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Industry's Drug Pricing Power Is Running On Fumes

JESSICA MERRILL jessica.merrill@informa.com

The pharmaceutical industry is facing a big headwind in 2019, as net price declines become the new normal. With most big pharma manufacturers having now reported fourth quarter financials and provided some financial outlook for 2019, it is clear industry's drug pricing power has been greatly diminished, at least when it comes to price increases on mature marketed medicines, and the result will impact growth.

Overall, drug makers mostly met or exceeded 2018 financial guidance, but big pharma companies made it clear investors should brace for volume growth, not price growth. Some drug makers like **Pfizer Inc.**, **Johnson & Johnson** and **AbbVie Inc.** are forecasting flat or even declining revenues in 2019. "The fairly consistent themes suggest significant changes are afoot in the industry," SVB Leerink analyst Geoffrey Porges said in a research note Jan. 30. Of the biopharma subset covered by Porges, the aggregate implied top-line growth for 2019 is 0% compared to 6% in 2018 and 4% in 2017, with US pricing headwinds and loss of patent exclusivities being the main culprits of curbing growth.

"This is a significant change to the steady diet of low- to mid-single-digit top-line growth and high single- to low double-digit bottom-line growth to which biopharma investors have become accustomed," Porges said.

In January, the research firm IQVIA forecast that the global pharmaceutical market is poised for a slowdown, growing at a compound annual growth rate of 3%-6% over the next five years, from a 6.3% growth rate the last five years, with US pricing pressure being one of the contributors. *(Also see "Global Pharma Growth Poised To Moderate, IQVIA Predicts " - Scrip, 29 Jan, 2019.)*

POLICY WINDS KEEP CHURNING

While industry already is bracing for the impact of a new era when it comes to drug pricing, those headwinds could become even more fierce if major legislation is enacted, further curbing drug prices.

Longstanding selling practices already are poised for a shakeup with new HHS proposals around Medicare Part B and, most recently, rebate reform under Medicare Part D. The proposal to eliminate the safe harbor protection on prescription drug rebates from prosecution under federal anti-kickback rules will have a big impact on the way drug makers negotiate for formulary access and provide discounts for medicines. Though the industry view is largely favorable on rebate reform, it remains to be seen exactly what the consequences might be. *(Also see "No More Rebates: HHS Proposed Rule Revises Anti-Kickback Safe Harbor" - Scrip, 31 Jan, 2019.)*

"It seems like nearly every week we see some new proposed regulatory rule or introduction of some idea on the Hill as it relates to US drug pricing," **Eli Lilly & Co.** CEO David Ricks said during the company's fourth quarter sales and earnings call Feb. 6.

The drug industry will be under the national microscope, too, at a Senate Finance Committee hearing on drug

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from the editor

eleanor.malone@informa.com

Pharma companies selling drugs in the world's biggest market, the US, are going to have to sell more medicines to drive their sales growth, because payers and government won't tolerate price rises any more (see cover story). It seems like a reasonable expectation for most industries when all is said and done: find new customers for existing products and introduce new products that people want. That sounds like sustainable business growth.

Still, contrary to opinion in some quarters, pharma hasn't only been growing by hiking prices. In fact, the complexity of the US drug market means that even while list prices may have continued rising, net prices are on the wane.

Meanwhile, volume growth can be hard given the level of competition in some therapeutic spaces. The R&D renaissance and surge in new drug approvals has brought its own challenges. Innovative drugs offering treatment breakthroughs cannot always be counted on to follow a long upwards sales trajectory and drive company growth for years. Their sparkle may fade as others rapidly join and usurp them in the new markets they have opened. Look at the pages of this issue. Spinraza, a quantum leap forward for spinal muscular atrophy barely two years on the market, is facing at least two serious contenders in a space that can only expand so far (see p5 & p6). In other areas, notably oncology, products can become obsolete before they've even completed development, such is the density and pace of competitive activity.

Paradoxically, then, big pharma firms face stagnation even though the collective R&D engine is firing on all cylinders.

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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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christopher.keeling@informa.com

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Merck's Keytruda Lead Widens Over Competing Checkpoint Inhibitors

EMILY HAYES emily.hayes@informa.com

The sales lead for **Merck & Co. Inc.**'s PD-1 inhibitor *Keytruda* over **Bristol-Myers Squibb Co.**'s closely competing *Opdivo* and other checkpoint inhibitors widened in the fourth quarter, as the drug brought in almost $2.2bn, and the lead is expected to grow throughout the year.

As usual, the company was pressed by analysts during its earnings call on Feb. 1 about its reliance on Keytruda, need to diversify and prospects for M&A activity. But the company narrowly beat consensus and the Street seems largely satisfied with the course it's on.

Compared with 2017, sales for Keytruda (pembrolizumab) were up 66% to almost $2.2bn in the fourth quarter and up 88% to about $7.2bn for all of 2018, the company reported. That compares with about $1.8bn in the fourth quarter and $6.7bn in yearly sales for Bristol's PD-1 inhibitor Opdivo (nivolumab). Despite flat performance from Q3, Opdivo's Q4 total was up 33% year-over-year and far exceeds other non-Merck competitors.

Non-small cell lung cancer (NSCLC) always has been the most valuable indication and top prize for the family of PD-1/L1 checkpoint immunotherapies. Keytruda has demonstrated strong and consistent performance across trials in patients with nonsquamous and squamous histologies and was the first to get approved in first-line NSCLC, both as monotherapy and in combination with chemotherapy.

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To read the rest of this story go to: https://bit.ly/2WVZpSP

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pricing scheduled for Feb. 26. Seven drug makers have been invited to testify: AbbVie, **AstraZeneca PLC**, **Bristol-Myers Squibb Co.**, Johnson & Johnson, **Merck & Co. Inc.**., Pfizer and **Sanofi**. All have confirmed their CEOS will attend, with the exception of J&J, which will send Worldwide Chairman Pharmaceuticals Jennifer Taubert.

The hearing should set up quite a showdown between industry and lawmakers at a time when Republicans and Democrats appear willing to come together on bipartisan drug pricing legislation.

It will be the second for the committee after drug pricing hearings kicked off in January in both the House and Senate, though industry representatives declined to participate in the first round.

The tensions are rising, and even though drug makers have made moves to rein in drug price increases starting in 2018 and again in 2019 (though they are still taking price hikes), it doesn't always seem that the industry is fully aware of the scale of the frustration over drug costs in the US. *(Also see "J.P. Morgan 2019: Industry Throws A Bonanza, With An Elephant In The Room " - Scrip, 9 Jan, 2019.)*

AbbVie CEO Richard Gonzalez sounded confident during the company's fourth quarter sales and earnings call Jan. 25, pointing out that the company only raised the price of its blockbuster *Humira* (adalimumab) by 6.2% in January, adding that the company has no intention of further raising the price in 2019.

"The industry has adjusted, to some extent, I believe, to the environment as it relates to pricing," he said.

But it's not at all clear that industry is gaining any ground in the court of public opinion, despite making some price concessions and honing its message.

Industry antagonist John Arnold, founder of the Laura and John Arnold Foundation, which dedicates resources to a mission of lowering drug prices commented on Twitter Feb. 7, "I've been hearing some version of the argument that everyone should lay off pharma because the rate of price hikes has slowed in recent years. Umm … drug inflation has declined exactly because of recent pressure from payors, policymakers and reformers. Don't stop now."

NET PRICE DECLINES ALL AROUND

Most big pharmas are forecasting net price declines in the US for 2019; that's the cost after rebates and discounts taken off the list price.

As Pfizer CEO Albert Bourla put it during the company's fourth quarter sales and earnings call Jan. 29, "It's very clear that pricing is not going to be a growth driver for us now and I think in the future."

The company is guiding for largely flat revenue growth in 2019, with a forecast of $52bn-$54bn, as the company also faces the loss of exclusivity of *Lyrica* (pregabalin) in mid-2018. Pfizer is poised for mid-single digit growth after cycling through the loss of Lyrica, Bourla said, but that growth will be driven by volume, not price increases.

Lilly reported Feb. 7 that its US net prices declined 6% on average in the fourth quarter and it forecast a mid-single digit decline in its average US net price in 2019, offset by increased sales volumes. The company is forecasting revenue of $25.1bn-$25.6bn in 2019, growth of around 2%-4%.

Novartis AG said Jan. 30 that it expects US net prices for innovative medicines to decline in the low single-digit range, though competitive rebating for key growth drugs *Cosentyx* (secukinumab) and *Entresto* (sacubitril/valsartan) is poised to stabilize. Net sales are expected to grow in the mid-single digits.

Amgen Inc. said net prices declined 1% in 2018 and are expected to decline further in 2019, by mid-single digits, reporting earnings Jan. 29.

CEO Robert Bradway pointed to the company's decision to forgo mid-year price increases in July 2018 and the company's decision to cut the list price of *Repatha* (alirocumab) by 60%. *(Also see "Amgen Drops Repatha List Price 60% To Cut Medicare Co-Pays And Boost Use" - Scrip, 24 Oct, 2018.)*

"For many Amgen medicines, there are no planned price increases," he said. "As has been the case for the past few years, our strategy for growth will be driven by volume, not price."

Sanofi also pointed to price declines, including for some products like the insulin glargine products *Toujeo* and *Lantus* that will not be compensated by volume growth.

A drug trends report released by the pharmacy benefit manager **Express Scripts Holding Co.** Feb. 6 confirmed that lower net prices appear to be lowering costs. Unit costs for traditional branded drugs covered by employer-sponsored insurance declined 6.5% in 2018 versus the year before, despite a 7.3% rise in list prices, Express Scripts said. The decrease was attributed to rebates.

