intensifying fight for talent as a new crop of ventures begins to develop into full-fledged biotech operations.

Starting May, Wu left Pfizer to become the GM of China and president of BeiGene Ltd, a local subsidiary of Nasdaq-listed **BeiGene (Beijing) Co. Ltd.**. An industry veteran, Wu had been with Pfizer since 2003 when he started at Wyeth. In 2009, he became Wyeth's China country manager and managing director.

Wu is also well known for first starting his career as a medical sales rep for Bayer in Germany, and later returned to China to lead the company's local commercial operations. He became the Regional President of Pfizer Essential Health, Greater China after the merger with Wyeth.

Unlike his counterparts who have limited term assignments spanning three to five years on average, he is the longest-serving country GM for any multinational drug maker in China.

A NEW DAWN?

Many see the move representing a new era for startups like BeiGene. Armed with a stellar performance since listing on Nasdaq, BeiGene has decisively moved to become a full-fledged biotech spanning R&D to manufacturing to commercial activities.

Previously, BeiGene quietly recruited the majority of its R&D and regulatory talent from MNCs, including a global head of regulatory affairs from Bayer. As it moves to the commercial stage, its need for experienced executives only intensifies.

Reporting to BeiGene CEO John Oyler, Wu is expected to immediately lead BeiGene's takeover of Celgene product sales in China, and in the long term to ready the biotech to launch its own suite of oncology biologics. In a high-profile deal,

Shutterstock: Yuriy Kulik

Helped by policy tailwinds, hot money inflow, and favorable listing conditions, biotech startups are eager to take off into the next growth phase

BeiGene obtained the rights to market and sell Celgene's three major anticancer products, *Abraxane* (paclitaxel), *Revlimid* (lenalidomide), and *Vidaza* (azacitidine).

"His strong leadership has allowed him to build exceptional teams, launch impactful patient therapies, and drive outstanding results for these organizations; all of which will be critical to helping BeiGene reach the next stage in its growth," noted Oyler in a statement.

"Dr. Wu builds a successful professional organization and a culture of compliance, and under his leadership. Pfizer grew to be a leading MNC drug maker in China," noted Pfizer China in a statement, translated from Chinese.

As a vice chairman of the R&D-based Pharmaceutical Association Committee (RDPAC), a trade group representing multinational pharma companies in China, Wu also actively promotes market access to quality drugs and vaccine products, added Pfizer.

Pfizer China meanwhile has appointed **Miao Tianxiang** as its president of Essential Health for Greater China and China GM, and **Wu Feng** as the new head of Essential Health for China. Miao is currently VP, Financing and Wu the head of Commercial and Diversified Business.

On the same day as Wu's arrival at BeiGene, the company also announced internally that former J&J China's Human Resources executive in charge of hiring, **Wang Zijian**,has joined the company as its VP and head of human resources in China.

For Wu, the move seems to be one of seeking greener pastures. "The future of BeiGene is bright, and I am excited to be a part of this truly unique company," he said in a statement.

AZ SVP JOINS CANSINO

Helped by policy tailwinds, hot money inflow, and favorable listing conditions, biotech startups are eager to enter into the clinical and commercial stages to take off into the next growth phase.

On the heels of Wu's move, **Tianjin CanSino Biotechnology Inc.** May 2 appointed former **AstraZeneca PLC** senior executive **Shoubai Chao** as its CEO.

Chao was previously senior VP, bioventures and technical operations and manufacturing at **MedImmune LLC**, where he oversaw vaccines, biologics and biosimilars.

CanSino is a vaccine developer based in Tianjin, which has developed China's first Ebola vaccine, approved by the China FDA in October. Additionally, the company has Pneumococcal 13, human papillomavirus and other vaccines in its development pipeline.

"Dr. Chao has nearly three decades' experience in vaccines and biologic manufacturing, quality control and supply… and his arrival will bring the company to a new height," noted CanSino co-founder and chairman Yu.

The biotech startup's need for manufacturing, quality control and commercial talent is only starting, and there could be more to come.

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From the editors of PharmAsia News.

