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AbbVie Defends Humira With Aggressive Discount In EU

JO SHORTHOUSE joanne.shorthouse@informa.com

AbbVie Inc. is ready for a fight to keep rivals away from having their piece of the biosimilar adalimumab market if reports of a price cut of 80% are anything to go by.

The discount in an, as yet, unknown market, is not expected to hurt AbbVie much financially. Even with the 80% discount, the gross margin on manufacturing *Humira* would be above 75%.

The news was broken in an analyst note by Bernstein's Ronny Gal. He said: "We expect the biosimilar players who are not up to scale yet and need to recoup their initial investment would not bid that low."

At the time of writing, details of the tender process are scarce. When approached for comment, AbbVie has declined to confirm or discuss the matter.

But this is the first solid indication of how AbbVie may defend its share of the Humira market in Europe, worth $4.4bn per year. Rivals bidding on the European adalimumab market are **Sandoz International GMBH** (*Hyrimoz*), **Samsung Bioepis Co. Ltd.** and its European partner **Biogen Inc.** (*Imraldi*), **Amgen Inc.** (*Amgevita*), **Mylan NV** and **Fujifilm Kyowa Kirin Biologics Co. Ltd.** (*Hulio*) and **Boehringer Ingelheim GMBH**, which has told *Scrip* it will not be launching *Cyltezo* in Europe to enable it to concentrate on the US market.

Pricing information, from the association of statutory health insurance doctors for the North Rhine region in Germany, the KVNO, shows six syringes of Humira at a list price cost €5,300. Amgen's Amgevita is listed at €4,533, while Hyrimoz and Imraldi are priced at €4,206 and €3,354 respectively, offering a discount of 15%, 21% and 37% on Humira.

"Not all buyers will achieve the kind of discount achievable by a national tender. However, the band of pricing will move lower. We would expect average discount would have to be above 50%," elaborated Gal.

"The adalimumab situation is a reflection of the challenge posed by biological medicines, and how patent expiration does not automatically translate in the marketing of cheaper biosimilars," commented Jaume Vidal, European policy advisor to the NGO Health Action International. "What we have here is a pharmaceutical company protecting an already blockbuster product by gaming the IP protection system."

HAI's Vidal told *Scrip:* "AbbVie is taking advantage of a regulatory framework that makes it very difficult for other pharmaceutical companies to develop and market their biosimilar products. At the core of it is an all-too-familiar problem: the abuse of the IP protection system and lack of transparency on the purported development costs that are used to justify exorbitant prices."

US IMPLICATIONS

Gal says he suspects that the AbbVie strategy is "in-effect targeting the US market."

AbbVie "will hold the EU volume despite very large discounts. The objective is to defend the US market by denying the biosimilars in-market experience and then arguing the European 'chose' Humira over the biosimilars for quality reasons beyond price," he said.

In the US, Humira made $12.4bn in sales in 2017, making it Humira's biggest market by far. AbbVie has recently settled

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US Pricing Proposals
Winners and losers (p9-10)

from the editor

eleanor.malone@informa.com

Even though the *Humira* biosimilar threat has been looming on AbbVie's horizon ever since the company was carved out of Abbott laboratories at the start of 2013, the actual launch of the copycats in Europe last month evidently still held nasty surprises for investors. AbbVie's share price has fallen by as much as 15% since a clutch of European biosimilar adalimumabs were launched on Oct. 16, suddenly making that threat to the drug that brings in nearly two-thirds of the company's revenues a whole lot more real.

The fact that AbbVie apparently won one European tender did little to un-spook investors, since it reportedly relied on an 80% price cut (see cover story). CEO Rick Gonzalez admitted that the company's previous estimates of biosimilar erosion this year and next needed to be upped by seven to eight percentage points to 26-27% (see p4-5). But he continued to maintain that the ex-US erosion will moderate after 2019, something that analysts dispute, citing evidence from previous biosimilar launches and other factors favoring increased biosimilar uptake in Europe.

Elsewhere in this week's issue you can read the latest batch of third-quarter earnings updates, from GSK's focus on cutting less-promising programs and seeking external assets to build up a stronger pipeline (p6) to how Amgen achieved a healthy launch for migraine treatment *Aimovig* (but could be embracing a broader strategy of building sales volume at the expense of profit margins, p7), and from Pfizer's outgoing CEO's comments on the US drug market (p13) to Takeda strengthening its underlying business in advance of the Shire acquisition (p18).

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LEADERSHIP
Phil Jarvis, Mike Ward, Karen Coleman

SUBSCRIPTIONS
Dan Simmons, Shinbo Hidenaga

ADVERTISING
Christopher Keeling

DESIGN SUPERVISOR
Gayle Rembold Furbert

DESIGN
Paul Wilkinson

EDITORIAL OFFICE
Christchurch Court
10-15 Newgate Street
London, EC1A 7AZ

CUSTOMER SERVICES
US Toll-Free: +1 888 670 8900
US Toll: +1 908 547 2200
UK & Europe: +44 (20) 337 73737
Australia: +61 2 8705 6907
Japan: +81 3 6273 4260
Email: clientservices@pharma.informa.com

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Sanofi's Vaccines Performance Helps Offset Diabetes Decline
https://bit.ly/2JGy28S
Performance of Dupixent, which just picked up a new indication, was a third quarter highlight and bodes well for future growth, but sales of the blockbuster insulin glargine Lantus are crumbling.

Diabetes Drug CV Oucomes Trials May be Needed For Market Success But Not Approval, US Panel Says
https://bit.ly/2Pfs196
Longer, broader premarketing trials should replace the requirement for dedicated outcomes trials to demonstrate CV safety, but competitive pressure may drive sponsors to voluntarily conduct outcomes studies to demonstrate CV benefit, FDA advisory committee members said.

Teva: No Reason To "Panic" When It Comes To Ajovy Access
https://bit.ly/2AOuVJc
Discussions with payers for market access for the migraine drug will continue through November and into December. The level of rebating in the category will be around 25%, management forecast.

Grifols Slows Alzheimer's Progression With Plasmapheresis
https://bit.ly/2PNkmOO
Plasmapheresis with Grifols' Albutein could provide a new treatment avenue for Alzheimer's disease, but more data will be needed to convince.

Allergan's Botox Holds Its Own In Migraine, Despite CGRP Competition
https://bit.ly/2Fj6NTB
In the third quarter, generics of dry eye drug Restasis did not emerge as expected and Botox enjoyed double digit sales for therapeutic indications in the US, despite the entry of new competition in migraine treatment.

Daiichi Sankyo Hauls Back Mid-Term Profit Outlook As It Builds Oncology
https://bit.ly/2zwEOJZ
Big cut in mid-term profit outlook hits Daiichi Sankyo shares but company says it is reallocating more to R&D to accelerate the strategic build-out of its oncology franchise.

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legislation with Sandoz over the timing of the latter's Hyrimoz launch in the US, with the **Novartis** company agreeing to delay launch until September 2023, as well as paying royalties to AbbVie of any Hyrimoz sales in Europe. Three other companies have already signed similar agreements with AbbVie. *(Also see "Sandoz And AbbVie Biosimilar Humira Settlement: What Does It Mean?" - Scrip, 12 Oct, 2018.)*

In a previous analyst note on the subject of the European defense of Humira, Gal had noted that "AbbVie appears much more prepared than prior defenders and their key objective is to prevent the creation of large patient databases ahead of US biosimilar introduction. AbbVie is much more likely to give up price than volume." *(Also see "Biosimilar Infliximab Success Paves The Way For Adalimumab In Europe" - Scrip, 16 Aug, 2018.)*

TENDERING STRATEGY

One market where AbbVie may find it difficult to cut out its biosimilar competitors is the UK. NHS England has changed its procurement mechanism for biosimilar adalimumab to encourage competition and sustainability. The tender process will award contracts in lots; this is based on the assumption that there will be four biosimilar products and four bids by Dec. 1. If only three offers are received, then three lots will be awarded as three distinct lots, and so on. The size and shape of each lot will depend on the offers received and the relative prices, the NHS England Specialist Pharmacy Service (SPS) said in a strategy document.

"The strategy means that no supplier of adalimumab will be awarded the whole market but will have a strong incentive to offer their best price at the point of tender. If all tendered prices are similar, the shares awarded will on an equitable basis. If there are price differentials, awarded shares will be higher for the most competitively priced suppliers, but all suppliers will get access to at least some of the market upon receipt of a compliant bid to avoid dominance."

Humira will be a separate line in the tender. Humira is approved for use in Crohn's disease, ulcerative colitis, psoriasis, psoriatic arthritis, and ankylosing spondylitis.

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Additional reporting by Ian Schofield.

AbbVie Hit Harder By EU Humira Biosimilars Than Projected

JOSEPH HAAS Joseph.Haas@informa.com

The event **AbbVie Inc.** has planned for and investors have obsessed about since the Chicago-area firm's spinout from **Abbott Laboratories Inc.** in 2014 has finally begun, and biosimilar competition to *Humira* (adalimumab) in Europe is having a bigger initial impact than the pharma projected.

Four sponsors launched adalimumab biosimilars simultaneously in Europe in mid-October. Chairman and CEO Rick Gonzalez said during AbbVie's third quarter earnings call Nov. 2 that discounting, which occurs on a market-by-market basis in the EU, has been greater than expected, ranging from 10% to 80% depending on the country. The pharma now anticipates 26%-27% ex-US sales erosion for its top-seller, compared to prior expectations of 18%-20% erosion in 2019, the first full year of adalimumab biosimilars. *(Also see "AbbVie's Spin-Out Culture Helped Set Post-Humira Strategy, Execs Say" - Scrip, 5 Dec, 2017.)*

Overall, AbbVie's total net revenues of $8.24bn in the third quarter provided nearly 18% growth year-over-year. Humira posted quarterly sales of $5.12bn, with the US total of $3.55bn up 12.5%, while ex-US sales of $1.58bn still accounted for 4.2% growth compared to third quarter 2017.

Hepatitis C drug sales of $862m were down sequentially from $973m in the second quarter, but still substantially higher than the $276m the HCV franchise was bringing in for AbbVie a year earlier, almost entirely on the strength of two-drug combo *Mavyret* (glecaprevir/pibrentasvir). *(Also see "AbbVie HCV Revenue Surprises Again, But Falloff Is Coming" - Scrip, 27 Jul, 2018.)* Gonzalez noted that Mavyret gives AbbVie approximately 50% market share in HCV globally at present. Mavyret totaled $839m in worldwide sales from July through September, with $444m in the US and $395 ex-US.

HCV competitor **Gilead Sciences Inc.** announced in September that it would spin out an affiliate next year to market authorized generics of its HCV drugs – *Harvoni* (sofosbuvir/ledipasvir) and *Epclusa* (sofosbuvir/velpatasvir) – in an effort to win market share back from AbbVie. *(Also see "Gilead's HCV Authorized Generics Effort Will Draw Market Share From AbbVie" - Scrip, 24 Sep, 2018.)*

In other therapeutic areas, Gonzalez pointed to AbbVie's oncology franchise as a source of continuing growth past the Humira patent cliff. "Today, our hematological oncology portfolio is now annualizing above $4bn and growing at a robust rate, including growth of more than 48% in the third quarter," he told the call. "As we continue to generate data that validates the utility of both *Imbruvica* and *Venclexta* across a wide range of patient populations and cancer types, we expect this franchise to drive significant growth for many years to come."

The oncology drugs did better than expected – nine points above consensus. *Imbruvica* (ibrutinib) posted global sales of $972m, good for 41.3% year-over-year growth, including $812m in domestic sales. *Venclexta* (venetoclax) continues its growth trajectory as well, with its $96m – $69m US/$27m ex-US – comprising better than 100% growth across the board compared to third quarter 2017.