LET'S BE FRIENDS

In that regard, industry's top CEOs will be heading into the Feb. 26 Senate hearing on drug pricing with some support to back up its arguments. And industry likely will be eager to position itself as a willing partner when it comes to cooperating on rebate reform.

Several industry leaders sought to show their early support for such a policy, despite the uncertainties around potential consequences to the health care system, including how it might impact the cost of insurance premiums, or the financial impact to manufacturers.

"We support the administration's approach in terms of what was said about safe harbor, which is about bringing transparency to the pricing value chain," **GlaxoSmithKline PLC** CEO Emma Walmsley said, during the company's sales and earnings call Feb. 6, just days after the proposal was announced. "Obviously, we're digesting what's coming through, and we're looking to collaborate as ever with the administration on participating in next steps, but we are broadly supportive."

Sanofi CEO Olivier Brandicourt echoed a similar sentiment during the company's Feb. 7 call.

"We believe the proposal, which has been released last week by the administration – the aim to eliminate the rebate safe harbor – will create certainly short-term uncertainty," he said. "But we also believe that it has the potential to be an important step towards our shared goals of reducing out-of-pocket costs for our consumers."

Lilly CEO Ricks called it a potential win for patients, particularly those taking insulin, during the company's call. He said it also could remove artificial barriers to competition, creating opportunity for innovation.

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Novartis Pharma CEO Sees Zolgensma Supplanting Spinraza

KEVIN GROGAN kevin.grogan@informa.com

Novartis AG is confident that *Zolgensma*, its closely watched gene therapy for spinal muscular atrophy, will quickly take over from **Biogen Inc.**'s Spinraza as standard of care for the disease. It is preparing a variety of payment plans for the one-off treatment that could command a price of over $4m.

The FDA is expected to give the green light to Zolgensma, formerly known as AVXS-101, which Novartis got hold of through its $8.7bn acquisition of AveXis last year, in the first half of 2019. It will go up against *Spinraza* (nusinersen), currently the only approved treatment for SMA, but in an interview with *Scrip* after Novartis' annual press conference in Basel this week, the company's head of pharmaceuticals Paul Hudson said that for clinicians, patients and payers, Zolgensma will become standard of care - and soon.

He said that the cost of Spinraza is about $2.2m over five years and patients have to take it for the rest of their lives via injection in the spine. "That can cause post-traumatic stress disorder and some kids say they would rather get worse than go to have that injection again: it's a complicated process."

However Biogen is not going to throw the towel in and this week the company revealed that Spinraza global sales in 2018 nearly doubled to $1.7bn, although growth flattened in the fourth quarter. On the earnings call, Michael Ehlers, VP of R&D, downplayed Zolgensma, claiming that "a number of questions remain for this experimental approach as data on the safety, efficacy and durability [of Zolgensma] remain limited with results reported to date for only 15 patients followed up for 2.5 years, seven of whom are reported to have subsequently initiated treatment with Spinraza. This is in contrast to the Spinraza clinical trial program which has included more than 300 patients followed up for up to six years."

This cut very little ice with Hudson, who said Spinraza "is the main driver of what's happening over there so they clearly want to defend it." He told *Scrip* that "this piece of anecdotal feedback that patients are getting Spinraza on top of gene therapy is driven by one thing only. Zolgensma is not approved, so if you're a parent of a three-month-old with SMA type 1 (the most severe subtype and the only one in which Zolgensma has been studied) and you give them gene therapy, which is free because it's in a study, the next thing they do is say 'we want Spinraza too.'"


Paul Hudson

He added: "The clinician says 'why?' and they say because 'we've got to do the best for our child.' There's no clinical evidence, but the parents say 'it doesn't matter, the insurer will cover it, we're going to do it.' We have spoken to the treating physician of every single patient who has got both, they said they recommended against it, they've seen no additional benefit for having it but the parents wanted to know they have done the best for the child, which means give them everything that's approved and everything that's not approved."

Hudson said that in clinical practice "that just simply will not happen. If you've got something that's painful that you have to take for the rest of your life versus a short infusion where you will never know you even had the disease - well that's not a competitor you want to fight with. If we get the right label and it's broad enough for use in presymptomatic patients there's no point in the other mechanism."

Aside from the clinical benefits, a big issue for Zolgensma will be price, although Novartis' case was boosted at the end of 2018 by a report from the Institute for Clinical and Economic Review (ICER) in the US which said that although the drug would not be cost-effective at a price of $2m, it would still represent better value than Spinraza.

The figures that have been mentioned by others, including Novartis previously, have been in the region of $4-5m. Hudson did not commit to any specific cost but noted that the company is constantly looking at innovative pricing mechanisms and is working with healthcare systems on those mechanisms to ensure access to new drugs.

He mentioned that Novartis had introduced outcomes-based agreements for its heart failure drug *Entresto* (sacubitril/valsartan), which after a slow start has become a blockbuster (fourth-quarter sales shot up 76% to $318m). He also noted that the company runs a lot of pilots involving 500-1,000 patients "that cost a lot of money to monitor and manage" to trial possible payment solutions.

However, "when you say, let's treat 100,000 patients, even though the data says it'll save the health system money right from the first year, and it's cheaper than anything else they could do," payers look at the investment needed "and they sort of think that's a bit big, let's go more slowly. That's where the resistance is, where the inertia comes from," Hudson said.

Where gene therapy is concerned, he told *Scrip* "there is no resistance because there are maybe 20 babies a month in the whole of the US, they will all be known by first name by the federal government or state, so there's no 25,000-patient program that we need to monitor. You don't need anything for that."

When it comes to actually paying for these therapies, Hudson agreed that some form of installment system could be the route to take. Novartis will be ready with alternative payment models as soon as approvals for Zolgensma are granted, he said.

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Roche Makes Case For Its Oral SMA Drug Risdiplam As Filings Beckon

ALEX SHIMMINGS alex.shimmings@informa.com

Roche is aiming for mid-year filings of its oral therapy for spinal muscular atrophy, risdiplam, based on promising Phase II/III data and positive regulator feedback. With a hoped-for approval in 2020, the product could add a convenient new therapy option into the SMA mix, and one that is likely to have its own impact on the treatment landscape.

SMA is the leading cause of genetic death in infants, affecting around one in 10,000 live births. The arrival of **Biogen Inc.**'s antisense product, *Spinraza* (nusinersen), in 2017 changed the outlook for these patients and gave Biogen a product bringing in blockbuster sales in only its second year on the market.

But its reign is set to be short-lived. **Novartis AG**'s highly anticipated one-time gene therapy, *Zolgensma*, is currently with the regulators in the US, EU and Japan for use in type 1 disease, and Roche's product, which acts in a similar way to Spinraza, but can be given orally rather than by intrathecal injection, is also giving chase.

Novartis's head of pharmaceuticals Paul Hudson recently told *Scrip* that Zolgensma would soon supplant Spinraza as standard of care (*see page 5*).

But Biogen's VP of R&D Michael Ehlers has downplayed the threat, claiming that a number of questions remain for this experimental approach. "Data on the safety, efficacy and durability [of Zolgensma] remain limited with results reported to date for only 15 patients followed up for 2.5 years, seven of whom are reported to have subsequently initiated treatment with Spinraza," he said during Biogen's Q4 earnings call which revealed that global sales of Spinraza in 2018 nearly doubled to $1.7bn.

While the two companies continue to debate the relative merits of their therapies, Roche Group CEO Severin Schwan told analysts during its Q4 results presentation that he saw risdiplam, likely to be third to market for SMA, as providing a layering effect for patients for three disease subtypes. In the most serious type 1 disease, SMA symptoms are present from birth to six months. Onset between seven and 18 months is known as type 2 disease, while type 3 disease presents after 18 months of age. Type 4 disease has its onset in adulthood.


Severin Schwan

> "We think our molecule has a place next to gene therapy, which will not work for all patients. And we will develop our molecule for all types of SMA: one, two and three."

"We think our molecule has a place next to gene therapy, which will not work for all patients. And we will develop our molecule for all types of SMA: one, two and three. It could be a very important complementary option to other therapies." The product already has a US FDA breakthrough therapy designation and a EU PRIME designation.

Roche Pharmaceuticals' new CEO Bill Anderson outlined to analysts further data from the Phase II/III FIREFISH Part 1 study of risdiplam in Type 1 SMA, data from which were first reported last June. *(Also see "Roche's Risdiplam Data Stir Up SMA Market" - Scrip, 18 Jun, 2018.)*

He said 20 out of 21 babies (95%) were alive and without need of permanent ventilation at 10.5 months, compared with 50% of babies at the same age in natural history studies. No patients have lost the ability to swallow or reached permanent ventilation.

Among babies with eight months treatment, median change in CHOP-INTEND (a measure of patients' motor skills) was 16 points and 21% achieved unassisted stable sitting.

Overall, the data show increasing levels of functionality as patients stay on therapy. Even patients who did not start to receive therapy until five to seven months had "very large" gains despite being quite ill when they began, Anderson said. "But [there were] even larger gains and a better outcome when the patients started younger," between three and five months, he said.

Roche has now started the RAINBOWFISH study, which is accruing patients that are 0 to six weeks old. "We hope to see yet better data with that, but we're very pleased with what we're seeing in terms of how it compares to competitive therapies. And the regulators are very impressed as well," Anderson said. They have urged the company to submit the data from the type 1 study as well as the type 2 and 3 SUNFISH studies (due in Q2), he said, and "we plan to begin those submissions in the middle of this year. We'll have rolling submissions and we look forward to approval of this molecule, hopefully, in 2020."