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

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

Selected clinical trial developments for the week 4–10 May 2018

LEAD COMPANY/PARTNER	COMPOUND	INDICATION	COMMENTS
PHASE III INTERIM/TOP-LINE RESULTS			
Johnson & Johnson	esketamine, nasal spray, flexible dosing	major depressive disorder, treatment-resistant, adults	TRANSFORM-2; primary endpoint met.
Johnson & Johnson	esketamine, nasal spray, flexible dosing	major depressive disorder, treatment-resistant, in the elderly	TRANSFORM-3, missed primary endpoint, but some improvement
Alkermes PLC	ALKS-5461	major depressive disorder	FORWARD-2; durable responses.
Daiichi Sankyo Co. Ltd.	quizartinib	acute myeloid leukemia, relapsed, with FLT3-ITD mutations	QuANTUM-R; prolonged overall survival versus chemotherapy.
Otsuka Holdings Co. Ltd./Servier SA	*Lonsurf* (trifluridine/ tipiracil)	gastric cancer, metastatic, refractory	TAGS; met primary endpoint, overall survival.
Faron Pharmaceuticals Oy	*Traumakine*	acute respiratory distress syndrome (ARDS)	INTEREST; missed primary endpoint.
Exelixis Inc./Roche	*Cotellic* (cobimetinib) plus *Tecentriq* (atezolizumab) versus regorafenib	colorectal cancer, heavily pre-treated, locally advanced or metastatic	IMblaze370; missed primary endpoint of increased overall survival.
Sumitomo Dainippon Pharma Co. Ltd.	*Latuda* (lurasidone)	major depressive disorder with mixed features	RESOLVE 3; well tolerated, improved symptoms.
UPDATED PHASE III RESULTS			
Intra-Cellular Therapies Inc.	lumateperone	schizophrenia	ITI-007-303; well tolerated in long-term safety study.
Sumitomo Dainippon Pharma Co. Ltd.	*Latuda* (lurasidone)	bipolar disorder in children and adolescents	ILLUMINATE; improved symptoms.
PHASE III INITIATED			
Amneal Pharmaceuticals LLC	IPX203	Parkinson's disease, advanced	An extended-release carbidopa-levodopa formulation.
PHASE III ANNOUNCED			
Advicenne SA	ADV7103	cystinuria	France's regulator clears trial to start.
PHASE II INTERIM/TOP-LINE RESULTS			
KemPharm Inc.	KP415	attention deficit hyperactivity disorder	Abuse potential not observed.
UPDATED PHASE II RESULTS			
SAGE Therapeutics Inc.	SAGE-217	major depressive disorder	Sustained symptom reduction.

Source: Biomedtracker

Protecting Against Hearing Loss: Acousia Pursues A New Approach

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Hearing loss is proving to be a difficult area in which to develop new therapies, but the German start-up, **Acousia Therapeutics GmbH**, believes it is gaining some traction in the sector, and has just raised €10m ($12m) in a series B financing to support its move into clinical trials with its promising lead compound, ACOU085.

The Tubingen, Germany-based biotech has attracted several new investors including the leader of the round, Stuttgart-based LBBW Venture Capital, and also Creathor Ventures and Bregua Corporation. Two existing investors, the corporate investor, Boehringer Ingelheim Venture Fund (BIVF) and the financial institution, Kreditanstalt fur Wiederaufbau (KfW), took part in the series B funding. Acousia was founded in 2012 and previously raised €2.5m in a series A round in 2016, also supported by the BIVF, KfW and the Milan, Italy-based partner research organization, **Axxam SRL**.

"Acousia is pursuing the repair, restoration and functional improvement of inner-ear sensory cells, not their regeneration," emphasized CEO Christoph Antz in a *Scrip* interview. The company has identified an undisclosed target for drugs that could protect existing sensory hair cells in the inner ear from the anticancer drug, cisplatin, which has been associated with hearing loss. The lead candidate, ACOU085, is in preclinical studies, and could enter the clinic in 2020.

One interesting aspect of Acousia's small molecules is that they appear to have both a cytoprotective activity and a functional improvement activity. The design of clinical studies has yet to be decided, Antz noted, adding that the ototoxicity associated with cisplatin appears to depend on the cumulative dose.

Of course, hearing loss can be treated by a range of hearing aid devices that are becoming ever more sophisticated, particularly for age-related hearing loss. However, there are a number of other conditions, including cisplatin and other chemotherapy-induced dysfunction, noise trauma, various infectious diseases, and ischemia-reperfusion injury, where there are unmet clinical needs for effective therapies. There is also sudden idiopathic hearing loss, seen especially in middle aged men.

However, developing drugs for hearing-related conditions is not easy. Fellow European biotech, **Auris Medical Holding AG**, for example, reported disappointing Phase III results with a potential tinnitus therapy two months ago. And there are only a handful of companies active in the area, according to the drug development database, Biomedtracker.