HUMIRA BIOSIMILAR DISCOUNTS STEEPER THAN ABBVIE EXPECTED

Good news elsewhere did not deter analysts from the topic of Humira biosimilar impact, now that the initial copies have reached the market in Europe. AbbVie has reached multiple settlements with generic drug makers that stave off US biosimilar competition until late 2023, and the company continues to guide for continued overall growth for the autoimmune powerhouse. *(Also see "Sandoz And AbbVie Biosimilar Humira Settlement: What Does It Mean?" - Scrip, 12 Oct, 2018.)*

The first query during the call's Q&A portion brought up the topic of the EU launches of adalimumab biosimilars by **Amgen Inc.**, **Sandoz International GMBH**, **Samsung Bioepis Co. Ltd.** and **Mylan NV**. Clearly prepared for the topic, Gonzalez launched into a lengthy and detailed answer. The launches

only occurred about two weeks ago, he noted, but that still has given AbbVie a view on pricing of the products in virtually every EU market.

"The discounting has been on the higher end of the planning scenarios that we have laid out, and still within the planning scenarios that we have laid out, but a little bit on the higher end of that," he began, adding that the discounts are also at the higher end of what was seen for biosimilars of **Johnson & Johnson**'s *Remicade* (infliximab) and Amgen's *Enbrel* (etanercept), which AbbVie saw as indicators for what to expect with Humira.

With discounts ranging from 10% to 80%, AbbVie has seen the highest discounts in the Nordic countries "where it's winner-take-all," Gonzalez said. Similar trends were seen in the Nordic region for biosimilar infliximab and etanercept, he added. What occurred in the Nordic markets was not a surprise, the exec continued, and "not a big part of our business" – accounting for about 4%-5% of international Humira revenues.

AbbVie announced it had agreed upon its first tender Nov. 1, accepting an 80% discount but not specifying the country of the agreement. *(Also see "AbbVie Defends Humira With Aggressive Discount In First EU Tender " - Scrip, 1 Nov, 2018.)* Based on Gonzalez's commentary, it seems likely that tender was made in one of the Nordic markets.

Overall outside the US, about two-thirds of Humira revenue will come from what Gonzalez calls "blocked" markets – those in which the branded product and biosimilars compete at the same tendered price. France is an example of a market where AbbVie now will compete with adalimumab biosimilars at identical pricing.

The other one-third of markets where biosimilars of Humira are registered are still being negotiated, he said. "We have pricing in those markets," Gonzalez said. "We have a pretty good idea of where we stand, but there's still an opportunity for some movement in those markets." He noted AbbVie will need "probably another month or two for that to be able to play out and for us to have a firm understanding of where the discounting will settle out and where our volumes will settle out."

AbbVie now estimates that biosimilar erosion in 2018-2019 will be higher than it estimated previously, at 26%-27% rather than 18%-20%, the exec said. But the company expects this discounting to moderate after 2019 – an assertion that multiple market analysts disagreed with in same-day notes.

BMO Capital Markets analyst Alex Arfaei said he has long expected that a moderating trend of erosion in Europe was unlikely due to multiple factors. "We continue to disagree with AbbVie's updated commentary because we doubt Humira's ex-US erosion will moderate after 2019, because we expect [an] increased number of biosimilar entrants in current and new geographies, availability of interchangeable biosimilars by roughly 2021-2022, and more aggressive adoption of biosimilars in Europe per recent trends," he wrote Nov. 2.

Leerink Partners analyst Geoffrey Porges also diverged from Gonzalez's prediction, saying "we do not have evidence from prior EU biosimilar launch dynamics that the pace of discounting will slow in the second year of availability of biosimilars, and with multiple entrants and a still substantial revenue base (about $4.5bn) we would expect erosion to intensify in 2020, not slow."

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Novo Nordisk Ups Lay Offs In R&D Push; Preps UK Supply Chain For Hard Brexit

STEN STOVALL sten.stovall@informa.com

Lars Fruergaard Jørgensen, Novo Nordisk's CEO

Novo Nordisk AS has increased the number of planned lay-offs to 1,300 world-wide from an initially announced 400 to reallocate resources needed for drug discovery exploration in new disease areas, including use of stem cell therapy, the Danish group's CEO told journalists when presenting the company's third-quarter update.

Novo Nordisk in September announced it was cutting 400 R&D jobs in Denmark and China to allow better expansion and diversification of its pipeline and raise its investment in biological and technological innovation.

Since then, additional restructuring steps across functions and geographies have been taken, aimed at eventually accelerating the group's push for new innovative products.

Consequently the total workforce across the company is being cut by around 1,300 employees before the end of 2018, with most of these lay-offs already implemented, Lars Fruergaard Jørgensen said.

UPGRADING R&D NEEDS RESOURCE RE-ALLOCATION, CEO SAYS

"We need to do this to ensure we can achieve long-term sustainable growth in an increased competitive environment," said on a media call, adding: "How you use resources is probably what matters most,

so if the 42,000 Novo Nordisk employees who are left all work in a more efficient way, that matters much more than taking people out."

He said no further large layoffs are planned in the near term. "We have addressed what we need to for the moment," he added.

Asked what new therapeutic areas are of interest to him, Fruergaard Jørgensen replied: "Based on our experience in diabetes we have developed capabilities and have assets that can also be used in other therapy areas. Our expansion into obesity is an example of that," he said, referring to obesity drugs like *Saxenda* (liraglutide).

"The same goes for a disease area like NASH, or non-alcoholic fatty liver, and also cardiovascular disease, so there are some adjacent disease areas that lend themselves well for Novo Nordisk to be active in, and those are the disease areas that we're trying to diversify into and we'll start by using assets we already have and then we'll do business development activities to further build our pipeline using, for example, bolt-on acquisitions while also doing organic discovery partnerships," the CEO said.

Its R&D revamp will bring in more use of artificial intelligence and computer skills for drug discovery and development at Novo Nordisk.

Stem cell research will be an increasingly important area of research for the group going forward.

"For more than 20 years, we at Novo Nordisk have been working in the diabetes space to mature stem cells into beta cells to produce insulin. We believe that could be a very strong benefit for patients living with difficult to control type 1 diabetes."

"What we do really well is working with cells so we're trying to leverage the experience we have from that to now look more broadly and at more disease areas where stem cell therapy could be relevant," Fruergaard Jørgensen said.

Stem cell therapy is quite different from classical drug development, he noted.

"It's not the classical manufacturing of medicine put into the supply chain which is then promoted to physicians and then made available in pharmacies for patients."

"It's more of a supply chain where you must be in control of the manufacturing process, and how the respective stem cells are matured into the cells that you are targeting."

Novo Nordisk has consequently invested in such a manufacturing capability by tying up with regenerative medicines company **Asterias Biotherapeutics Inc.** who have a facility in Piedmont, California.

"We are making partnerships in different therapeutic areas to get needed protocols for maturing these cells in different disease areas."

"So you should see it as a strategy that's based on a portability around producing the cell and then we can mature these cells into different disease areas. We have the first two or three maybe four diseases areas in mind," the CEO said, but declined to elaborate.

HARD BREXIT PREPARATIONS

Fruergaard Jørgensen said Novo Nordisk was taking seriously the possibility that the UK might leave the EU without a negotiated deal at the end of March 2019. In preparation for such a scenario, the Danish diabetes company will build up 16 weeks' worth of insulin inventories from the seven weeks' supply normally held, and do so by year-end.

Novo Nordisk's products need to be refrigerated so there's a limit as far as how much the group can effectively stockpile.

But it plans to at least double its inventories so that there will be four months of supply in the country at the end of March. Stockpiling by the Copenhagen-based group is set to begin in the fourth quarter of this year. "We are prepared to help those who depend on our products. Also after a Brexit, where it might become difficult to move products across the UK border." He declined to give details, however.

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GSK Prunes The Pipeline To Make Way For The New

JESSICA MERRILL jessica.merrill@informa.com

GlaxoSmithKline PLC CEO Emma Walmsley told investors she is sticking to her pledge to remove bureaucracy from the drug development process and prioritize investment in high-value candidates, during the firm's third quarter earnings call Oct. 31.

"We have clearly said we will be more decisive with our pipeline and, this quarter, we've also decided to terminate five development programs," she said. "These decisions were data-driven, primarily based on interim analysis and will allow us to focus our efforts on other assets with greater chances of becoming important medicines," she added.

GSK's new President-R&D Hal Barron laid out the initial plans for an R&D turnaround during an investor event in July, centered around an effort to focus on breakthrough medicines rather than incrementally beneficial ones. The company is focused on building up in immunology and oncology, as well as therapy area-agnostic development, underpinned by genetics.

Among the drugs GSK is terminating are three mid-stage respiratory projects: danirixin for chronic obstructive pulmonary disease, a TRPV4 blocker in chronic cough (although a Phase I study in acute respiratory distress is continuing), and a TLR7 agonist in asthma.

Walmsley said the company has cut some programs to focus on other internal programs but is also interested in business development to build out the pipeline. In April, GSK recruited a new head of worldwide business development for pharmaceuticals R&D, Kevin Sin, who was previously global head of oncology business development at Genentech, and who is located with Barron in San Francisco. *(Also see "Appointments: Novartis And GSK Announce New R&D Heads, LNC Therapeutics Gets A New CEO, Plus Announcements From Zelluna and BC Platforms " - Scrip, 19 Apr, 2018.)*

Barron also weighed in, noting, "Strengthening our pipeline clearly is critical and inorganic growth will definitely play an important role to achieve this." Business development efforts are focused on immunology and particularly immuno-oncology, as well as human genetics and machine learning.

Barron's first big deal at GSK was a partnership with the Silicon Valley gene testing company **23andMe Inc.**, involving a four-year drug discovery collaboration.

Barron said the partners have already identified 13 targets and are exploring whether or not any could be drug candidates.

"We're going to continue to look for other opportunities but [are] keeping an appropriately high bar," he said.

While investors wait to see the results of new R&D initiatives, the company is focused on transitioning its respiratory franchise from *Advair Diskus* (fluticasone/salmeterol) to newer products like *Breo Ellipta* (fluticasone/vilanterol), *Anoro Ellipta* (umeclidinium/vilanterol), *Trelegy Ellipta* (fluticasone/umeclidinium/vilanterol) and *Nucala* (mepolizumab) and driving growth from new HIV launches. Advair, the company's big respiratory blockbuster, could face generic competition shortly. **Mylan NV** has an ANDA pending at the US FDA with action expected in October, following two complete response letters.

Pharmaceuticals revenues grew 1% to £4.22bn ($5.38bn) in the third quarter, while vaccines sales surged 14% to £1.92bn ($2.45bn) on the strength of the new shingles vaccines *Shingrix*.

Shingrix generated £286m ($364.9m) in the US and Canada. GSK updated guidance to reflect higher than expected sales of the vaccine of £700m-£750m ($893m to $957m) in 2018. But the growth of Shingrix is constrained by supply, not demand.

'We have clearly said we will be more decisive with our pipeline and, this quarter, we've also decided to terminate five development programs,' said Emma Walmsley.

"We need to get the supply expanded as fast as possible because we can pretty much sell anything that we make now in the US," President-Global Pharmaceuticals Luke Miels said. The company is in the process of building up its manufacturing capacity.

HIV also continues to be a strong area for GSK under the **ViiV Healthcare** umbrella. HIV sales increased 11% at average exchange rates to £1.21bn ($1.54bn) in the quarter, driven by *Triumeq* (abacavir/dolutegravir/lamivudine) and *Tivicay* (dolutegravir).

The company filed regulatory applications in the US and Europe in October for a single-tablet, two-drug regimen of dolutegravir and lamivudine for the treatment of HIV and expects regulatory approval in the second quarter of 2019. GSK also announced positive results from a second Phase III study testing a long-acting, once-monthly injectable two-drug regimen of cabotegravir and rilpivirine, which it expects to file for regulatory approval in the first half of 2019.

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Amgen's Aimovig Riding High With Strong Prescriber, Payer Acceptance

MANDY JACKSON mandy.jackson@informausa.com

The quick transition of free initial prescriptions to reimbursed product helped carry **Amgen Inc.**'s CGRP inhibitor *Aimovig* (erenumab) to $22m in third quarter sales, the firm reported Oct. 30, as payers agree more often than not to cover the cost of the migraine prevention therapy.