COMPARE AND CONTRAST

Anderson and Schwan also discussed with analysts the raft of unknowns with Zolgensma, and risdiplam's potential advantages over the intrathecally delivered Spinraza.

Zolgensma is under review for type 1 patients but will not be suitable for patients who have already been exposed to the virus used as its vector, a problem which increases with age. The fact that risdiplam is being developed for types 1-3 is also "a big part of the market potential," Schwan said.

But there are other questions over gene therapies and how they will work in the clinic, Schwan noted.

"Whilst you have the advantage with babies who get a gene therapy because they are not yet immune against the vector, the problem with a baby is the turnover of the organs is very fast. And as you know, the gene therapies only work in the cells where they are given in, but when the cell divides, it's not in the cell which is divided. So if the organ turns over, then, of course, you lose the effect of the gene therapy. Now how many years does it take until you lose this effect simply because your organ has turned over?"

What this means for the duration of gene therapy is a question that "nobody can seriously answer because we simply do not have the data," he said. "But what we do believe is there is almost certainly a place for molecules next to gene therapy… either it's a separate segment because gene therapies simply don't work or if the effect of the gene therapy goes down, then you would add another medicine to complement the effect. So we'll see how it evolves."

Compared with Spinraza, Schwan said, the big difference is that the antisense product is delivered to the central nervous system via an intrathecal injection, whereas risdiplam is an orally available small molecule. "So again, the data have to read out, but what we would hope is that this systemic effect would have advantages from a clinical efficacy point of view, especially over time. But again, that's a hypothesis at this stage."

Anderson added that the upcoming efficacy data would be paramount. "We're particularly interested in that efficacy data we're going to get on the newborns because that will really say what happens if you get in there from the very beginning. But again, based on what we've seen in type 1 and types 2 and 3, we're pretty encouraged."

Safety could also be a key differentiator. "We want to make sure that we've got a well-tolerated drug because, again, we don't know the effects of administering a splicing modifier over time in a developing child." Analysts at Jefferies said risdiplam had exciting potential as one of Roche's "high risk, substantial reward readouts" in its underappreciated pipeline, in a Feb. 4 research note.

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GSK Makes I-O Move With Merck KGaA Deal Worth Up To €3.7bn

KEVIN GROGAN kevin.grogan@informa.com

GlaxoSmithKline PLC's return to the oncology space has been confirmed by the UK major making a hefty €300m upfront payment to get access to **Merck KGAA**'s bifunctional immunotherapy M7824 (bintrafusp alfa).

M7824 has been designed to simultaneously target two immuno-suppressive pathways - transforming growth factor-β (TGF-β) trap and an anti-programmed cell death ligand-1 (PD-L1). The aim of the bifunctional antibody is to increase efficacy "above and beyond that achieved with individual therapies or combinations," Merck said, adding that M7824 "has the potential to offer new ways to fight difficult-to-treat cancers beyond the established PD-1/PD-L1 class."

The drug has been tested in over 700 patients in 10 different tumor types and eight "high priority clinical development" studies for M7824 are ongoing or expected to commence in 2019, Merck noted, including trials in non-small cell lung cancer (NSCLC) and biliary tract cancers. These include a Phase II study to investigate M7824 compared with **Merck & Co. Inc.**'s market-leading checkpoint inhibitor *Keytruda* (pembrolizumab) as a first-line treatment in patients with PD-L1-expressing advanced NSCLC.

In addition to the €300m upfront sum, Merck is eligible for potential development payments of up to €500m and future approval and commercial milestones of up to €2.9bn. The total potential deal value is up to €3.7bn and all profits and costs from the collaboration will be shared equally on a global basis.

For GSK, the Merck alliance is a further step in the company's priority to strengthen its cancer drug pipeline and follows the company's recent acquisition of Tesaro and its PARP inhibitor *Zejula* (niraparib) for $5.1bn. Commenting on the pact, president of R&D Hal Barron noted that despite recent medical advances, "many patients with difficult-to-treat cancers don't currently benefit from immuno-oncology therapies, leaving them with limited treatment options." *(Also see "GSK Embraces PARP Promise With Tesaro Buy" - Scrip, 3 Dec, 2018.)*

He added that M7824 "brings together two different biological functions in a single molecule and we have observed encouraging clinical results in treating certain cancer patients, particularly those people with NSCLC. I'm excited by the potential impact this first-in-class immunotherapy could have." *(Also see "R&D Heads At GSK & AZ Say Key To Success Lies In Smart Risk Taking" - Scrip, 15 Nov, 2018.)*

On a conference call, Belén Garijo, CEO of healthcare at Merck, said that securing an alliance for M7824 involved a "highly competitive process" but GSK "clearly emerged as the ideal partner." This is due to its strong commitment to oncology, and the M7824 project in particular, a proven track record in collaborative R&D and the strong industry talent it has recruited, she said, claiming that M7824 "has the potential to bring new answers to patients living with cancer. Together with GSK we aim to drive a paradigm shift in the treatment of cancer as the leader in this novel class of immunotherapies."

Merck CEO Stefan Oschmann was also enthusiastic about having GSK on board, especially as the latter has "re-established" itself in oncology. He added that the alliance will also benefit from GSK's global commercial footprint.

Oschmann went on to say that the deal reflects Merck's strategic approach of progressing promising clinical stage assets as efficiently and rapidly as possible then seeking out external collaborations, such as the pact it has with **Pfizer Inc.** on the immunotherapy *Bavencio* (avelumab). He added that "we have a bit of a luxury problem in that we have a very, very rich pipeline."

UNDERAPPRECIATED ASSET

Analysts were impressed, with Wimal Kapadia at Bernstein claiming that the deal is "an important event which helps crystallize the value of an underappreciated asset by bringing on board a credible partner." In an investor note at the end of last year, he noted that M7824 is "an interesting drug, designed on solid science," with the data to date continuing to impress "but we appreciate it is small numbers."

While the focus is on first-line NSCLC and biliary tract cancers for now, Kapadia argued that opportunities in gastric and human papillomavirus-associated cancers for M7824 "are real, where we could see early filing." This is Merck's game changer, he wrote in a Nov. 16 note last year and mentioned peak sales in the region of €3.6bn.

He went on to acknowledge that "sceptics will suggest this is just a bullish analyst increasing peak sales of an early-stage asset. However, we are comfortable doing so and believe our estimates are cautious." Kapadia concluded by stating that "ultimately, it is hard to argue against the data, even if early, and we ask what value would be ascribed to a small biotech with the same asset? Merck remains catalyst rich and the risk/reward positive."

At Deutsche Bank, analyst Richard Parkes said that GSK had made a "bold move for an intriguing but still risky oncology asset." He acknowledged that initial data for M7824 have indicated "intriguing levels of response" in second-line lung cancer, gastric cancer, biliary tract and HPV-associated cancers "that seem to be higher than would be expected with a PD-1/PD-L1 inhibitor alone." In isolation, however, Parkes wrote in an investor note that the patient numbers in these individual trials had been small, "making it difficult to draw firm conclusions."

He went on to say that "we warn the industry has been guilty of over-interpreting similar data from single arm trials in the past." For him, the most meaningful study is the head-to-head with Keytruda in first-line NSCLC and the outcome of the trial, due by the end of 2021, "should give a definitive answer as to whether the drug's dual mechanism adds to PD-1 inhibition alone in this setting and could be registration enabling. However, at this stage the outcome of the trial still looks extremely high risk to us."

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Bristol Approached Celgene Nearly Two Years Ago, Got A Better Deal Later

JOSEPH HAAS joseph.haas@informa.com

As the April 12 shareholder vote for the proposed **Bristol-Myers Squibb Co./Celgene Corp.** merger draws closer, SEC documents have offered a clearer picture of how the deal announced Jan. 3 came to be, including talks that began in early 2017, a late effort by Celgene to get a competing bid, and Bristol's successful 11th-hour gambit to reduce its upfront cash commitment in the transaction.

Ultimately, Celgene agreed to be acquired by Bristol in a deal valued at $102.43 per share, with its stock closing Jan. 2 at $66.64 per share. *(Also see "Bristol Values Celgene's Hematology, Immunology Portfolio At $74bn, But Does It Price In Risk?" - Scrip, 3 Jan, 2019.)* Back when the two companies began talking about a "merger of equals" in April 2017, Celgene was trading well above $120 per share – but both companies decided to abandon that possibility in mid-2017.

Still, with some of the deal's potential value tied up in a $9-per-share contingent value right (CVR) based on US FDA approvals for three Celgene pipeline candidates, the two companies apparently hold different views about who came out ahead in the negotiations. Mizuho Securities analyst Salim Sayed pointed out in a Feb. 1 note that Celgene thinks it has a 66% chance of earning the CVR, while Bristol puts the likelihood of all three approvals by the stated deadlines at 45%.

According to a Bristol S-4 statement filed with the US Securities and Exchange Commission (SEC) on Feb. 1, Celgene's board asserted at a special meeting Jan. 2 that if the CVR was realized and Bristol's share price was equal to its closing stock price on Sept. 20 ($61.75), the day before its first firm offer of $110-per-share to acquire Celgene, the deal would be valued at $120.75 per share.

> Ultimately, Celgene agreed to be acquired by Bristol in a deal valued at $102.43 per share.

The ability of shareholders to capture that value depends on a lot of variables, including the shareholder vote on the deal April 12, the regulatory fate of the three Celgene candidates, and the value of Bristol's share price during the period where the CVR either is or isn't earned. But even at a total deal value around $120 per share, it's unlikely that Celgene shareholders will see a big gain relative to the company's valuation nearly two years ago when the original merger idea was first discussed.