That might be expected though, from what we know about the ear: "The spatial complexity of the inner ear, with its highly sophisticated structure, is a significant challenge," Antz noted. Not only that, it is much more difficult to gain access to, compared, say, with the eye. The inner ear "is embedded in a bony structure, and is a tiny, tiny, organ," he added.

Acousia was founded by researcher Hubert Lowenheim, clinical director of the ENT University Clinic in Tubingen, the local drug discovery firm, EMC microcollections GmbH, and the BIVF.

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GlaxoSmithKline's chief financial officer ***Simon Dingemans*** has informed the board of his intention to retire and to step down from the board in May 2019. The board will now conduct a global search both internally and externally to identify a successor. Dingemans joined GSK in 2011 and as CFO, Mr Dingemans has led finance and a number of other group functions, including technology and IT, real estate and procurement. GSK noted that, as a voluntary leaver, Dingemans would not receive any severance payment when he leaves the company.

The clinical-stage biopharmaceutical company **DBV Technologies** has appointed ***Michel de Rosen*** has to its board to replace ***George Horner III***. He is currently chairman of the boards at Faurecia, a global supplier of automotive equipment, and the pharmaceutical company Pharnext. Previously, de Rosen was chairman and chief executive officer of Eutelsat, ViroPharma and Rhône-Poulenc Santé.

Complexa Inc., a clinical stage biopharmaceutical company, has appointed ***Francisco D. Salva*** as its president and CEO, effective immediately. Most recently, Salva was a founder and vice president of operations for Acerta Pharma, culminating in a $4bn investment by AstraZeneca for a controlling ownership interest. While at Acerta Pharma, Salva was responsible for the company's financial and operational activities. Before Acerta, he was senior director of corporate development at Pharmacyclics.

Aoife Brennan has accepted the position of interim president and CEO of **Synlogic Synlogic Inc.**, a clinical-stage company applying synthetic biology to probiotics to develop novel, living medicines – effective immediately. This appointment follows the resignation of ***Dr. Jose Carlos Gutiérrez-Ramos***, as Synlogic's president and chief executive officer and a member of its board.

Novel antibiotic company **Motif Bio** has announced that ***Dr. Stephanie Noviello*** has joined the firm as vice president, clinical development. She will report to chief medical officer ***Dr. David Huang***. Noviello will be a key contributor to the European Marketing Authorisation Application submission for iclaprim. Noviello joins from Bristol-Myers Squibb, where she was most recently clinical program lead, virology. Previously she worked at Schering-Plough Research Institute as a director in hepatology.

The private biopharmaceutical company **TP Therapeutics Inc.** has appointed ***Dr. Athena M. Countouriotis*** as executive vice president and chief medical officer.

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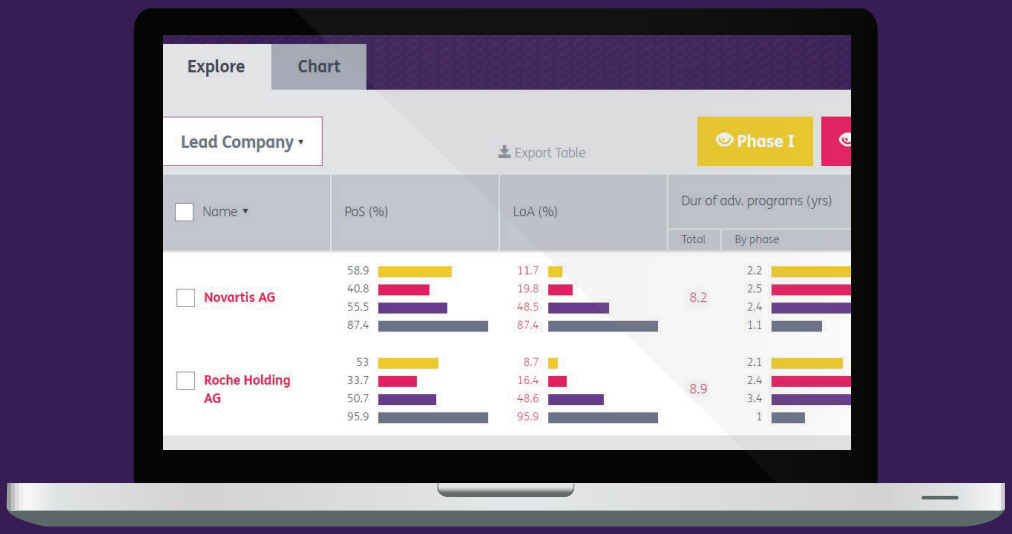

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