Amgen's third quarter revenue of $5.9bn and its non-GAAP earnings per share (EPS) of $3.69 grew 2% and 13%, respectively, year-over-year and beat analyst consensus of $5.75bn and $3.42. But with big declines for multiple legacy products suffering from biosimilar competition and pricing pressures in crowded therapeutic areas, growth driven by new products like the **Novartis AG**-partnered Aimovig is crucial for longer-term gains.

That's why new Executive Vice President-Global Commercial Operations Murdo Gordon spent much of his first Amgen earnings call fielding questions from analysts about Aimovig sales growth and reimbursement. Gordon praised the commercial team shaped by his predecessor Tony Hooper, whose retirement was announced during the company's second quarter earnings call in July.

That commercial team and its peers at Novartis have been able to convince about 12,000 doctors to write prescriptions for Aimovig, which have led to some 100,000 patients initiating therapy since the monoclonal antibody's launch in May.

Gordon described Aimovig as "one of the strongest launches that I've seen in my experience in this industry, both within this therapeutic area and even more broadly."

ACCESSIBLE PRICING DRIVES UPTAKE, PAYER SUPPORT

He pointed to Aimovig's "accessible" price of $575 per month, or $6,900 annually, which has resulted in favorable rates of payers approving reimbursement of prescriptions for the biologic. *(Also see "Amgen's Aimovig Aims To Capture As Many Migraine Patients As Possible With $6,900 Price" - Scrip, 17 May, 2018.)*

Amgen and Novartis have provided the migraine therapy to patients for free until payers agree to cover those prescriptions going forward, but Novartis declined in its third quarter earnings report to say what percentage of patients have transitioned from free drug to reimbursed product. *(Also see "Eight Things To Know From Novartis' Third Quarter Call " - Scrip, 18 Oct, 2018.)*

However, Gordon said one of the reasons for the Aimovig launch's "fantastic success" is that physician feedback suggests about 70% of prescriptions are now being covered by payers. He noted that prescribers also like the lack of a loading dose requirement for Aimovig.

Gordon pushed back against analyst suggestions that the product is not very differ-

ent from competing CGRP inhibitors that have now entered the market – **Teva Pharmaceutical Industries Ltd.**'s *Ajovy* (remanezumab) and **Eli Lilly & Co.**'s *Emgality* (galcanezumab). *(Also see "Best-In-Class Or First-In-Class: CGRP Inhibitors Line Up To Win The Migraine Market" - Scrip, 8 May, 2017.)* He cited the Amgen product's first-to-market advantage, its easy-to-use *SureClick* autoinjector, and the fact that it targets the CGRP receptor and not CGRP itself.

Aimovig, along with Emgality, also has the advantage of being covered by one of the biggest commercial payers in the US; the Amgen/Novartis and Lilly products were added to the **Express Scripts Holding Co.** formulary while Teva's Ajovy was excluded.

Gordon said "we're feeling quite good about what we've been able to do with payers" and noted that in addition to the Express Scripts decision discussions with **Anthem Inc.**, **Kaiser Permanente** and other payers are progressing well. He acknowledged that discounts are being negotiated in the form of rebates to commercial payers, but did not disclose the difference between gross and net Aimovig pricing.

Jefferies analyst Michael Yee said in an Oct. 30 note that "yes, gross-to-net and rebating will play a role but they really want patients to get access (implies they're OK with lower pricing if [patients] gets access, in our view)."

Increased payer coverage undoubtedly will improve Aimovig sales figures in the near and long term, but Gordon noted that Amgen expects the rate of sales growth to moderate as patient demand moderates. However, this was not attributed to the market entry of Teva's Ajovy and Lilly's Emgality. Instead, Amgen has said for several months that it expected a big bolus of initial prescriptions for Aimovig, because of the pent-up demand for effective migraine prophylaxis, so the company expects the product's sales growth rate to slow somewhat as that bolus of patients is able to access treatment.

AIMOVIG STRATEGY RESEMBLES NEW REPATHA PATH

The price of Aimovig, which came in lower than expected and within a range suggested to be cost effective for CGRP inhibitors, is likely be a big driver of uptake and reimbursement. *(Also see "ICER Says Amgen/Novartis Migraine Drug Aimovig Is Cost Effective At $5,000 Net Price" - Scrip, 1 Jun, 2018.)* The drug's price also seems to reflect lessons that Amgen learned from the launch of its PCSK9 inhibitor *Repatha* (evolocumab) – another biologic for a large market with reasonably effective generic drugs.

'We're feeling quite good about what we've been able to do with payers'

Repatha was expected to be a blockbuster product based on substantial lowering of LDL cholesterol in several clinical trials, and a reduction of cardiovascular risk in the FOURIER trial completed last year. *(Also see "Outcomes Claim May Help Amgen Make Case For PCSK9 Inhibitor Repatha" - Scrip, 1 Dec, 2017.)* But with a list price of $14,523 in a market where generic statins rule, the PCSK9 inhibitor has not come close to the $1bn mark in annual sales – even with millions of patients who can't tolerate statins and could benefit from the novel therapy.

In fact, Repatha's sales rose 35% year-over-year to $120m in the third quarter, but fell 19% sequentially from $148m in the second quarter as the product lost out to **Sanofi/Regeneron Pharmaceuticals Inc.**'s PCSK9 inhibitor *Praluent* (alirocumab) on the Express Scripts formulary, and faced pricing and competitive pressures generally. *(Also see "Let's Make A Deal: Sanofi/Regeneron Extend A Hand On Praluent, Express Scripts Takes It" - Scrip, 1 May, 2018.)* Higher Repatha demand was offset by lower net pricing as Amgen offered additional discounts and rebates to drive sales.

The company announced a plan on Oct. 24 to cut Repatha's list price by 60% to $5,850, primarily to increase uptake among patients covered by Medicare Part D plans, which represent a majority of people eligible for treatment but a minority of patients taking the drug.

Medicare Part D patients have higher co-payment requirements than those covered by commercial health plans, because their co-pays are based on the $14,523 list price. According to Amgen, this leads to 75% of Medicare Part D patients abandoning their Repatha prescriptions at the pharmacy counter.

The new list price could result in the addition of Repatha to Medicare Part D formularies before the next review cycle for those plans, and it could lead to renegotiations with commercial health plans, potentially leading to higher uptake across the board.

LOWER PRICE, HIGH VOLUME STRATEGY HERE TO STAY?

The lower price, higher volume tactic for both Aimovig and Repatha may reflect Amgen's pricing strategy going forward in an environment in which payers and politicians – particularly, President Donald Trump – are putting increased pressure on pharma companies to cut drug prices.

Amgen CEO Robert Bradway acknowledged the ongoing pressure from the Trump administration, including a recent proposal to index Medicare Part B prices to lower ex-US prices for the same drugs. *(Also see "Part B's Foreign Price Bench-marking Will Only Hurt Bad Negotiators, HHS's Azar Argues" - Scrip, 25 Oct, 2018.)*

Bradway said at the start of the call that "while we're in a midst of a period of high volatility driven by a variety of macro and political factors, our fundamental objectives of innovating for the benefit of patients and delivering for shareholders remain intact and unchanged. Looking to the future, there are bound to be headwinds, but we're confident in our ability to navigate them from a position of strength."

"With price under pressure, having innovative products, which can deliver volume growth by meeting the needs of large numbers of patients is ever-more important," Bradway added.

He noted that Amgen will work with the Trump Administration on its drug pricing proposals, including the Part B plan, "but our objective and our commitment is to continue to work with the administration and Congress to try to improve the competitiveness and access for innovative drugs in our system."

Jefferies' Yee noted that the CEO's comments were consistent with the industry's talking points, noting that "they're working with the administration for market-based reforms – increase competition without undermining [the] innovation ecosystem."

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Genentech, Amgen Face Big Impact From Part B International Pricing Index

CATHY KELLY catherine.kelly@informa.com

Genentech Inc. and **Amgen Inc.** could face major reductions in US prices for important drugs if the Medicare Part B international pricing index model demonstration project moves ahead as currently envisioned.

Announced by the Centers for Medicare and Medicaid Services Oct. 25 in an advance notice of proposed rulemaking, the demonstration would attempt to lower Part B drug prices by an average of 30% in three ways, including by using an average of international prices in developed countries as a reference.

The model, which initially would target single source drugs and biologics, also would use private sector vendors, such as wholesalers or specialty pharmacies, to negotiate prices, take title to drugs, and then compete for physician and hospital business to supply the drugs.

And, it would de-link prices from provider payments (and potentially reduce physician incentives to prescribe higher cost drugs) by using a set payment amount and increasing Medicare's add-on payment to providers to cover storage and administration costs from the current de facto add-on of 4.3% of average sales price to 6% of historical drug costs.

LOOK AHEAD FIVE YEARS

The demonstration is scheduled to begin in 2020 and the impact will be gradual, as the model is phased in over five years. The pricing model could be implemented nationwide at the end of that period if the demonstration shows that it saves money without sacrificing the quality of care.

Based on CMS' 2016 data, it appears that Genentech and Amgen will face the biggest impact – but many of their top drugs are facing biosimilar competition currently or will in the near term, so should capture less of overall Part B spending as time goes on. The impact of the model on companies like **Bristol-Myers Squibb Co.** could become more evident at that point as their drugs control proportionally larger shares of overall Part B expenditures.

Changes In Medicare Part B Spending Based On International Index Price (Ranked by estimated difference in spending)

DRUG	US MARKETER	MARKETER ABROAD	2016 MEDICARE CHARGES ALLOWED	PART B SPENDING AT INTERNATIONAL INDEX PRICE	DIFFERENCE IN SPENDING
Rituxan (rituximab)	Genentech/Roche	Roche most markets	$1.7bn	$639.6m	$1.1bn
Neulasta (pegfilgrastim)	Amgen	Amgen most markets	$1.4bn	$424.6m	$946.1m
Eylea (aflibercept)	Regeneron	Bayer	$2.2bn	$1.2bn	$892.3m
Lucentis (ranibizumab)	Genentech/Roche	Novartis	$1bn	$188m	$852.6m
Prolia/Xgeva (denosumab)	Amgen	Amgen most markets	$1.1bn	$234.5m	$850m
Avastin (bevacizumab)	Genentech/Roche	Roche	$1.1bn	$567.1m	$553m
Herceptin (trastuzumab)	Genentech/Roche	Roche	$703.6m	$339.7m	$379.4m
Orencia (abatacept)	Bristol-Myers Squibb	Bristol-Myers Squibb most markets	$586.5m	$255m	$326.8m
Opdivo (nivolumab)	Bristol-Myers Squibb	Bristol-Myers Squibb most markets	$1.2bn	$933.1m	$317.4m
Sandostatin LAR (octreotide)	Novartis	Novartis	$411.5m	$154.8m	$259.3m
Alimta (pemetrexed)	Lilly	Lilly	$511.8m	$253.8m	$255m
Treanda (bendamustine)	Teva	Astellas, Mundipharma and others	$263.8m	$41.2m	$225.6m
Tysabri (natalizumab)	Biogen	Biogen	$306m	$104m	$199.3m
Remicade (infliximab)	J&J	J&J and Merck	$1.3bn	$1.1bn	$199m
Xolair (omalizumab)	Genentech/Roche	Novartis	$328m	$147m	$180.3m

Source: CMS and IQVIA MIDAS. Analysis based on data released Aug. 17, 2018.

Under the model, Medicare reimbursement for Genentech's cancer drug *Rituxan* (rituximab) and its treatment for macular degeneration *Lucentis* (ranibizumab) could be significantly reduced in those geographic regions where the model is implemented.

CMS estimates the difference between 2016 Medicare spending for Rituxan and spending at the international volume-weighted average price could approach $1.1bn., according to an HHS report and technical appendix of prices released in conjunction with the ANPR *(see chart on previous page)*. The report compares US and international prices for the top Medicare Part B drugs.