Celgene's stock closed at $124.77 per share on April 4, 2017 – the day that it and Bristol agreed to confidentiality consider a

merger. The two companies decided against merging in June and while the date of that decision has not been disclosed, Celgene's stock closed on June 30, 2017 at $116.41.

Bristol renewed its internal discussions about acquiring Celgene last September, deciding to propose a deal in which Celgene shareholders would own a percentage of the new company in the mid-30% range. Bristol offered to buy Celgene on Sept. 21 for $100 per share, about a 25% premium to Celgene's closing price of $88.30 on Sept. 20.

The company's stock declined by 29% between the first discussions of a merger and the acquisition offer from Bristol (April 4, 2017-Sept. 20, 2018) due to a series of missteps, including the announcement in October 2017 that the high-profile inflammatory bowel disease candidate mongersen (GED-0301) failed in a Phase III Crohn's disease study. *(Also see "Celgene IBD Pipeline In Question As Mongersen Crohn's Disease Trial Ends" - Scrip, 20 Oct, 2017.)*

Within a week of that announcement, Celgene's only commercial inflammation and immunology drug *Otezla* (apremilast) – a key asset in the company's diversification strategy – fell short of both internal and external sales estimates. *(Also see "Celgene Admits It Screwed Up Otezla Estimates; Investors Lose Confidence" - , 26 Oct, 2017.)*

Those disappointments were followed by the unexpected news that the US FDA issued a refuse-to-file letter in response to a new drug application for the sphingosine 1-phosphate (S1P) receptor modulator ozanimod for relapsed or remitting multiple sclerosis. *(Also see "More Bad News: Celgene Reveals Refuse-To-File Letter For Ozanimod In MS" - Scrip, 27 Feb, 2018.)*

CELGENE DECLINES FIRST ACQUISITION OFFER

With an offer on the table in the fall of 2018 that was above its dramatically decreased stock value, Celgene mulled Bristol's new overture, but turned it down on Oct. 16. At that point, Celgene's share price had increased slightly to $88.89.

Bristol countered with a new offer Dec. 5, under which Celgene shareholders would get $55 in cash plus 0.93 Bristol shares for each full share in Celgene, a 43% premium to Celgene's stock price, which had tumbled to $72.47. The company determined that this offer was worth $112.43 a share, but declined it anyway.

Negotiations continued, with Bristol offering $55 plus one full share for each full share of Celgene on Dec. 5, then increasing its offer that same day to $57 in cash plus one Bristol share for each Celgene share. The companies then conducted mutual due diligence sessions on Dec. 13 with advisors to the two companies estimating on Dec. 14 that the offer would value Celgene at $118.75 per share. Celgene said it was inclined to consider this offer acceptable, which Bristol said was its final and best offer.

Celgene's share price continued to fall, closing at $69.74 on Dec. 13 as stocks in general declined due to a variety of macroeconomic issues, though biopharma companies slumped even more so than broader stock indices.

Celgene appeared to be in a position to improve upon the terms originally offered in September. Perhaps emboldened by this, the company decided to seek a counteroffer and its executives reached out to another company on Dec. 17 called

"Party A" in the SEC filing to see if it was interested in making an offer to acquire Celgene.

This unnamed company is described in the filing as "a large publicly traded pharmaceutical company, which, in the view of the Executive Committee of the Celgene Board, was the only company that potentially would have a strategic fit with Celgene that was as strong as that between Celgene and Bristol-Myers Squibb, as well as the scale to enable it to present a proposal that could be competitive with Bristol-Myers Squibb's revised proposal, if desired."

The most logical fit would seem to be **Merck & Co. Inc.**, which has battled in recent years with Bristol for supremacy in the immuno-oncology arena. No other company seems to offer Celgene "a strategic fit" that would be "as strong" as one between Celgene and Bristol, although deep-pocketed **Pfizer Inc.**, always the center of biopharmaceutical M&A speculation, can't be ruled out.

Party A informed Celgene on Dec. 18 that it would not make an offer; the big biotech's stock closed trading that day at $66.63 a share. Meanwhile, Celgene and Bristol were deep in discussions about their possible merger, with Bristol wanting to announce a deal by Jan. 2. The pharma proposed a transaction break-up fee of 3.75% for either side exiting the deal unilaterally. Celgene proposed lower break-up fees for itself, as low as 2% of the estimated aggregate deal value.

At that point, Celgene likely thought it was going to formally accept an offer at the terms generally accepted on Dec. 14 – $57 and one Bristol share for each Celgene share. But Bristol – perhaps noticing that Celgene's share price was continuing to fall – said on Dec. 27 that it would only agree to a price of $50 in cash, one share and a CVR tied to certain regulatory outcomes for each Celgene share. Celgene's stock price had closed at $62.51 on Dec. 26.

WORKING OUT CVR SPECIFICS

Apparently resigned to the lower cash amount, Celgene countered Dec. 28 by requesting a $10 CVR tied to US approvals of five pipeline candidates, with each approval eligible to trigger a $2-per-share payment to Celgene stockholders.

The following day, Bristol amended its offer to include a $9 CVR requiring US FDA approval of three drugs: ozanimod for MS, to be resubmitted to the agency by the end of March; CAR-T candidate lisocabtagene maraleucel (JCAR017), which is expected to be submitted for FDA approval in diffuse large B-cell lymphoma (DLBCL) in the second half of this year; and the CAR-T therapy bb2121 for multiple myeloma, with pivotal trial results due in the back half of 2019. *(Also see "CAR-T Forecast: Celgene Follows, But Also Leads As Next Batch Of T-Cell Therapies Near Market" - Scrip, 3 Jan, 2019.)*

Approvals for ozanimod and JCAR017 have to occur by Dec. 31, 2020 to trigger the CVR, under terms agreed to between Dec. 30 and Jan. 2, but the approval date for bb2121 was pushed back to March 31, 2021.

Biomedtracker sees a 63% likelihood of approval for ozanimod in either MS or UC. For JCAR017, Biomedtracker estimates a 45% likelihood of approval. And, for bb2121, a filing is anticipated before the end of 2019, with a 19% likelihood of approval. All of those projections give the candidates higher likelihood than average for a candidate at that stage of development in its indication, and puts each on a potential timeline for approval prior to the CVR deadlines.

Mizuho's Syed thinks the shareholder vote on April 12 will prevail, noting that "this shouldn't really be a concern here in our view, as folks who already wanted in/out of either side bought/sold with their feet."

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Mentioned In Despatches: Ablynx's Story From The Frontline Of The Biotech Boom

JO SHORTHOUSE joanne.shorthouse@informa.com

Just over a year since **Sanofi** paid almost €4bn for **Ablynx NV**, it has received US approval of the Belgian biotech's lead product *Cablivi* (caplacizumab) for acquired thrombotic thrombocytopenic purpura (aTTP), a rare blood disorder.

Cablivi is the first FDA-approved therapy specifically indicated for the treatment of aTTP. It is already approved in Europe and launched in Germany in October 2018. The drug made Sanofi €3m in Q4 2018. Analysts at Berenberg at the time of EU approval believed the drug could become a €500m-plus product, and forecast sales approaching €600m by 2025.

Sanofi expects to launch Cablivi in the US late in Q1. The list price for treating a typical aTTP episode with Cablivi is $270,000, and the disorder affects fewer than 2,000 adults in America each year.

These recent developments in a potentially lucrative, albeit small, market will go some way to validating Ablynx's share price of €45 at the time of the sale.

Cablivi was the central but not sole focus of the deal. At the time of the sale, eight of Ablynx's Nanobody antibody fragment drug candidates were in the clinic, with more than 45 in development in a range of therapy areas including inflammation, hematology, respiratory disease, immuno-oncology and oncology.

Edwin Moses Tells His Side Of The Ablynx Acquisition

GAME CHANGERS

Over the preceding 10 years Ablynx's CEO Edwin Moses had been "putting in the shoe leather" to expand and realize the value of the company on both sides of the Atlantic.

A public company in Europe since 2007, Moses wanted to attract more US investors and had been visiting the US six times a year for 10 years to acquaint the firm and its team, pipeline and prospects with American financiers.

All around him, Moses was seeing European biotechs listing on US stock exchanges, and while this too was the Ablynx endgame, Moses felt strongly that there had to be a catalyst for the listing, "something that would really make the market take note," he recalled. Ablynx had been steadily working on caplacizumab, a first-in-class anti-von Willebrand factor (vWF) Nanobody. The company knew Phase III data would not be ready for some months, which afforded the company time to put in seven months of preparatory work with lawyers and banks to prepare a prospectus, taking the risk that if the data weren't good the company would not go public.

Edwin Moses

Everything hinged on caplacizumab's Phase III readout, and when Moses received an email from the first person to have sight of the data with just four words: "We've got a winner", the game changed. "I thought 'wow'," laughed Moses. "He's a very sensible, conservative chap and that meant that he really was very excited."

Based on caplacizumab's impressive Phase III data, the wheels were officially set in motion for the US IPO which was announced the same day as the data. Moses and his team did a US roadshow in four and a half days and got an order book of close to $450m, three times oversubscribed. "It was perfect timing," he recalls. Little did he know it then, but these data catalyzed four months of activity that would change the company's trajectory.

From his 10-year assault on the US investment community, Moses had built strong relationships, by the time Ablynx went public in the US, around 40% of its shares were owned by American investors.

Ablynx listed in the US for $200m on Oct. 24 2017, propelling the company's market capitalization to over €1bn. "It's one of the things that made us smile, when people said the IPO was an overnight success. It was an overnight success that took 10 years to establish," said Moses. "I think people think you can just wander in, say: 'I'm gonna go public, and raise the money. It takes a lot more than that."

THE INSIDE STORY

Two years prior to the pivotal Phase III data readout, when management started

to think the Nanobody might be a goer, it started talking to its advisor, JP Morgan, about preparing a valuation case for the company to "figure out what you might really be worth, not what the stock market says," Moses explained. This included training management and the board about how to react if a company made a bid for Ablynx so the team would act in concert.

"The valuation work we did, was absolutely critical when Novo made its first approaches to us," told *Scrip*.

Novo Nordisk AS had its first sniff of caplacizumab's potential when Ablynx took the compound out to see if the Danish diabetes specialist, among others, might be interested in licensing the product as it neared Phase III.

"Novo were by far the most interested; really, really fell in love with the product," explained Moses. "It fit into Novo's portfolio very well but after talking to them, we concluded that our American investors wanted us to commercialize as much of that product as we could on our own."

The enthusiasm of US investors added a tailwind to the biotech's confidence, and it started to establish a sales force. "The whole IPO ethos in the US was that people wanted you to take the risk, commercialize and be in control of that commercialization. You could do that with probably 100 people in Europe and the US altogether. It was a clear message from the investors."

Ablynx came back from completing its American IPO, and told Novo that it would not be licensing the drug to it or any other party. Within three weeks of this knockback Novo made its first private bid for the company.

"The first two Novo approaches were a big surprise to us because Novo did not have a reputation for acquisition. It hadn't made an acquisition for 30 years and that had never been part of our discussion on licensing. So, when we received the approach it really was out of the blue," said Moses.

He says it was "quite a shock to suddenly be pursued in this way". The first two bids from Novo were rejected because Ablynx had done the valuation groundwork and knew the firm was worth more.

Another private bid from Novo, followed by another rejection from Ablynx and in January 2018, during JP Morgan, Novo went public with their offer of €2.6bn, €28 per share.

"I'm always quite surprised that some CEOs, and even some public figures, don't fully understand how that can change the game," said a bemused Moses. In terms of the effect on the share price, it resulted in a 40% uplift.

"When Novo announced the bid, and in the same breath we rejected that bid publicly, our stock price just went up to over €30," Moses said, recalling investors congratulating him on standing his ground but stating the company now had to be sold. "You are put into an auction, whether you like it or not."

Although Ablynx had not been in discussions about a sale to any other parties, it had relationships through partnering with companies such as **Merck KGAA**, **Boehringer Ingelheim GMBH** and Sanofi, the latter of which had paid Ablynx €23m upfront for access to its Nanobody-based therapeutic platform; and the pair had plans to develop novel treatments for various immune mediated inflammatory diseases.

On the back of this agreement, Moses reached out to Sanofi, and two days later was standing in front of the executive team in San Francisco.

"There was an immediate chemistry between them and us," he recollected. "They seemed to like everything, which was very reassuring." Novo had been very positive about the lead program, as was Sanofi, but the French major also liked a lot of the other things that Ablynx had to offer, such as the discovery and antibody platforms.

Just three weeks later, Sanofi publicly announced that it would acquire Ablynx at €45 a share, a 112% premium to its undisturbed price. Due diligence was completed in a week.

Moses credits Sanofi for moving "extraordinarily rapidly". The antibody collaboration had been ongoing for nine months and had been "extremely positive", he said. "It was oil that helped grease the whole discussion and get the sale put away."

BOARD POSITIONS

Moses is now chairing the board of three UK companies, **Achilles Therapeutics Ltd.**, **Virion Biotherapeutics** and **Evox Therapeutics Ltd.**. With all three companies Moses stipulated that he wants to be very involved. "I'm not trying to be a CEO," he explained. "I've got to support them, not try and subvert them in any way, but I wanted to feel involved because that gives me the most fun."

Talking specifically about Achilles, which develops cancer immunotherapies targeting clonal neoantigens, Moses says the company is "where all biotechs want to be," with two products potentially going into the clinic and a fundraising round to look forward to in 2019.

"You want to be with them when they're going through rapid periods of change and growth, hiring people, landing some facilities, looking for new investors, expanding their pipeline and moving towards the clinic, those are part and parcel of the biotech experience. Its what makes it so exciting and makes you want to get up in the morning."

Evidently Moses is not ready to hang up his biotech brain just yet.

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Sanofi Poised To File Isatuximab In Multiple Myeloma, Going Up Against J&J's Darzalex

JESSICA MERRILL jessica.merrill@informa.com

Sanofi's CD38-targeting antibody isatuximab could be the company's next new cancer drug as it looks to rebuild in oncology. The pharma said Feb. 4 that it will file isatuximab with regulatory authorities in the US and Europe in the first half of 2019 based on the positive results from a Phase III trial in relapsed/refractory multiple myeloma (r/rMM).

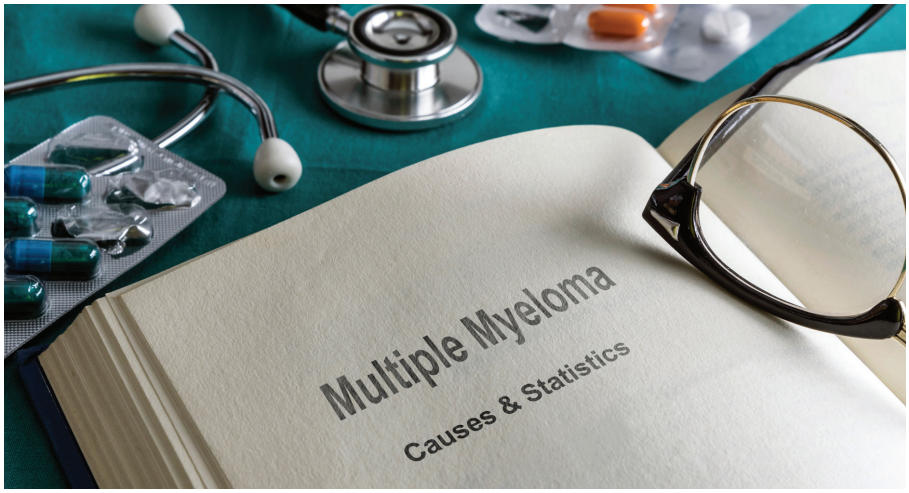
But isatuximab, if approved, will be in a come-from-behind position following **Johnson & Johnson/Genmab AS**'s *Darzalex* (daratumumab), which was approved in June 2016 as the first human anti-CD38 monoclonal antibody to treat r/rMM. *(Also see "Janssen/Genmab Win 1st Anti-CD38 In Multiple Myeloma" - Scrip, 17 Nov, 2015.)* Darzalex, which is approved in combination with various regimens for multiple myeloma, generated $2.03bn in 2018 sales.

Succeeding in multiple myeloma on the commercial front won't be easy. The category is one of the most competitive in oncology, with lots of new drugs in development. *(Also see "Multiple Myeloma: A Growth Market Set To Shrink As Revlimid Generics Hit" - Scrip, 11 Sep, 2018.)*

Sanofi's Phase III trial showed isatuximab extended progression-free survival in r/r multiple myeloma patients in combination with the current standard of care, **Celgene Corp.**'s *Pomalyst* (pomalidomide) and low-dose dexamethasone, versus pomalidomide and dexamethasone alone. The full results will be presented at an upcoming medical meeting, Sanofi said. Overall survival is a secondary endpoint that is continuing to be monitored.

The Phase III study, known as ICARIA-MM, enrolled 307 patients with r/r multiple myeloma, who received at least two or more prior anti-myeloma therapies, including Celgene's *Revlimid* (lenalidomide) and a proteasome inhibitor given alone or in combination.

Darzalex is approved with this same combination in multiple myeloma patients who have received at least one other treatment regimen.



CD38 is highly expressed on multiple myeloma cells, so it has become a hot target for drug developers. Isatuximab targets a specific epitope of CD38 that can trigger multiple mechanisms of action believed to promote programmed tumor cell death and immunomodulatory activity, according to Sanofi.

The Phase III study is one of four ongoing Phase III trials evaluating isatuximab in combination with currently available treatments in both r/r multiple myeloma and newly diagnosed patients. It also is being studied for the treatment of other hematologic malignancies and solid tumors.

Sanofi is studying isatuximab in two first-line trials: IMROZ in combination with **Takeda Pharmaceutical Co. Ltd.**'s *Velcade* (bortezomib), Revlimid and dexamethasone (VRd) and GMMG HD7, assessing isatuximab with the combination as an induction treatment and Revlimid maintenance therapy.

J&J's Darzalex recently showed a positive impact on PFS in patients with front-line MM in combination with Revlimid and dexamethasone. *(Also see "Darzalex Excites As Potential Grows In Multiple Myeloma" - Scrip, 30 Oct, 2018.)* It already obtained FDA approval in the front-line setting for some patients who are ineligible for autologous stem cell transplant, but in combination with a three-drug regimen known as VMP – Velcade, melphalan and prednisone – that is more commonly used in Europe and Japan than in the US. *(Also see "This Isn't The Big One: Darzalex Wins US Approval In First-Line Multiple Myeloma" - Scrip, 8 May, 2018.)*

Sanofi is in the process of trying to reenergize its oncology portfolio. Last year, the company, with its longtime partner **Regeneron Pharmaceuticals Inc.**, launched *Libtayo* (cemiplimab-rwlc) for cutaneous squamous cell carcinoma, an initial indication that the companies hope to expand upon broadly. It was the sixth PD-1/L1 inhibitor to reach the market, but marks the companies' entry into immuno-oncology and Sanofi's return to oncology. *(Also see "Sanofi/Regeneron's IO Springboard Libtayo Cleared For Skin Cancer " - Scrip, 28 Sep, 2018.)*

Sanofi has had a significant footprint in oncology, though largely in chemotherapy. It missed out with next-generation targeted therapies and the initial immuno-oncology wave. Now, it is hoping to course correct under the leadership of new head of R&D John Reed, who previously led early drug development at **Roche**.