The difference in spending for Lucentis would be $852.6m. Drug prices could be further reduced by pressure from purchasing vendors and even, indirectly, by the new approach to compensating providers with a flat storage and administration fee.

Genentech would also see price reductions for its cancer treatments *Avastin* (bevacizumab) and *Herceptin* (trastuzumab). CMS estimates its spending for the two drugs would be $553m and $379m lower under the model.

Amgen's prices for its blockbusters *Neulasta* (pegfilgrastim), a granulocyte colony stimulating factor for neutropenia, and *Prolia* and *Xgeva* (denosumab) for osteoporosis and bone fracture prevention also could face big changes. Medicare spending on Neulasta – for which the first biosimilar recently launched in the US – would be $946m lower. Expenditures on Prolia/Xgeva would be $850m less using the international reference price, CMS said.

The potential difference in reimbursement for **Regeneron Pharmaceuticals Inc.**'s treatment for macular degeneration and other retinal disorders, *Eylea* (aflibercept), would similarly be substantial – $892.3m less with the new approach.

The difference in spending gives a sense of the level of decline in pricing that might occur under the model. But it would not necessarily represent the amount of price declines during the demonstration period. The model will only apply to 50% of Part B expenditures and the target price for Part B drugs will be phased in gradually over the course of the demonstration.

Genentech and Amgen were cautious in their early individual reactions to the model and emphasized their interest in shaping the demonstration in the coming months. Genentech said in an e-mailed statement it is still reviewing the ANPR, but "we believe by working together on solutions to complex challenges, we can bring about positive change for benefit of the entire health care system and – most importantly – patients.

"However, as we do this, it is absolutely critical we protect and sustain scientific innovation in the United States so that people with serious diseases throughout this country continue to benefit from the life-changing medicines they need," the company maintained.

Amgen CEO Robert Bradway emphasized during the company's earnings call Oct. 30 that "at this point, it is just a proposal. We expect there will be quite a bit of interest in trying to help shape the eventual outcome of that, but our objective and our commitment is to continue to work with the Administration and Congress to try to improve the competitiveness and access for innovative drugs in our system, and that includes in Part B."

He added: "We think there are some things that can be done to eliminate unnecessary cost and friction in the system and make sure the patients who need innovative therapies can get them, and we will continue to advance those ideas in our discussions in Washington. But again, I just would underscore it's a proposal at this point and there will be plenty of time to see the proposal take shape."

CMS will accept comments on the ANPR until Dec. 31. A proposed rule on the demonstration is scheduled to be released in the spring of 2019, followed by a final rule later that year. CMS is allowing ample time for comments and likely will get many that are critical from manufacturers and physicians. What eventually emerges could be significantly different from what is described in the ANPR.

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Industry Wants US Rebate Reform, But What Does That Mean?

JESSICA MERRILL jessica.merrill@informa.com

The drug industry is generally advocating in favor of US rebate reform, but while the industry wants changes that could take extra costs out of the system and shine a light on the steep offsets they pay, a transformational change like the elimination of rebates would be a big challenge to operationalize. Some industry insiders are in favor of replacing the current system with a new discount system or passing rebates onto consumers at the point-of-sale instead.

A new upfront discount that would still allow for confidential price negotiations is one top contender under discussion to replace the current model, though for now, the industry is largely in wait and see mode. Any new system will stem from government policy. A proposal around rebates is pending at the Department of Health and Human Services, though new actions on Medicare Part B were released first in October, so it's uncertain how that could impact the timeline.

Rebate changes have also been a focus of HHS Secretary Alex Azar. HHS' Office of Inspector General is preparing a proposed rule that could remove the safe harbor that protects negotiated rebates from the anti-kickback statue in Medicare Part D or replace it with something else.

The anti-kickback statute applies to government programs so the expectation is that the proposed rule will apply to Part D, though it may then likely spread to the commercial market. One issue that is being reviewed is how eliminating rebates might impact insurance premiums, since pharmacy benefit managers say the price offsets are passed onto insurers and eventually patients through lower insurance premiums.

Pending policy changes are spurring a lot of dialogue about what the elimination of rebates would mean for a system that has relied on them to negotiate reimbursement, or what kind of replacement would be most beneficial to patients – and the industry.

As much as the industry is eager to educate the public and regulators about how much it spends on rebates to offset list prices for drugs and remove some of the incentives that have led to increasingly higher list prices, rebates have also been a powerful tool leveraged by drug makers to buy market access. Industry seems uncertain about eliminating altogether the tools it has relied on.

As one big pharma market access specialist said, "There is a misconception. Nobody is saying that negotiations shouldn't happen. Nobody is saying that blind bidding shouldn't happen. What we are saying is that doing it through a tactic of rebating is not the best way to do it."

"A good replacement would be something like a net price negotiation for the medicine, which would still be that we provide concessions based on negotiations, but it would be upfront and it would be in a discount form. That's what is being discussed right now," this market access specialist said.

AstraZeneca PLC US President Ruud Dobber agreed in an interview. "I don't think a country like the US, you move to a net realized price. It is still a hard negotiation you need to have with PBMs," he said. "I don't envision that if you are moving away from a rebate system that there is no negotiating."

The Pharmaceutical Research and Manufacturers of America (PhRMA) advocated for something similar in comments on Trump's drug pricing blueprint, pointing out that while industry would like to see rebate reforms, moving away from rebates altogether may be challenging to operationalize. The trade group recommended a system "where the supply chain does not retain compensation based on a percentage of the list price" or one where rebates are passed onto patients at the point-of-sale instead.

On the other hand, some drug companies say they are open to more disruptive change as long as it is phased in over a lengthy timeline, with consideration given for unintended consequences.

"We are aligned with the underlying premise of Secretary Azar's intent and that is that the rebate system has grown so significantly that it is distorting a naturally functioning marketplace," **GlaxoSmithKline PLC**'s Senior VP-Managed Markets and Government Affairs Jamey Millar said in an interview.

"We would prefer that any remuneration to health plans or payers would be delinked from list price. If that ends up being the complete removal of the rebate system, then we think that's right," he said. GSK is one company that has had to front enormous rebates in the competitive respiratory category, where some drugs – including GSK's own *Advair Diskus* – have been excluded from formularies, driven by rebate negotiations.

WHAT WOULD BE DIFFERENT ABOUT AN UPFRONT DISCOUNT?

A new upfront discount system would be less transformational that eliminating rebates, but advocates say it would have benefits over rebates. It would help the government and other stakeholders better track the flow of money through the system, even if drug pricing might not necessarily become more transparent to the patient. Information would be more transparent to other stakeholders in the system. Under the current rebate system, it's not always clear who keeps what portion of the rebate and how the savings are directed.

"It's not all that different from a rebate, but you have to figure out then exactly how the flow of money works," said Howard Deutsch, a principal at the consulting firm ZS Associates working in pricing and market access.

The upfront discount would also eliminate the incentives for high list prices/high rebates that has evolved under the current system, which pharma says is driven partly by the administrative fees PBMs collect as a percent of the rebate.

A discount taken upfront would flow through the system immediately and to the patient, which would realize the savings when they pay out of pocket in a way they currently do not. With a rebate, based on utilization, the rebate is paid directly to the PBM or the health plan long after they accrue.

Some health economics experts also believe that negotiations – and particularly confidential negotiations that are kept out of public view – are an important element to keeping drug costs down.

"It's not a good idea to just eliminate [the rebates] without replacing it with some other way of giving discounts," said Harvard Medical School Professor of Health Economics Richard Frank. "And, there are advantages for the discounts not being public."

But some stakeholders say they'd rather see more transparency on pricing for patients, which could open competition and impact drug prices.

Memorial Sloan Kettering's Center for Health Policy and Outcomes Director Peter Bach said the upfront discount idea would be a move in the right direction, but that the system should ultimately move toward one where drugs compete directly on price.

"We need to continue to be more rational and ultimately have prices travel with the value of products' benefits," he said. "If you factor through to the end, a rational system doesn't have rebating in it." But, he added, "What happens during the transition is hard to predict."

Sean Karbowicz, the founder and general manager of MedSavvy, which develops report-card style grades for patients to evaluate drugs and cost information, also argued in favor of transparency. "Looking at other [categories] where products are able to compete, without these types of distortions, prices do come down," he said. MedSavvy is owned by the non-profit health solutions company Cambia Health, which also offers health insurance and pharmacy benefit services.

Changing the back-end rebate to an upfront discount would be more like a "tweak," he said. "I have a hard time understanding how that is going to inject competition and increase quality and lower prices for consumers over all."

For now, all eyes are on HHS and what drug price reforms will come down next.

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[Scrip's sister publication IN VIVO will feature a deeper review of US rebate reform in the upcoming November issue.]

Novartis Gives Up On Rituxan Biosimilar For US Market

KEVIN GROGAN & ALEX SHIMMINGS

Novartis AG has thrown in the towel on getting US approval for a biosimilar of **Roche**'s lymphoma, leukemia and rheumatoid arthritis drug *Rituxan* (rituximab), after the FDA asked for more information on the company's version of the drug, which is approved already in Europe and elsewhere.

In May, Novartis generics unit Sandoz received a complete response letter from the FDA for its Rituxan biosimilar and no reasons for the rejection were disclosed, nor were any timelines mentioned for a potential refiling. At the time, the company limited itself to saying that it "stands behind the robust body of evidence included in the regulatory submission."

Now, following an evaluation of the FDA's request for additional information "to complement the filing," Sandoz said it will not pursue a re-application for a Rituxan biosimilar stateside. Instead, the firm will focus on "progressing its biosimilar pipeline in areas of greatest unmet access needs."

Sandoz global head of biopharmaceuticals Stefan Hendriks said in a statement that "we appreciate the important conversations with the FDA, which have provided specific requirements for our potential US biosimilar rituximab, but believe the patient and marketplace needs in the US will be satisfied before we can generate the data required."

He went on to say that "we are disappointed to have to make this decision and stand behind the safety, efficacy and quality of our medicine, which met the stringent criteria for approval in the European Union, Switzerland, Japan, New Zealand and Australia."

Speaking to *Scrip* at the company's R&D day in London, Novartis CEO Vas Narasimhan said that when it comes to biosimilars, "the US is very complex – almost product by product, I was going to say 'adventure' but I'm not sure that's the right word!" He added that with *Zarxio*, its version of **Amgen Inc.**'s *Neupogen* (filgrastim) and other biosimilars, the company has enjoyed successful launches but now with rituximab "we have hit some bumps with the FDA obviously…that's been an interesting experience because we are approved in Europe, Japan, Australia, Canada and a bunch of other countries."

> 'We are disappointed to have to make this decision and stand behind the safety, efficacy and quality of our medicine'

Narasimhan noted that the FDA had actually asked Novartis to repeat the pivotal study for its version of Rituxan and "in my judgement, it is not a good investment of our investors' dollars to repeat a study that will be many years…we walk away at this point rather than continuing to throw money into it."

TALE OF TWO CONTINENTS

Biosimilars "has been a tale of two continents in my mind," he told *Scrip*, as Europe "has been extraordinarily successful. It's where we have had great launches, we have a broad portfolio and most of the uptake is faster than we would have expected." He pointed out that Novartis has been in biosimilars in Europe since 2010 and the experience gained has made it easier to get approvals and rapidly get to the market.

Narasimhan stressed that the experience with rituximab in the US "doesn't signal a strategic shift in our focus" and while there is still a lot to work to do there, "I think there is a lot of goodwill among all policy makers who agree biosimilars could reduce a lot of waste..but it's looking to be a few more years before it fully materializes."

The decision to give up on biosimilar Rituxan in the US will be welcomed by Roche and co-marketing partner **Biogen Inc.** Sales of the branded blockbuster, which is sold as *MabThera* outside the US and Japan, have been battered by biosimilars in Europe, down 48% to CHF731m for the first nine months of 2018, but are still rising in the US, up 4% from January to September to CHF3.19bn.

However, there is likely to be some competition soon across the Atlantic in the form of **Celltrion Inc.** and **Teva Pharmaceutical Industries Ltd.**'s *Truxima*, also known as CT-P10. Last month, the FDA's Oncologic Drugs Advisory Committee voted 16-0 that the totality of evidence supports licensure of CT-P10 as a biosimilar to Rituxan for three non-Hodgkin's lymphoma (NHL) indications, with panel members concluding that small analytical differences between the products were not clinically meaningful.

The Celltrion case is especially interesting, given that the South Korean firm is

only seeking approval in the US for three of Rituxan's eight labeled indications due to "the current intellectual property and exclusivity landscape." Missing from the biosimilar's proposed label are a fourth NHL indication, as well as indications for chronic lymphocytic leukemia, rheumatoid arthritis, granulomatosis with polyangiitis and pemphigus vulgaris. *(Also see "Celltrion's Biosimilar Rituximab Brings Indication Carve Outs To US FDA Panel Review" - Pink Sheet, 12 Sep, 2018.)*

In Europe, however, Truxima was approved in February 2017 for all MabThera indications. Quoting IQVIA data last month, Celltrion said Truxima's market share in the five major European countries (the UK, Germany, France, Italy and Spain) averaged 34% - 64% for the UK alone.

Commenting on Novartis' decision, Bernstein analyst Ronny Gal issued a note saying "this should be viewed as a rebuke to the FDA requirement bar in terms of preclinical characterization. We are hearing the echoes of internal debate within the agency as preclinical guidance is being re-examined." He added that "this leaves Teva/Celltrion with a material lead," noting that **Amgen Inc.** and **Pfizer Inc.** are yet to submit their Rituxan biosimilar "and it may end up being a very limited market."

As for Sandoz, which has seven approved biosimilars worldwide, three of which have the green light in the US, Hendriks stated that "we believe we should now focus on opportunities in the US and around the world where we can best meet rapidly evolving patient and healthcare system needs."

Sandoz, like a host of other companies, has decided that a version of the world's best-selling drug – **AbbVie Inc.**'s *Humira* (adalimumab) – meets those criteria. At the end of last month, the FDA approved *Hyrimoz*, Sandoz's biosimilar of the mega-blockbuster and despite a patent settlement recently agreed with AbbVie, it will not be launched in the US until September 2023. However, it was launched in Europe in October immediately after the Humira patent expiry. *(Also see "Sandoz And AbbVie Biosimilar Humira Settlement: What Does It Mean?" - Scrip, 12 Oct, 2018.) (Also see "AbbVie Defends Humira With Aggressive Discount In First EU Tender " - Scrip, 1 Nov, 2018.)*

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On Drug Price Increases, Pfizer's Read Expects 'Business As Normal'

JESSICA MERRILL jessica.merrill@informa.com

Pfizer Inc. CEO Ian Read suggested the company isn't going to back off its customary January price increases, even with ongoing pressure coming from the Trump Administration. Read was pressed by analysts during the company's third quarter earnings call Oct. 30 about expectations for the annual drug price increases that are generally taken at the beginning of the year.

"I expect our approach by the end of the year will be what I would characterize as business as normal," Read said. "We price to the marketplace. We price competitively. And we will make those decisions towards the end of the year and early in January."

Pfizer led a charge across the industry to hold off on drug price increases in mid-2018 after the company was targeted by President Trump in a Tweet for raising drug prices.

The company promised at the time not to raise drug prices for the remainder of the year or until Trump's pricing blueprint was implemented. Several other drug makers followed Pfizer's lead, vowing to hold off on any more price increases for the remainder of 2018.

The question now is how much scrutiny drug makers will come under when they increase prices in 2019, and if the president will get back on his social media megaphone. The problem for the industry is that many companies have relied on hefty price increases to pad lackluster volume growth.

Led by HHS Secretary Alex Azar, the Trump administration has also been working on new policy proposals that could have an enormous impact on the industry as it looks for ways to lower drug costs. The Centers for Medicare & Medicaid Services released an advanced notice of proposed rulemaking Oct. 25 addressing changes to Medicare Part B, including a hot button proposal to link some drug reimbursement to an international price index. Unsurprisingly, Read came out against such a policy maneuver. "I don't think it's in the best interest of patients; it effectively imports price controls from abroad [to] the US and we hope that the administration would reconsider its position on that," he said.

HHS is also expected to issue new proposals around rebating, the volume-based offsets drug makers pay to payers to secure market access. HHS' Office of Inspector General is preparing a proposed rule that could remove the safe harbor that allows negotiated rebates from the anti-kickback statue, which has protected the discounts. There are a lot of questions about the action and whether it will result in the elimination of rebates altogether or some kind of replacement discount.

Read was bullish on the probability of near-term rebate reform during Pfizer's second quarter call, and this time he said he continues to expect action between now and the end of the year. "It is the most effective way the administration can lower prices for patients at the point of purchase," he said, adding that there could be a variety of ways to reform the rebate system.

READ'S FINAL BOW

Read presided over the call for the last time as the CEO of Pfizer. The company revealed Oct. 1 that Chief Operating Officer Albert Bourla will succeed Read as CEO effective Jan. 1, while Read will remain with the company as executive chairman.

Bourla will be tasked with driving growth at Pfizer while the company navigates through the upcoming loss of exclusivity of *Lyrica* (pregabalin), the company's second best-selling drug behind the pneumococcal vaccine *Prevnar*. Lyrica generated sales of $1.13bn in the third quarter. The drug is poised to lose market exclusivity on Dec. 30, but Pfizer has filed for pediatric exclusivity, which could extend exclusivity by six months to June 30 if granted by the FDA.

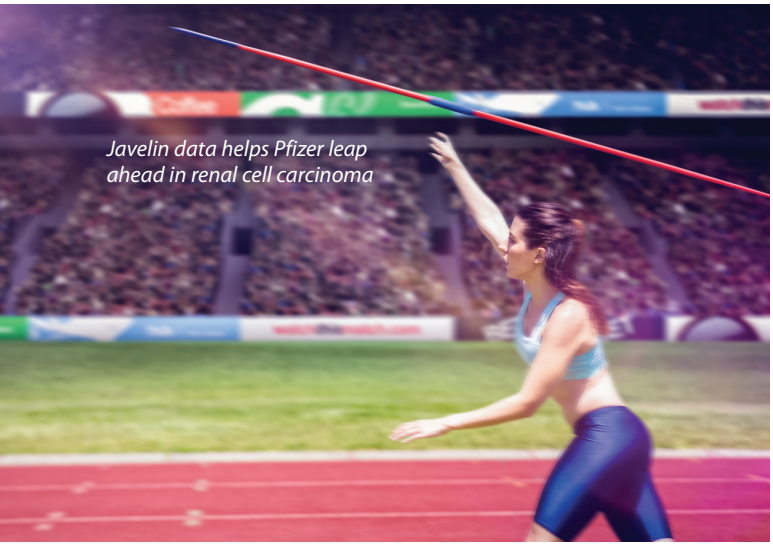
The company is preparing to increase R&D investments and commercial costs as it prepares for the launch of several new drugs in the next five years, Bourla said.

"To partially offset these incremental cost increases, we will generate cost-reduction opportunities particularly in indirect SG&A," Bourla said. "We are taking steps to simplify the organization, increase expense control and reduce organizational layers." The company confirmed in October that it is planning to reduce its workforce by a few percentage points. *Published online 30 October 2018*

Pfizer Well-Placed To Lead First-Line Advanced RCC Market

KEVIN GROGAN kevin.grogan@informa.com

The likelihood of **Pfizer Inc.** becoming the leader for first-line treatment of advanced renal cancer has increased on the back of recent data read-outs that put the behemoth at the heart of the checkpoint/tyrosine kinase inhibitor (TKI) combos that look set to be practice-changing.



Javelin data helps Pfizer leap ahead in renal cell carcinoma

Support for that view comes from the full data readout from the JAVELIN Renal 101 Phase III study presented at this month's ESMO meeting in Munich which showed that Pfizer and **Merck KGAA**'s immune checkpoint blocker *Bavencio* (avelumab) plus the former's TKI *Inlyta* (axitinib) significantly improved progression-free survival (PFS) in previously untreated patients with advanced renal cell carcinoma (RCC) compared to the current first-line standard of care, Pfizer's older TKI *Sutent* (sunitinib).

Median PFS was 13.8 versus 7.2 months in favor of the combo in patients with PD-L1+ tumors, but importantly median PFS in patients irrespective of PD-L1 expression was 13.8 versus 8.4 months. Noting that JAVELIN Renal 101 is the first positive Phase III trial combining a checkpoint inhibitor with a TKI compared to TKI alone in the first-line treatment of advanced RCC, lead investigator Robert Motzer, of the Memorial Sloan Kettering Cancer Center in New York City, told journalists at a press briefing at ESMO that the findings support the potential of the combo as a new treatment approach for patients with advanced RCC.

Motzer stressed that the benefit was shown in all subgroups (good, intermediate, and poor risk) and whether tumor cells were stained positive for PD-L1 or not. He does not believe it would be necessary to test for PD-L1 to choose patients to be on the combo – PD-L1-negatives made up 37% of the overall trial population – going on to stress that the clinical benefit seen "exceeds the effects of the respective drugs alone, without compromising toxicity."

Commenting on the results, Thomas Powles of the Barts Health NHS Trust in London described them as "eye-catching." He noted that "the response rates are twice as good as previous standards of care, and progression-free survival is entering into very impressive territory for a randomized trial."

No analysis of the co-primary endpoint of overall survival (OS) was presented at ESMO as the data are immature. Given this, Powles added that "there is uncertainty around whether this will translate into a similarly impressive" OS survival signal.

It all looks promising, however, and Chris Boshoff, head of immuno-oncology, translational and early development at Pfizer, told *Scrip* in an interview at ESMO that JAVELIN Renal 101 fits well with the company's heritage in kidney cancer. With Sutent and Inlyta, plus *Torisel* (temsirolimus), Pfizer has had three drugs approved in the space in the last 10 years.

Boshoff spoke about the clear rationale that the firm had identified in combining an anti-angiogenesis agent, a class which has become fundamental to treating RCC, and immunotherapy, noting that kidney cancer is one of the malignancies that is very sensitive to checkpoint blockers, having shown single-agent response rates of around 20-30%. However, JAVELIN Renal 101 has shown that the combo works better than each agent on its own and has a very acceptable side effect profile.

There will have been no little relief for Pfizer and Merck at the data presented at ESMO being so positive, especially as a couple of days before the Munich meeting kicked off, **Merck & Co. Inc.** stole a bit of their thunder and announced that its immunotherapy blockbuster *Keytruda* (pembrolizumab) in combination with Inlyta had hit both PFS and OS endpoints in the Phase III KEYNOTE-426 study in first-line advanced RCC patients.

When asked about the Merck news, Boshoff noted that it was no great surprise, as Pfizer obviously works with its US rival in providing Inlyta and the studies started at a similar time. He said it was difficult to compare the trials before full data are revealed from KEYNOTE-426 but two successful studies of Inlyta with two distinct immunotherapies reinforce the view that the TKI/checkpoint inhibitor combo is a "clinically meaningful game changer."

Having two high-profile positive trials that use Inlyta potentially puts Pfizer in an extremely strong position in terms of future marketing. Even though Keytruda/Inlyta may ultimately top Bavencio/Inlyta on clinical data, on the commercial front Pfizer's ownership of both parts of the latter combo will be key.

While Motzer and others believe the Bavencio/Inlyta combo a new first-line standard of care for advanced RCC, physicians and analysts are looking at how it matches up to Bristol-Myers Squibb Co.'s immunotherapy combo of its PD-1 inhibitor *Opdivo* (nivolumab) and CTLA-4 inhibitor *Yervoy* (ipilimumab).

BMS got the thumbs-up from the FDA in April for Opdivo/Yervoy as first-line treatment of advanced RCC in patients with intermediate or poor risk based on the CheckMate-214 head-to-head trial with Sutent. However, patients with a favorable prognosis in that trial gained no benefit with Opdivo/Yervoy compared to Sutent.