(Also see "Zerhouni Retires, Sanofi's New R&D Chief John Reed Brings Early Research Experience From Roche" - Scrip, 24 Apr, 2018.)

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How Novartis Is Making SENSE Of Clinical Data In Digital Age

KEVIN GROGAN kevin.grogan@informa.com

The buzz has been deafening for years across the pharmaceutical sector about how the digital revolution is going to transform the way business is done but **Novartis AG** has been demonstrating a system that is already up and running and allows it to make sense of big data and manage hundreds of clinical trials worldwide from a 'control tower' in Switzerland.

CEO Vas Narasimhan repeatedly states that his vision is to create the leading medicines company in the world, powered by data and digital, and last week, ahead of Novartis' annual press conference, the firm showcased its Nerve Live data analytics platform. Specifically, journalists were invited into SENSE, the 'control tower' that helps to monitor its portfolio of studies and identify potential risks to timelines or costs.

Pharmaceutical companies produce huge amounts of data during clinical studies: typically just one Phase III trial collects more than a million data points. The challenge has been what to do with it all and how to process it, noted Badhri Srinivasan, head of global development operations at Novartis. He said that the monitoring of clinical trials across the sector "is still largely manual," with much of it being conducted via spreadsheets, email and telephone calls. This process is very inefficient: it can take four or five weeks to get information from a clinical trial site and by that time the information can be out of date, he pointed out.

For Novartis, there is a lot to coordinate. It has over 500 trials running across more than 70 countries, with 80,000 patients participating, and over the past two decades the company has collected 2 million patient-years of data through its clinical trials program.

However, as Luca Finelli, head of the predictive analytics and design group within Novartis' global drug development unit, noted, the company was sitting on those 20 years' worth of data but had problems analyzing it in a meaningful way. The company saw what tech giants were doing in the field of health care data projects, particularly **Google**'s decision in 2014 to acquire UK artificial intelligence startup **Deepmind** for £400m, and had to decide what Novartis itself should be doing.

Finelli said that getting new insights was proving difficult given that data were in "locked silos and we had to do some linking" so that the data could be cleaned, curated and optimized for deep analysis. That led to the establishment of the Nerve Live platform, built in partnership with **QuantumBlack**, a UK-based software company owned by the consultants **McKinsey**, which brings all the relevant data together and applies predictive analytics to generate insights on the design and performance of Novartis' global drug development operations.

With advanced algorithms processing data 24 hours a day and distilling new insights from it, the platform makes predictions around the performance of the company's trials, informing decisions such as where in the world Novartis should run a particular study, what resources will be needed and where efficiencies can be identified.

> "Vas was born in the generation of data and digital, it's not learned, so his minimum standard as someone in their early forties is very different than many of the pharma CEOs or any sector CEOs who are 10 or 15 years older."

Nerve Live uses machine learning to derive insights and signals difficulties that Novartis would want to spot early, such as a slowdown in enrolment at a particular site which could cause extensive – and expensive – delays to a trial. Srinivasan compared it to a GPS system "that tells you there's a traffic jam ahead," but in the case of Nerve Live, the predictive algorithms allow Novartis to see potential logjams in its clinical trials 12, 18 or 24 months down the road, and "by knowing this, I can correct it today" so the delay does not happen. Now, "access to information is instant."

The operation is directed from SENSE, the center that went live at Novartis' Basel headquarters in September 2018, which the company compares to an air traffic control tower that uses 'radars' to provide a global, real-time overview of all the firm's active studies. The room is manned by the portfolio management team and Finelli noted that adoption of the system across the company has been enthusiastic, with over 2,000 users having signed up.

Finelli told *Scrip* that getting Nerve Live up and running has been helped by the appointment of Narasimhan, a disciple of the digital revolution, as CEO just a little over a year ago. The project is moving quickly and has been backed financially by the firm; speaking at the annual press conference, chief digital officer Bertrand Bodson noted that "hundreds of millions of dollars" have been invested in the area.

Speaking to *Scrip* about the change in culture that Narasimhan is fostering, Paul Hudson, CEO of Novartis Pharma said that "Vas was born in the generation of data and digital, it's not learned, so his minimum standard as someone in their early forties is very different than many of the pharma CEOs or any sector CEOs who are 10 or 15 years older."

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Lilly/Incyte's Olumiant Breezes Ahead of JAK Pack In Atopic Dermatitis

JO SHORTHOUSE joanne.shorthouse@informa.com

The BREEZE Trials Show Olumiant's Potential In AD

Positive Phase III three results have propelled **Eli Lilly & Co.** and **Incyte Corp.**'s *Olumiant* (baricitinib) closer to becoming the first janus kinase (JAK) inhibitor approved for atopic dermatitis (AD), potentially a $2bn market.

It also puts baricitinib ahead of other more selective JAK1 rivals, such as **Pfizer Inc.**'s orally administered abrocitinib, for which data are from the Phase III JADE studies at the end of June, and **AbbVie Inc.**'s upadacitinib, which is being investigated in ongoing Phase III trials for AD.

Topline data from BREEZE-AD1 and BREEZE-AD2, two Phase III studies evaluating the efficacy and safety of the JAK1/2 inhibitor in monotherapy for the treatment of adult patients with moderate to severe AD, showed that, compared with patients treated with placebo, a statistically significant proportion of patients treated with baricitinib achieved the primary endpoint at week 16, which was defined by the Investigator's Global Assessment for AD (IGA) score of clear or almost clear (IGA 0,1).

These are two of five studies that will be part of the placebo-controlled data program intended to support a global registration.

Analysts at Informa's Biomedtracker said that approval in this indication "would help compensate for the missed US approval of the more effective 4 mg dose in RA, in agreement with the negative recommendation of an FDA advisory committee, due to concerns about safety."

SAFETY ISSUES

Olumiant was approved by the FDA for moderate-to-severe rheumatoid arthritis in June 2018, but only at the less effective 2 mg dose as the higher 4 mg dose was held back because of concerns over safety. *(Also see "Lilly May Need To Reassess Baricitinib Market After FDA Advisory Committee" - Scrip, 24 Apr, 2018.)*. Lilly also lowered the price to compete with RA rivals such as *Humira* (adalimumab) and Pfizer's first-in class JAK inhibitor *Xeljanz* (tofacitinib) by 60% and 50%, respectively. In the EU, Olumiant was the first JAK inhibitor approved for RA and was approved at both the 2 mg and 4 mg doses.

Like Xeljanz, the Olumiant RA label includes a Boxed Warning about the risk of serious infections and malignancies, but the Olumiant label also carries a warning about thrombosis.

The BREEZE-AD1 and BREEZE-AD2 studies began before the FDA's rejection of the 4 mg dose in RA and have reported evaluating low, mid, and high doses via tablets administered in concentrations of 1, 2, and 4 mg. "Importantly," said Biomedtracker analysts, "Lilly announced that no venous thromboembolic events or major adverse cardiovascular events were reported in these studies."

Besides looking at baricitinib in long-term AD studies, Lilly and Incyte have another ongoing US Phase III study (BREEZE-AD5) and additional global studies that are evaluating the drug in combination with topical corticosteroids.

ATOPIC DERMATITIS MARKET

In a statement, Lotus Mallbris, vice president of immunology development at Lilly, noted the lack of oral medications for AD in a disease that is already lacking in treatment options.

AD is largely treated by topical steroids, but the market was rejuvenated in 2017 by the approval of **Sanofi** and **Regeneron Pharmaceuticals Inc.**'s *Dupixent* (dupilumab), an injected first-in-class interleukin-4/IL-13 inhibitor. Informa's Datamonitor Healthcare forecasts that Dupixent could reach sales of $1.3bn by 2024.

While Olumiant, Pfizer's abrocitinib and AbbVie's upadacitinib are taking the JAK inhibitor approach to this lucrative market, **Novartis AG** is hoping its in-licensed novel IL-17C antibody, MOR106, from **MorphoSys AG** and **Galapagos NV**, will prove effective for the the skin disorder. *(Also see "Novartis Pushes Dermatology Momentum By Licensing Atopic Dermatitis MAb" - Scrip, 19 Jul, 2018.)*

Incyte is evaluating a proprietary topical formulation of another JAK inhibitor, its myelofibrosis therapy, *Jakafi* (ruxolitinib), in the pivotal Phase III TRuE AD 1 and TRuE AD 2 trials in adolescents and adults with mild-to-moderate AD.

Lilly will share the full data from both the BREEZE-AD1 and BREEZE-AD2 studies at future scientific venues and in peer-reviewed journals, as well as the topline data from other ongoing Phase III trials later this year.

Biomedtracker gives Olumiant a 71% likelihood of approval in AD, 7% above the average for candidates at this stage of development in this indication.

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Lilly Sees New Product Gains, But Older Drugs Still Limit Growth Potential

MANDY JACKSON mandy.jackson@informausa.com

Eli Lilly & Co. pointed to strong double-digit percentage growth for its newer products on Feb. 6, but with 7% revenue growth overall to $24.56bn in 2018, some of the biggest changes in terms of dollars delivered to the bottom line came from older drugs nearing the end of their patent-protected lives.

Lilly has been trying to refocus investors' attention from products facing loss of exclusivity to drugs commercialized since 2014 along with other near- and mid-term launches. But while many of the newer therapies generated impressive gains in the fourth quarter, they still have a long way to go to make up for legacy product sales, upping the pressure on recent launches and late-stage research and development programs to perform in line with expectations.