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IQVIA's Clinical Advance of the Year Award

This Scrip Award seeks to recognize success in a clinical trial of a new drug product that is expected to lead to an advance in healthcare.

Ablynx's Phase III HERCULES study of caplacizumab for acquired thrombotic thrombocytopenic purpura

Treatment with Ablynx's novel anti-von Willebrand factor Nanobody caplacizumab resulted in a significant reduction in time to platelet count response, the primary endpoint and a measure of prevention of further microvascular thrombosis in acquired thrombotic thrombocytopenic purpura, a disease for which there is currently no approved therapeutic.

Alexion Pharmaceuticals' Phase III REGAIN study of Soliris in myasthenia gravis

Soliris (eculizumab), the first approved complement inhibitor worldwide, was clinically proven in REGAIN to improve muscle strength and the ability to carry out activities of daily living in patients with generalized myasthenia gravis, representing the first new therapeutic advancement for patients in many years.

bluebird bio's Northstar-2 study of LentiGlobin in beta-thalassemia

bluebird bio's one-time LentiGlobin investigational gene therapy is designed to eliminate or reduce chronic blood transfusions in patients with the severe genetic disease, transfusion-dependent β-thalassemia. Early data indicated that LentiGlobin may enable transfusion independence for the majority of patients with non-β0/β0 genotypes, and that this effect has been durable.

GW Pharmaceuticals' Phase III GWPCARE4 trial of Epidiolex for refractory epilepsy

GW's pharmaceutical formulation of purified cannabidiol Epidiolex (CBD) demonstrated its anti-convulsive effects in refractory forms of paediatric-onset epilepsy – an area with an acute unmet need. In this study, Epidiolex significantly reduced the median monthly drop seizure frequency compared with placebo when added to existing treatment, and was generally well-tolerated.

Ipca Laboratories Phase IV study of hydroxy-chloroquine in type 2 diabetes mellitus in India

This trial of the first anti-inflammatory agent approved for type 2 diabetes in India found that hydroxychloroquine, with its pleiotropic benefits (lipid-lowering, anti-platelet, CV protection, renoprotective), can be beneficial in patients receiving stable doses of metformin and sulfonylurea for more than three months with HbA1c ≥7%.

Nanobiotix's Phase I/II trial of nanomedicine NBTXR3 in head and neck cancer

This trial showed that this first-in-class nanomedicine can significantly change cancer patient outcomes. When activated by radiotherapy, NBTXR3 is designed to destroy tumors through physical cell death and to induce immunogenic cell death. It produced a 78% complete response rate in evaluable patients, all aged 70 or over with bulky, locally advanced disease.

Licensing Deal of the Year
(Sponsored by Worldwide Clinical Trials)

Licensing is vital both in helping to keep pharma's pipelines replenished and in generating income for smaller firms.

AiCuris and Merck & Co (MSD) for Prevymis (letermovir) for cytomegalovirus

This deal between AiCuris and Merck & Co targeting human cytomegalo-virus came to fruition with the US approval in late 2017 of Prevymis to prevent CMV infection in CMV-seropositive recipients of an allogeneic hematopoietic stem cell transplantation. AiCuris received €110m upfront and was eligible for milestone payments of up to €332.5m.

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

This deal worth up to $8.5bn aims to maximize the potential of two anticancers, AZ's PARP inhibitor Lynparza and Merck's MEK inhibitor selumetinib, by exploring the growing scientific evidence that combination of each these two drugs with other drugs could offer even greater benefits to patients in multiple indications.

Avillion and Pearl Therapeutics for PT027 in asthma

Pearl Therapeutics, a wholly owned subsidiary of AstraZeneca, and Avillion entered into a co-development partnership to advance the respiratory product PT027 for the treatment of asthma in the US. This means AstraZeneca has been able to relieve its P&L from the clinical cost incurred by Avillion and free-up internal resources.

Emergent BioSolutions and Valneva for the Zika vaccine candidate VLA1601

Zika is one of eight diseases on the World Health Organization's R&D Blueprint list of priority diseases. In July 2017, Emergent and Valneva announced a partnership under which Emergent received global exclusive rights to Valneva's Zika vaccine technology. The companies are co-developing VLA1601, a highly purified inactivated vaccine candidate against the Zika virus.

F-star (through F-star Delta) and Merck KGaA for five bispecific antibodies in immuno-oncology

F-star expanded its long-standing relationship with Merck through a new strategic collaboration to develop five bispecific therapies in IO that have the potential to overcome tumor resistance. This flexible business model offers Merck the option to acquire the programmes through the buyout of F-star Delta. In return, F-star receives €115m upfront.

Halozyme and Bristol-Myers Squibb for the use of ENHANZE drug delivery technology in immuno-oncology drugs

Halozyme and Bristol-Myers Squibb forged a licensing and collaboration agreement with the potential value to Halozyme exceeding $2bn. The centerpiece of the agreement is Halozyme's ENHANZE technology, which may enable and optimize rapid subcutaneous drug delivery for appropriate co-administered therapeutics. The first target selected in the agreement is PD-1.

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In an investor note after ESMO, Morgan Stanley's David Risinger wrote that Pfizer "arguably may have the edge over Bristol in first-line RCC," noting that the Bavencio/Inlyta PFS data in intermediate/poor risk patients was better than Opdivo/Yervoy. Stressing that toxicity profiles are difficult to compare cross-trial especially given different patient populations, the latter combo appears better based on grade 3–4 treatment-related adverse events but Bavencio/Inlyta had lower discontinuations.

Analysts at Credit Suisse also pointed out that "the PFS benefit is better than the first-line RCC data we saw at last year's ESMO from Opdivo/Yervoy, which has now become a standard of care." However they noted comments from a discussant at the Munich meeting when JAVELIN Renal 101 was being presented who said he was unlikely to use Bavencio/Inlyta in the intermediate/unfavorable patient population, instead of Opdivo/Yervoy, as the OS data is immature. However, he would use the former in favorable-risk patients where TKI are the standard of care.

The space is getting crowded and the increased competition is likely to damage **Exelixis Inc.**'s TKI kidney cancer therapy *Cabometyx* (cabozantinib), which is partnered with **Ipsen** and is also approved for first-line RCC in all-comers. Ipsen started its own Phase III program, CheckMate9ER, for a Cabometyx/Opdivo combo more than a year ago in first-line RCC and results are expected in September 2019, although in an interview with *Scrip* last week, the French firm's CEO David Meek noted that "our window of opportunity in the second-line setting opens significantly because none of these IO trials are in the second line." *(Also see "Cash-Rich Ipsen Opens Up Checkbook For 2019" - Scrip, 25 Oct, 2018.)* *Published online 30 October 2018*

Eyes On Chugai's Hemlibra Supply Price As Sales Grow

IAN HAYDOCK ian.haydock@informa.com

Chugai Pharmaceutical Co. Ltd. has reported what analysts saw as a generally solid set of results for the third quarter ended September 30, logging strong increases for mainstay anticancer products at home and exports to majority owner **Roche**.

But it was the internal pricing practices for novel hemophilia drug *Hemlibra* (emicizumab-kxwh) that seemed to garner to most of the investor attention at a results briefing in Tokyo, with changes expected in the system in the next few months.

The bispecific Factor IXa and X-directed antibody was recently approved in the US for routine prophylaxis to prevent or reduce bleeding episodes in hemophilia A patients without Factor VIII inhibitors.

This is seen as significantly expanding its commercial opportunity beyond the small with-inhibitor population (approved in the US last November).

Overseas sales of rheumatoid arthritis antibody *Actemra* (tocilizumab) and cancer drug *Alecensa* (alectinib) remained strong

For around the last year or so, Chugai has been supplying the product – which it originated – to ex-Asia global partner Roche at an unspecified discounted internal unit transfer price. However, this arrangement will stop from the fourth quarter, with Roche to make up the gap over the earlier period through a temporary rise in royalties expected by some analysts to run into next year. Executive vice president and chief financial officer Toshiaki Itagaki told the briefing that Chugai had so far been using "our production cost plus a certain level of margin" in its export price, and that this had been "relatively low" to date but that supplies were taken demand and expected approvals into account.

CAUTIOUS, GRADUAL INCREASE?

However, adjustments through the future price and royalties will begin to be made from the fourth quarter, gradually and depending on the growth of Roche's sales of Hemlibra, the executive said. The Japanese company is expected to give more details and assumptions as part of its 2019 guidance early next year.

While some analysts appear bullish on early sales, Itagaki was cautious despite promising figures to date, saying only that "whether or not [US] non-inhibitor use is progressing faster than expectations is yet to be seen."

The possibility of any external impact from possible internal pricing changes is unclear, given that some analysts viewed Hemlibra as being aggressively priced "for rapid penetration" at the time of its original US launch for inhibitor patients.

The first-year wholesale acquisition cost was $482,000 (based on a patient of average weight), falling to $448,000 thereafter, the first figure being less that half that of **Shire PLC**'s *Feiba* (anti-inhibitor coagulation complex). *(Also see "Roche's Hemlibra Priced And Labeled To Beat Competition, Safety Concern" - Scrip, 17 Nov, 2017.)*

EARLY SALES TRENDS

Chugai noted in its Q3 results that overseas sales of Hemlibra to Roche were JPY2bn in the nine months, already reaching its current forecast figure for the year.

In Japan, where the drug was launched in May for use in inhibitor patients, sales of JPY1.5bn were booked in the nine months, again ahead of the earlier full-year forecast of JPY1.4bn, suggesting stronger than expected early growth.

"We…believe the company can maintain momentum into 2019, though the key focus to remain Hemlibra in hemophilia," Deutsche Bank research analyst Joseph Cairnes said in a note on the results. "Chugai shareholders should be encouraged by comments from management that early Hemlibra sales are exceeding expectations in the non-inhibitor setting."

However, Hemlibra is seen as having limited capacity for upside surprises into 2019, and the analyst expects "consensus estimates of the share of economics that Chugai receives on global Hemlibra sales will need to come down (currently consensus at around 40% of global sales)".

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Executive of the Year – For Large & Medium Cap Companies

Scrip's Executive of the Year Award is designed to acknowledge excellence in the leadership in pharmaceutical and biotechnology companies. This is focused on larger firms.

Edwin Moses, CEO of Ablynx

Edwin Moses led Ablynx through an IPO on NASDAQ in October 2017. The $230m raised represented the largest biotech IPO in the US for 2017. He also successfully defended Ablynx from a hostile €2.6bn bid from Novo Nordisk which Ablynx believed fundamentally undervalued the company. Ablynx's board then accepted an offer of €3.9bn from Sanofi.

John Maraganore, CEO of Alnylam

As founding CEO of Alnylam, John Maraganore has led the company's more than 15-year journey to translate the Nobel Prize-winning science of RNA interference (RNAi) into a clinically-validated platform, culminating in the potential launch of a new class of medicines for patients living with genetic diseases who have inadequate or no treatment options.

Alan Hirzel, CEO of Abcam

Alan Hirzel has positioned Abcam to deliver sustainable value whilst continuing to innovate in the reagents and tools space. From June 2017 to May 2018, the company's share price rose 24%, exceeding the increases on the FTSE AIM All Share index and FTSE All Share index. He has committed Abcam to a clear strategy for growth.

Jan van de Winkel, CEO of Genmab

Having brought Genmab through crisis years and stabilizing the company financially with the launch of Darzalex in 2015, Jan van de Winkel has turned his attention to expanding Genmab's proprietary pipeline and strengthening it for a commercial future. With two new programs created using the company's antibody technologies entering the clinic, 2017 was Genmab's fifth year of profitability.

Vas Narasimhan, CEO of Novartis

In 2017, Novartis announced Vas Narasimhan as CEO designate, following the departure of former CEO Joe Jimenez. Since taking the helm, Narasimhan has signaled his intention to further Novartis's commitment to digital health, with the goal of achieving a 'productivity revolution' by transforming Novartis from a traditional healthcare company into a medicines and data sciences company.

Niels Riedemann, CEO co-founder of InflaRx

InflaRx CEO and co-founder Niels Riedemann has had a successful year, leading InflaRx through an IPO in October 2017, resulting in gross proceeds of $100m and a follow-on primary and secondary offering which raised an additional $117.3m. Riedemann is an academic scientist and medical doctor, and has led the company to become an industry leader in the complement space.

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Executive of the Year – For Small Cap & Private Pharma Companies

Scrip's Executive of the Year Award is designed to acknowledge excellence in the leadership in pharmaceutical and biotechnology companies. This is focused on private and small firms.

Eduardo Bravo, CEO of TiGenix

Eduardo Bravo's leadership was instrumental in establishing TiGenix as a leader in allogeneic stem cell therapies with the successful EU approval of Alofisel for complex perianal fistulas. This marked the first ever allogeneic stem cell therapy to receive centralized approval in Europe. The company also strengthened its US operations with key senior appointments.

Jurgi Camblong, CEO and founder of SOPHiA GENETICS

Entrepreneur Jurgi Camblong's SOPHiA GENETICS made several major announcements this year, including the company's AI reaching a key milestone in helping better diagnose 200,000 patients, and the addition of radiomics capabilities. In September 2017 SOPHiA GENETICS closed a $30m Series D funding round, led by London-based Balderton Capital.

Carl Firth, CEO and founder of ASLAN Pharmaceuticals

In the last year, Carl Firth has led ASLAN to become the first Singapore biotech company to be publicly listed, with the completion of an IPO on NASDAQ and on the Taipei Exchange, setting the next stage for the company's imminent commercialization of its first drug for biliary tract cancer and gastric cancer.

Antony Loebel, executive vice president, chief medical officer, head of global clinical development of Sunovion Pharmaceuticals

Antony Loebel has a track record of leading the successful development of new treatments for patients with brain disorders, and bringing new innovation to R&D. He has undertaken innovative research initiatives aimed at improving the standard of care for patients with serious psychiatric conditions and neurological disorders.

Amy Schulman, CEO and co-founder of Lyndra

Amy Schulman has propelled Lyndra forward in its vision to develop ultra-long-acting oral medications that will make daily pills a thing of the past. Over the past year it has attracted partnerships with industry giants like Allergan, and established a global footprint through a Chinese joint venture.

Raman Singh, CEO of Mundipharma Singapore

Under Raman Singh's leadership over the past year, Mundipharma achieved an unprecedented expansion of its treatment portfolio through a combination of strategic licensing deals and new product launches. He has driven rapid growth in all metrics, including performance, number of medicines, country presence and number of personnel.

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R&D UPDATE

In an overview of R&D progress, R&D Portfolio Manager Dr Minoru Hirose highlighted the "very favorable safety" and subcutaneous route of Chugai's anti-IL-6 receptor antibody satralizumab in the recently reported Phase III SakuraSky study.

While only patients with anti-aquaporin-4 antibodies were evaluated in a study with **Alexion Pharmaceuticals Inc.**'s potential competitor *Soliris* (eculizumab) in the same target indication of neuromyelitis optica spectrum disorder (NMOSD), Hirose pointed out that the results for the Chugai antibody in this specific population (about 75% of NMOSD patients) were comparable. SakuraSky looked at all patients, for which it reduced the risk of relapse by 62% (79% in AQP4-positive patients). *(Also see "Chugai May Not Win Race For $500m Neuromyelitis Optica Market, But May Best Soliris On Ease Of Use" - Scrip, 15 Oct, 2018.)*

"We have not changed our forecasts in the light of the results," Hirose commented.

In other product developments, the anti-CD20 antibody *Gazyva* (obinutuzumab) was launched for follicular lymphoma in Japan in August by partner **Nippon Shinyaku Co. Ltd.**, while the HER2 dimerization inhibiting antibody *Perjeta* (pertuzumab) was approved in Japan in October for the additional indication of neoadjuvant and adjuvant use in HER2-positive early breast cancer.

Based on the global Phase III APHINITY and other studies, the clearance adds to the product's existing use in HER2-positive inoperable or recurrent breast cancer.

At an earlier development stage, Hirose referred to a new Phase I asset, GYM329, which has entered Phase I for neuromuscular disease in Japan. Roche has already shown early interest in the molecule (which it codes RG70240) by opting in for a license, although the R&D executive declined to disclose modality.

WIDER PERFORMANCE

More broadly, Chugai said overseas sales of rheumatoid arthritis antibody *Actemra* (tocilizumab) and cancer drug *Alecensa* (alectinib) remained strong, with sales of Actemra to Roche surging by 33% to JPY63.1bn in the nine months.

Avastin (bevacizumab) continued to lead Japanese sales with JPY69.5bn (+3%) in the same period, despite the industry-wide reimbursement price revision in the country in April.

The company's total revenues were up 10% in the nine months to JPY426.4bn, helped by the mainstay and export growth, while core operating profit jumped by 31% to JPY103.3bn, and core net income was JPY74.6bn (+25%).

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From the editors of PharmAsia News.

Takeda Bumps Forecast On 'Significant Momentum' Pre-Shire

IAN HAYDOCK ian.haydock@informa.com

Multiple factors have led **Takeda Pharmaceutical Co. Ltd.** to substantially raise its forecasts for the current fiscal year, including lesser than expected US generic competition to *Velcade* (bortezomib), gains from the continued shedding of non-core assets, and an ongoing company-wide operating cost saving program.

Sales of higher-margin mainstay products, particularly *Entyvio* (vedolizumab) for inflammatory bowel disease, were also solid in the fiscal first half ended September 30, providing what president and CEO Christophe Weber described as "significant business momentum".

These positive factors helped overcame the loss of revenue from business divestments and negative currency effects, leading Weber to tell a Tokyo investor briefing that he is "very satisfied with the dynamic of the business in H1."

Excluding the costs in the year to date relating to the planned acquisition of **Shire PLC**, the Japanese company now expects underlying core earnings growth in the "high teen" range rather then single-digit.

Excluding costs related to the planned Shire acquisition, total revenues in the year to next March 31 are now expected to be JPY1,750bn ($15.51bn), JPY13bn above Takeda's earlier forecast (-1% from last year's reported figure).

The operating profit outlook has been raised by JPY79bn to JPY280bn (+16%), driven by cost savings and mainstay growth, with the expectation for net profit attributable to owners raised by JPY67bn to JPY206bn (+10%).

VELCADE UPSIDE

A key factor behind the improved outlook was less than expected generic competition in the US to multiple myeloma drug Velcade.

Takeda now sees only one additional therapeutically non-equivalent competition in intravenous and subcutaneous formulation launching there, in March 2019, meaning the originally expected competition from this September (comprising two products rather than one) has not materialized. *(Also see "Takeda Looks To The New As It Braces For Velcade Generics" - Scrip, 21 May, 2018.)*

"We believe this [competitor launch forecast] is a conservative estimate by management," Deutsche Bank analysts said in a note on the results. The situation will provide an upside of JPY35.5bn to sales, Takeda Chief Financial Officer Costas Saroukos told the briefing, Weber adding this is "the most realistic assumption based on what we know."

SHIRE PROGRESS

Restating at length the rationale behind the proposed acquisition of Shire - perhaps seeking to diffuse continued criticism from some investors - the CEO reiterated that Takeda is approaching the deal from a position of strength in its own business.

Takeda sees the deal "as an opportunity to accelerate our transformation to create a values-based, R&D-driven global biopharmaceutical leader" headquartered in Japan, although 48% of combined sales will come from the US.

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Weber said this would continue to be the most "pro-innovation" market globally in terms of approvals and speedy access to new drugs, but added: "There's no debate about it, you are in our global headquarters [in Tokyo] today."

There has been some speculation that the deal will lead to an HQ relocation, possibly to the US.

Meanwhile, progress continues to be made on the post-deal structure, with the combined Takeda/Shire to have four regional geographical business units, and three global therapeutic units, for oncology, vaccines, and plasma-derived therapies.

The form of the executive team has also been finalized, with "some Shire leaders joining us," Weber noted.

EARLY 2019 CLOSE?

Under a now-decided record date, Takeda has until next January to organize a meeting for the shareholder approval of the deal on both sides, although the exact date has not been set yet.

"At this stage, we can only confirm that we believe the closure will happen in the first semester in H1 2019 calendar year," Weber said.

Deutsche Bank analysts said they now expect the Shire acquisition to close in early February, if the proposed remedy to EC anti-monopoly concerns is accepted (on which a decision is expected in late November).

To meet European anti-competition concerns, Takeda has just said that it plans to divest the Shire asset SHP647, in Phase III for ulcerative colitis and Crohn's disease, the same indications as Entyvio. Costas said that Takeda is "more considering [selling] global rights" rather than by region.

The CFO again stressed the company's general intention to de-leverage the debt it will take on to finance the deal, noting that it has generated more than JPY70bn so far this fiscal year from the disposal of non-core assets, while operating expenses fell by around 2% in the six months.

UNDERLYING REVENUE UP 4%

For the six months to September 30, total underlying revenue was up 4% to JPY880.6bn but static on a reported basis. Entyvio continued with what Weber described as "very strong momentum", surged 33% to JPY128.4bn globally, mostly in the US.

Led by Entyvio, the gastrointestinal area now accounts for close to two thirds of Takeda's total revenues. *Ninlaro* (ixazomib) for multiple myeloma also grew strongly, by +35% to JPY29.4bn.

Underlying core earnings were up 32%, or 13% on a reported basis, to JPY212bn, affected by comparison with one-off divestment gains last fiscal year, which also hit reported net profit of JPY126.7bn (-27%).

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From the editors of PharmAsia News.

Darzalex Excites As Potential Grows In Multiple Myeloma

JOHN DAVIS john.davis@informa.com

Positive top-line results from the Phase III MAIA study of **Genmab AS**'s MAb, daratumumab, in combination with lenalidomide (**Celgene Corp.**'s *Revlimid*) and dexamethasone for the front-line treatment of multiple myeloma, announced Oct. 29, did not go unnoticed by investors.

The Danish biotech's share price peaked at DKK950 ($144.7) on the morning of Oct. 30, an increase of 17%, before falling back as investors reacted to the emerging PFS data on the triple combination containing daratumumab, a biologic marketed by global licensee **Janssen Biotech Inc.** (Johnson & Johnson) as *Darzalex*.

In newly diagnosed patients who were not candidates for high-dose chemotherapy and autologous stem cell transplant (ASCT), the triple combination met the primary MAIA endpoint of improving progression-free survival (PFS) at a pre-planned interim analysis (HR=0.55; 95% CI: 0.43-0.72, p< 0.0001), resulting in a 45% reduction in the risk of progression or death.

In fact, the median PFS for patients treated with daratumumab in combination with lenalidomide plus dexamethasone (known as Rd) was not reached, compared with an estimated median PFS of 31.9 months for patients who received Rd alone. Side effects associated with the triple combination were consistent with the known safety profiles of the individual products, Genmab added.

Datamonitor Healthcare analysts believe the value of the total multiple myeloma market will increase from $11.9bn in 2017 to $20.9bn in 20222, with daratumumab eventually becoming the market leader, because of the high unmet need in patients with refractory disease. The value of the market will then decline because of the genericization of other pivotal drugs such as *Velcade* and Revlimid.

"This is the fifth randomized study showing a profound benefit when adding daratumumab to standard of care treatments in multiple myeloma," commented Genmab's CEO, Jan van de Winkel.

The lenalidomide plus dexamethasone regimen is the basis of therapies used in the US for newly diagnosed multiple myeloma in ASCT ineligible patients, and the MAIA results were highlighted by analysts. "These data will justify Darzalex plus Rd as the new standard of care, underpinning our confidence in $10bn worldwide peak sales," commented analysts at Jefferies. They are now eagerly awaiting details of minimal residual disease (MRD) rates in the daratumumab arm, which would be a surrogate for "cure".

Analysts at Bernstein noted, however, that the MAIA results should perhaps come as no surprise to investors, given the results of the previously reported POLLUX second-line study, which tested the same combination. However, it was nice to "finally get MAIA out of the way," they remarked. The growth of J&J's pharmaceutical business is being led by oncology products like Darzalax, the prostate cancer therapy, *Zytiga* (abiraterone) and *Imbruvica* (ibrutinib). In the third quarter, Darzalex sales increased by 57.1% to reach $498m.