The company's revised 2019 financial guidance reflects the risks associated with its new product-driven growth strategy. Lilly provided guidance for this year at the end of 2018, expecting $25.3bn-$25.8bn in 2019 revenue, but said in its fourth quarter report that it now expects this year's revenue to total $25.1bn-$25.6bn.

The $200m downward revision was attributed, in part, to the recent decision to stop promoting *Lartruvo* (olaratumab) based on a failed Phase III confirmatory study. *(Also see "Lartruvo Phase III Fail Rocks Lilly Oncology Plans" - Scrip, 21 Jan, 2019.)* Revenue and spending guidance also will be affected by the $8bn acquisition announced last month of **Loxo Oncology Inc.**, including the positive impact of anticipated sales of *Vitrakvi* (larotrectinib) and increased R&D expenses associated with Loxo's pipeline. *(Also see "Lift-Off For Lilly In Cancer Genetics With Loxo Buy" - Scrip, 7 Jan, 2019.)*

Lilly's stock closed down 1% at $119.27 on Feb. 6 based on the guidance update.

Q4 REVENUE RISES, BUT WITH SOME SURPRISES

Revenue rose 5% year-over-year to $6.43bn in the fourth quarter, beating analyst consensus of $6.28bn. As a result, the full-year revenue total of $24.56bn came in slightly above Lilly's expectation of $24.3bn-$24.5bn for 2018. *(Also see "Q4 Pharma Earnings Preview: GSK, Lilly, Sanofi And AstraZeneca" - Scrip, 4 Feb, 2019.)*

But while revenue for 2018 included $816.5m in fourth quarter sales and $3.1bn in full-year sales from **Elanco Animal Health Inc.**, which it spun out through an initial public offering last year, the company intends to launch an exchange of its Elanco shares for Lilly shares during the first half of this year – potentially within the next few days, depending on market conditions. *(Also see "Finance Watch: Lilly Completes Elanco Animal Health Spin-Out As New IPO Filings Keep Rising" - Scrip, 21 Sep, 2018.)*

Credit Suisse analyst Vamil Divan said in a Feb. 6 note that the Elanco/Lilly share swap opportunity will keep investors interested in Lilly for now, "while successful commercial execution is likely the key to further upside later in 2019." The company's pharmaceutical sales increased 5% in the fourth quarter to $5.62bn, including sales volume growth of 11%, a net drug price decline of 5% and a 1% negative adjustment based on foreign currency exchange rates. As a group, drugs launched since 2014 represented 38% of fourth quarter pharma revenue.

The biggest percentage gainers among products that hit the market during the past five years, include the Interleukin-17 (IL-17) inhibitor *Taltz* (ixekizumab) for psoriasis and psoriatic arthritis, which rose 78% to $307m in the fourth quarter. The CDK4/6 inhibitor *Verzenio* (abemaciclib) for breast cancer, which launched in October 2017 and generated $21m in fourth quarter sales that year, brought in $83.1m in the fourth quarter of 2018 – about $34m below analyst consensus estimates of $107m.

Not surprisingly, the biggest decliners in Lilly's commercial portfolio were among its established products, including a 41% slide for the erectile dysfunction drug *Cialis* (tadalafil), which is facing generic competition, but generated more sales than analysts expected (*see table overleaf*).

"Most key products came in at or slightly above our expectations this quarter," Divan said. "The main driver of the revenue beat was Cialis … but that product's recent patent loss makes it less meaningful to the story going forward."

BMO Capital Markets analyst Alex Arfaei had a similar take in a Feb. 6 note, pointing out that "Lilly continues to manage its mature franchises exceptionally well, but it won't get much credit for that."

"Launch franchises are mostly fine, with the exception of Verzenio, which was 22% below consensus, and 25% below our forecast. Lilly reported higher demand for Verzenio offset by lower inventory (buying patterns) and price," Arfaei continued. "Although, we see some downside risk to Verzenio estimates, because of slowdown of the overall CDK 4/6 market, it shouldn't be enough to meaningfully change Lilly's growth trajectory. This is one of the advantages of Lilly having multiple growth drivers."

VOLUME, NOT PRICE, WILL CONTINUE TO DRIVE GROWTH

"While the US pricing environment continues to evolve, our sustained success is driven by the execution of our volume-based growth strategy," Chief Financial Officer Joshua Smiley said during Lilly's fourth quarter earnings conference call.

In terms of new products contributing to growth this year, Smiley said Lilly is particularly excited about the launch of CGRP inhibitor *Emgality* (galcanezumab) for migraine headache prevention, which hit the US market in the fourth quarter and generated $4.9m in sales for the period. *(Also see "Lilly Looks To Emgality Access, Injector And Data To Differentiate Its CGRP Inhibitor " - Scrip, 28 Sep, 2018.)*

Lilly's Q4 Sales Performance, Top 5 Established Products Vs. Top 5 New Launches

ESTABLISHED PRODUCTS					
DRUG	**Q4 SALES**	**DOLLAR CHANGE**	**% CHANGE**	**CONSENSUS**	**DIFFERENCE**
Humalog (insulin lispro)	$770m	($11.8m)	(2%)	$753m	$17m
Alimta (pemetrexed)	$556.9m	$31.7m	6%	$538	$18.9m
Cialis (tadalafil)	$350.7m	($246.7m)	(41%)	$249m	$101.7m
Forteo (teriparatide)	$437.1m	($76.1m)	(15%)	$442m	($4.9m)
Humulin (human insulin recombinant)	$337.4m	($25.2m)	(7%)	$355m	($17.6m)
NEWER PRODUCTS					
DRUG	**Q4 SALES**	**DOLLAR CHANGE**	**% CHANGE**	**CONSENSUS**	**DIFFERENCE**
Trulicity (dulaglutide)	$924.7m	$275.7m	42%	$906	$18.7m
Taltz (ixekizumab)	$307m	$134.5m	78%	$292m	$15m
Basaglar (insulin glargine)	$232.2m	$78.4m	51%	$254m	($21.8m)
Cyramza (ramucirumab)	$220.6m	$15.8m	8%	$222m	($1.4m)
Jardiance (empagliflozin)	$193.2m	$50m	35%	$236m	(42.8m)

CEO David Ricks noted in a pipeline update during the company's call that Lilly's Emgality revenue and its headache franchise are on pace to grow with the recent submission of a supplemental biologic license application to the US FDA for Emgality in the prevention of episodic cluster headaches. This follows a new drug application filing with the FDA last year for the acute migraine drug lasmiditan. *(Also see "Lilly's Lasmiditan NDA Review Could Hinge On US FDA's Migraine Guidance" - Pink Sheet, 25 Nov, 2018.)*

Ricks also noted the recent start of the Phase III clinical trial program for the GIP/GLP-1 co-agonist tirzepatide in type 2 diabetes, the start of Phase II for a once-weekly basal insulin and automated insulin delivery system, and the initiation of a Phase II study for Verzenio in prostate cancer. *(Also see ""Impressive" HbA1c And Weight Reductions Spur Phase III Plans For Lilly's Dual Incretin Agonist" - Scrip, 4 Oct, 2018.)*

Also, while eight biologic candidates have entered Phase I testing across the company's therapeutic areas since Lilly's last earnings call, he said three early-stage molecules have been removed from the pipeline, including a Phase I heart failure candidate, the Phase II diabetes drug known as DACRA-042 and a BTK inhibitor partnered with **Hanmi Pharmaceutical Co. Ltd.** *(Also see "Hanmi To Step Up Global Drug Development As Lilly Returns BTK Rights" - Scrip, 23 Jan, 2019.)*

Some 2019 R&D pipeline milestones already achieved this year include initiation of a Phase III study of *Jardiance* in chronic kidney disease, Phase III data for the NGF inhibitor tanezumab in osteoarthritis pain with partner **Pfizer Inc.**, and Phase III results for the **Incyte Corp.**-partnered JAK1/2 inhibitor *Olumiant* (baricitinib) in atopic dermatitis. *(Also see "Pfizer: Time To Face The Lyrica Pain" - Scrip, 29 Jan, 2019.)*

OPTIMISM ABOUNDS FOR PIPELINE PROGRAMS

Safety is a big factor for NGF inhibitors, but Lilly is optimistic about tanezumab's profile based on data generated to date, Senior Vice President and Chief Scientific Officer Daniel Skovronsky said during the company's conference call.

"The risk, obviously, we've been looking at is rapidly progressive osteoarthritis (RPOA) and the data that we continue to get, I think, is a very encouraging picture," Skovronsky said. "This molecule, I think, if you take the context of the vast unmet medical need for chronic pain and the deficiencies with the existing therapies that are available, including opioids and NSAIDs, I think really this offers a compelling benefit."

President of Lilly Biomedicines Christi Shaw noted during the call that while results from two Phase III studies for Olumiant in atopic dermatitis were reported on Feb. 4, the company is waiting for data from three additional trials to support global regulatory submissions.

Both the 2 mg and 4 mg doses achieved the primary endpoint in the first two Phase III atopic dermatitis studies, though the higher dose had more success on secondary endpoints. Lilly is leaving the door open to seeking approval for both doses, but only a 2 mg dose is approved in the drug's first indication of rheumatoid arthritis in the US due to safety concerns, including thrombosis. *(Also see "Lilly Prices Olumiant For JAK Battle, But Misses Approval For Higher Dose" - Scrip, 2 Jun, 2018.)*

CEO Ricks commented on how the company is spending its cash going forward on driving sales increases for its approved products as well as investing in R&D for the next group of commercial assets, including licensing and acquisitions, such as the Loxo deal already this year.