Darzalex was granted an additional indication in the US earlier this year for use in newly diagnosed multiple myeloma patients ineligible for ASCT, when combined with **Takeda Pharmaceutical Co. Ltd.**'s *Velcade* (bortezomib), melphalan and prednisone.

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Ferring's New Chief Falk Talks

KEVIN GROGAN kevin.grogan@informa.com

Ferring Pharmaceuticals AS has plumped for a scientist – Per Falk – to take over the reins when Michel Pettigrew steps down as president of the executive board at the end of the year and the Swede is keen to consolidate the company's leading role in women's healthcare and expand in new areas by embracing advances in gene therapy and the microbiome.

Pettigrew and Falk met up with *Scrip* in London recently to talk about plans for the future for Ferring which has made considerable progress under the former's leadership. Pettigrew joined the Swiss firm in 2001, helping to take the company from revenues of €345m to nearly €2bn today and moving Ferring into the top 50 of global pharma firms.

Pettigrew noted that the company had been extremely successful in investing in established medicines such as *Menopur* (human menopausal gonadotrophin; HMG) for assisted reproduction, desmopressin for nocturia and mesalazine for ulcerative colitis and improving formulations, making them more convenient to use and better adapting them for patients' needs. However, "too much of the R&D spend went on life cycle management and not enough on new molecules but when Per came in, he made sure that balance shifted."

Falk joined Ferring as chief science officer at the beginning of 2015 after 12 years at **Novo Nordisk AS** where he held a number of key posts, including head of biopharmaceuticals research. Since his arrival, the company's R&D spend has jumped from below 14% of sales to 17% and Falk has been instrumental in transforming Ferring's development focus.

MALE INFERTILITY AN UNMET NEED

The firm's main speciality is reproductive medicine, an area which has been "tremendously under-invested in," Falk said. There are a lot of "completely white spaces" for more investigation and it is important to remember that "fertility not just a woman's problem, 50% of the problem is men" and male infertility represents a huge unmet medical need.

> We need to be the go-to company for anybody with a good idea in fertility – male or female

He argued that the model for solving fertility problems "has been stale for decades and the number of women being helped has not increased significantly in the last ten years and neither has the number of clinics dedicated to IVF increased much." In Europe, 4%-5% of children are born using assisted reproductive technologies, while in China and the US, the figure is about 1%.

Falk said that the success rate of IVF is still relatively low, and "it is a laborious and invasive process for women to go through; it is not completely risk-free." Ferring "has placed a stake in the ground" to improve safety and efficacy of existing products and develop better ones, he said, citing a recently-inked pact with US women's health genomics company **Celmatix Inc.** to help generate new insights into ovarian biology. *(Also see "Ferring Plots Genomics Path With Celmatix Pact" - Scrip, 30 Aug, 2018.)* Falk said that "as a leader in a particular field you have to explore." The more dependent you are on a certain area, the more you have to make sure you are at the forefront. To keep being the leader, you have to be first at everything and not miss out on anything. If you stick to your old ways, the worst thing that can happen is someone disrupts your model and then you have nothing." *(Also see "Interview: Ferring Forges Ahead With mAbs For Reproductive Meds " - Scrip, 15 Feb, 2018.)*

Per Falk

With Ferring and fertility, Falk told *Scrip* that "technology-wise, there is no risk we will not be prepared to take to make sure we are the leader and the first in everything. We need to be the go-to company for anybody with a good idea in fertility – male or female, obstetrics, safer pregnancies - Ferring should be the first name that crops up in anyone's brain who has an idea in this space."

The company is expanding in other areas, most notably into the microbiome drug development space through its recent acquisition of the US firm **Rebiotix Inc.**. It is an area of huge interest for Falk, who noted that scientific activity began 50-60 years ago, then momentum started building 20 years ago, "which is when you get the hype and you are blessed with ignorance so you have lots of interesting data that takes you into tons of different directions."

Falk cited his friend and mentor Jeffrey Gordon of the Washington University School of Medicine in St Louis and a pioneer

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

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

Selected clinical trial developments for the week 26 October–1 November 2018

LEAD COMPANY/PARTNER	COMPOUND	INDICATION	COMMENTS
PHASE III RESULTS PUBLISHED			
Alkermes	ALKS 5461 (buprenophine/ samidorphan)	major depressive disorder	FORWARD-4, -5; *Molecular Psychiatry*; Oct. 29, 2018.
PHASE III INTERIM/TOP-LINE RESULTS			
GlaxoSmithKline plc	daprodustat	anemia due to chronic renal failure, dialysis-dependent	Met primary endpoint in Japan study.
Melinta Therapeutics Inc.	*Baxdela* (delafloxacin)	community-acquired pneumonia	Study 306; positive results.
AbbVie/Roche	*Venclexta* (venetoclax) plus obinutuzumab	chronic lymphocytic leukemia, front-line	CLL14; met primary endpoint.
ViiV Healthcare	cabtegravir/rilpivirine once-monthly injectable formulation	HIV/AIDS	FLAIR; met primary endpoint.
Theratechnologies Inc.	*Trogarzo* (ibalizumab-uiyk)	HIV/AIDS	Clinical benefit over the longer term.
Pharmacosmos	*Monofer* (iron isomaltoside)	anemia	FERWON-IDA; met primary endpoint.
Ultragenyx Pharmaceuticals Inc.	UX007 (triheptanoin)	glucose transporter type-1 deficiency syndrome	Glut1 DS; missed primary endpoint, development stopped in this disorder.
Genmab/ Johnson & Johnson	*Darzalex* (daratumumab) plus lenalidomide, dexamethasone	multiple myeloma	MAIA; met primary endpoint.
Esperion Therapeutics Inc.	bempedoic acid	dyslipidemia	CLEAR Wisdom; effective and well tolerated.
Novo Nordisk	oral semaglutide	diabetes, type 2	PIONEER 8; improved blood sugar control.
Takeda/Lundbeck	*Trintellix* (vortioxetine)	major depressive disorder	Promising personal goals approach to assessment.
UPDATED PHASE III RESULTS			
Shanghai Green Valley Pharmaceutical	GV-971	Alzheimer's disease, mild-to-moderate	Improved cognition.
Novartis AG	brolucizumab	wet age-related macular degeneration	HARRIER, HAWK; more effective than aflibercept.
Astellas/Fibrogen	roxadustat	anemia due to chronic renal failure, dialysis dependent	Safe and effective in Japan study.
GenSight Biologics SA	GS010, gene therapy	Leber's hereditary optic neuropathy	REVERSE; clinical improvements.
Allergan plc/Molecular Partners AG	abicipar pegol	wet age-related macular degeneration	CEDAR, SEQUOIA; met primary endpoints.
Johnson & Johnson	*Symtuza* (darunavir, cobicistat, emtricitabine, tenofovir alafenamide)	HIV/AIDS	AMBER; durable responses after 96 weeks.
ViiV Healthcare	fostemsavir (BMS-663068)	HIV/AIDS	BRIGHTE; positive results at 48 wks.
Clearside Biomedical Inc.	*Xipere* (triamcinolone acetonide)	macular edema due to non-infectious uveitis	PEACHTREE; effective and well tolerated.
Seattle Genetics Inc.	*Adcetris* (brentuximab vedotin) after ASCT	Hodgkin's lymphoma	AETHERA, ECHELON-1; clinical responses.
EyePoint Pharmaceuticals Inc.	*Yutiq* (fluocinolone acetonide) intravitreal implant	chronic non-infectious uveitis	Inflammation controlled.
Gilead Sciences Inc.	*Biktarvy* (bictegravir/ emtricitabine/tenofovir alafenamide)	HIV/AIDS	Study 1490; durable responses at 96 wks.

Source: Biomedtracker | Informa, 2018

CONTINUED FROM PAGE 21

in microbiome research who told him that "we have a problem because any area that has more review articles written than original papers is overheated and if an original paper ends up in *The Economist*, *The Times* or the *New York Times* and is described as an interesting new frontier in healthcare, we also have a problem because it is being pushed too fast." *(Also see "Ferring Looks For Early Microbiome Wins, But Willing To Do Heavy Lifting" - Scrip, 2 May, 2017.)*

REBIOTIX READOUTS EXPECTED IN 2019 1H

However, while microbiome strategies were previously based on "hope and promise, now we can see that with the microbiome, there is a tremendous opportunity to change healthcare, without a doubt it is a new frontier but that does not necessarily mean it will be faster or easier. In fact it will be more complicated than drug development is at present because these critters are alive and if they don't live, they don't work."

The acquisition of Rebiotix in April gave Ferring a Phase III non-antibiotic treatment for recurrent *Clostridium difficile* infection - RBX2660 - which is a contender to be the first approved human microbiome product. Initial readouts are expected in the first half of next year and Falk believes that the first therapeutics will come to the market in the next two-four years, as much work needs to be done in terms of regulatory frameworks for these products and the field will develop relatively slowly because of the complexity of the human microbiome.

One thing that Falk can rely on is time and financial backing to drive Ferring's new projects, such as its microbiome efforts and the recent move into gene therapy with a late-stage licensing deal signed in May this year for a novel bladder cancer treatment from Finland's **FKD Therapies OY**. The Saint-Prex-headquartered company is privately owned with Frederik Paulsen as the current chairman (his father founded Ferring). Pettigrew said that for the chairman "financial motives are secondary," with the firm paying much more attention to science and patients than feeling the need to demonstrate double-digit quarterly earnings growth. *(Also see "Ferring Makes Foray Into Gene Therapy With FKD Pact" - Scrip, 3 May, 2018.)*

OPERATING IN 60 COUNTRIES

Ferring operates in 60 countries and while it is a profitable business, earnings could be significantly higher if the firm followed the big pharma model and concentrated on the US and the top five markets in Europe and not much else. However, Pettigrew stressed that it simply was not the way Ferring works and it wants to have a presence where its patients are.

Falk echoed Pettigrew's stance on the Ferring philosophy and said the decisions were taken principally on therapeutic rather than financial grounds. He concluded by saying that in future, Ferring will not shy away from risky projects and would focus on new technologies. "We will not just perfect therapies in categories where we dominate – we will enter new categories addressing entirely new categories of patients."

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APPOINTMENTS

Executive	To Company	New Role	From Company	Previous Role	Effective Date
Joao Siffert	Abeona Therapeutics Inc	Chief Medical Officer, Executive Vice President and Head, Research and Development	Nestle Health Science	Chief Scientific and Medical Officer	18-Oct-18
Stephen Mitchener	Axcella Health Inc	Chief Business Officer and Senior Vice President	Novartis Pharmaceuticals	Head, US Oncology Strategy, Partnering and Operations	22-Oct-18
Alise Reicin	Celgene Corp	President, Global Clinical Development	EMD Serono	Senior Vice President, Head, Global Clinical Development, R&D	1-Nov-18
Simon Jose	Idorsia Pharmaceuticals Ltd	Chief Commercial Officer	GlaxoSmithKline plc	Senior Vice President, Head, Global Franchises and Platforms	1-Dec-18
Gary Lee	Senti Bio	Chief Scientific Officer	Sangamo Therapeutics Inc	Vice President, Cell therapy	23-Oct-18
Kevin Horgan	Seres Therapeutics Inc	Chief Medical Officer and Executive Vice President	AstraZeneca plc	Vice President, Clinical Development	22-Oct-18
Michael Ma	United Neuroscience	Head, Research and Development Operations and Project Management	Ferring Pharmaceuticals	Director, Project Management	16-Oct-18
Sharon Tamir	United Neuroscience	Head, External Alliances	Karyopharm Therapeutics	Head, Neurodegenerative and Infectious Diseases	16-Oct-18

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

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General Enquiries:

Jo Kirkpatrick | Tel: +44 (0) 20 7017 7180 | Email: jo.kirkpatrick@informa.com