"We see a period ahead of prolonged revenue growth for the company, because we have a relatively new lineup of products that should continue to grow," he said. "We're adding to that even this year and next with additional launches. We do see ourselves balancing R&D spending, both on the balance sheet [with] M&A as well as partnerships, and [we] continue to spend, I would say, toward the top of the industry on internal income statement-based R&D, because we see good opportunities today."

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Sanofi Prioritizes Cancer And Rare Diseases In Pipeline Shake-Up

KEVIN GROGAN kevin.grogan@informa.com

Sanofi has posted a solid if unspectacular set of financials for the fourth quarter but much more interesting was an update on the French major's R&D strategy and its increased focus on oncology, immunology and, having just got FDA approval for blood disorder drug *Cablivi* (caplacizumab), rare diseases.

Following the arrival from **Roche** of John Reed as its new head of R&D last summer, Sanofi said that it has carried out "a rigorous pipeline prioritization review to accelerate investment behind its most promising programs and to discontinue those with a less attractive expected return profile." As a result, Sanofi is fast-tracking 17 programs, including eight in oncology, while 13 development and 25 research projects are being discontinued "to enhance the company's focus on delivering first and best in class medicines."

> Analysts believe that Cablivi, a Nanobody-based therapy, could have peak sales in the region of $500m.

The R&D pipeline now contains 81 projects including 33 new molecular entities in clinical development, and 35 projects are in Phase III or have been submitted to regulatory authorities. Sanofi's annual R&D spend will be approximately €6bn annually through 2021.

A couple of priority programs center around Sanofi's CD38-targeting antibody isatuximab, which is set to be filed with regulatory authorities in the US and Europe in the second quarter of 2019 based on positive results from a Phase III trial in relapsed/refractory multiple myeloma, making it a possible challenger to **Johnson & Johnson**'s blockbuster *Darzalex* (daratumumab). Sanofi noted that it has initiated Phase II trials for isatuximab in combination with its recently-launched PD-1/L1 inhibitor *Libtayo* (cemiplimab) in lymphoma; the latter, which is partnered with **Regeneron Pharmaceuticals Inc.** and is approved for cutaneous squamous cell carcinoma, had US sales of $15m in the fourth quarter.

Sanofi is also running a Phase II trial looking at a combination of isatuximab and Roche's PD-L1 inhibitor *Tecentriq* (atezolizumab) in solid tumors, while another Phase II has been initiated for SAR440340, an anti-IL33 monoclonal antibody which is being evaluated for atopic dermatitis. The company also noted that positive Phase I data for SAR408701, an anti-CEACAM5 antibody drug conjugate, in a subgroup of lung cancer patients, will lead to a broad development program starting before the end of 2019.

As for the discontinuations, a number of cardiovascular and metabolic disease assets were terminated, including SAR425899, a GLP-1/GCGR agonist which was in Phase II for obesity in type 2 diabetes patients, and SAR438335, a Phase I GLP-1/GIP agonist for diabetes. The moves highlight Sanofi's shift in focus from one of its historically strong areas – diabetes sales in the fourth quarter fell 10.5% to €1.38bn, due mainly to lower sales in the US of its insulin glargine products *Lantus* and *Toujeo*.

On a conference call, Reed said that the firm's approach to research will be "quick win, fail fast," with the objective of having 80% of the pipeline consisting of potential first or best in class candidates. About 70% of the pipeline will be biologics, with two-thirds of projects coming from internal R&D versus 50% at the moment and he added that Sanofi could potentially submit nine new medicines and 25 additional indications to regulatory authorities from 2019 to 2022.

CABLIVI GETS FDA NOD

Sanofi's enthusiasm for the rare diseases space, and particularly for its newly-formed rare blood disorder franchise, was vindicated Feb. 6 with FDA approval for its acquired thrombotic thrombocytopenic purpura (aTTP) therapy Cablivi, the main asset behind its €3.9bn acquisition of Belgium's Ablynx last year.

The US approval comes a few months after Cablivi got the thumbs-up in Europe in August 2018 in combination with plasma exchange and immunosuppressive therapy for aTTP, a rare blood-clotting disorder. It will be launched in the US later this quarter at a price of $270,000 per typical aTTP episode, before any rebates and discounts, and is the first US drug approval for Sanofi's rare blood disorders franchise, which also includes hemophilia drugs acquired through the purchase of **Bioverativ Inc.** last year. *(Also see " Cablivi CHMP Backing Helps Validate Sanofi's €3.9bn Ablynx Purchase" - Scrip, 29 Jun, 2018.)*

Analysts believe that Cablivi, a Nanobody-based therapy, could have peak sales in the region of $500m. In the US, aTTP affects fewer than 2,000 adults each year but it is a severe, life-threatening disease. It is estimated that up to 20% of patients die from TTP episodes, despite the currently available treatments of plasma exchange and immunosuppression, with most deaths occurring within 30 days of diagnosis.

As for the Q4 financials, sales were up 3.9% to just shy of €9bn, while earnings per share increased 4.7% to €1.10, with net income expected to increase 3%-5% in 2019. Of its new products, Sanofi noted strong demand for its eczema treatment *Dupixent* (dupilumab), which had sales of €280m, up from €118m for the same period of 2017, driven by an expanded approval in asthma and bolstered by a direct-to-consumer campaign in the US.

The cholesterol therapy *Praluent* (alirocumab) rose 51% to $82m, thanks to price cutting in the US to increase uptake and

Sanofi noted that it expects higher US rebates to impact sales of the injectable PCSK9 inhibitor. Performing much better was the multiple sclerosis pill *Aubagio* (teriflunomide) which jumped 12.6% to €446m. *(Also see "New US Cholesterol Guidelines Hit PCSK9s Hard On Pricing, Value" - Scrip, 19 Nov, 2018.)*

The results were seen by the investment community as solid and the research update was welcomed. Analysts at Morgan Stanley issued a note saying that "we view the R&D strategy revamp as a clear positive." They welcomed the pivot towards "an increasing focus on innovation, rare diseases and oncology, bringing with it pricing power and a specialist focus, and away from increasingly commoditized areas such as diabetes which are susceptible to net pricing risk going forward."

In an investor note, Jefferies analysts said they are optimistic about future sales for "the focus growth driver Dupixent, which offsets greater caution on Lantus." They added that "we believe the pipeline offers intriguing optionality, overlooked by many, and see steady future margin expansion."

Analysts at Deutsche Bank noted that there was no explicit cost cutting plan mentioned "which to some extent we expect to be a disappointment to some investors that hoped for this." On the conference call, Sanofi CEO Olivier Brandicourt confirmed there would be no dedicated announcement "but we seek to find efficiencies in the company every day."

He also suggested that there is little chance of Sanofi divesting its animal health or consumer healthcare units, saying "I think we have the right structure," and added that despite spending around €13bn on Ablynx and Bioverativ last year, there is still cash available for bolt-on acquisitions.

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What Advair? GSK Plays Up Budding Oncology Pipeline In Q4 Call

JESSICA MERRILL jessica.merrill@informa.com

GlaxoSmithKline PLC has its eye on the horizon, which means on its growing oncology pipeline, not its maturing respiratory portfolio.

Management spent most of the company's fourth quarter sales and earnings call Feb. 6 highlighting new pipeline opportunities, particularly in the budding area of oncology, rather than dwelling on the loss of its blockbuster asthma drug *Advair Diskus* (fluticasone/salmeterol) to the first generic competition.

While GSK has long accepted the eventual loss of Advair and has been working to minimize the impact, one question is what cross-over effect a generic launch might have on some of the newer next-generation products in GSK's portfolio such *Breo Ellipta* (fluticasone/vilanterol) and the triple combination *Trelegy*. The company said it expects an impact to be minimal. Advair, meanwhile, generated £2.42bn ($3.13bn) in revenue in 2018, a 23% decline over 2017 as the product has come under intense pricing pressure and lost ground to some of the newer Ellipta products. Ellipta product sales grew 29% in 2018 to £2.05bn ($2.65bn), putting them nearly on par with Adair.

A generic launch is expected in February after **Mylan NV**'s generic was the first approved by FDA Jan. 31. The commercial value of Advair has diminished in recent years due to competitive dynamics and GSK's success transitioning patients to newer products. Advair generated £1.1bn ($1.42bn) in the US in 2018. That reflects a slow and steady decline from the peak sales of Advair in 2013 when global sales were £5.27bn ($6.82bn) and US sales were £2.77bn ($3.58bn).

GSK is particularly fortunate that the shingles vaccine *Shingrix* will help to close some of the gap. Shingrix generated £784m ($1bn) in 2018, its first year on the market and running at reduced manufacturing capacity. *(Also see "GSK Shingrix Shingles Vaccine Seen Displacing Zostavax After US FDA Approval" - Scrip, 23 Oct, 2017.)*

Management didn't spend a lot of time talking about the impact of Advair, but was rather focused on turning attention to its budding oncology pipeline, which now includes the **Tesaro Inc.** portfolio of products as well as a newly in-licensed bifunctional immunotherapy M7824 (bintrafusp alfa).

16 ONCOLOGY DRUGS IN THE CLINIC

The oncology portfolio has grown to include 16 drugs in clinical development, double the number when the company held an R&D overview in July 2018. *(Also see "GSK's Big Reveal: An R&D Overhaul Poised To Yield Long-Term Cultural Change" - Scrip, 25 Jul, 2018.)*

"We now also have a number of molecules with diverse mechanisms of action, providing an opportunity for many innovative combination studies," President of R&D Hal Barron said.

Business development has helped to bolster the pipeline. GSK closed on the $5.1bn acquisition of Tesaro in January, adding the PARP inhibitor *Zejula* (niraparib) and three other Phase I oncology

assets. *(Also see "GSK Embraces PARP Promise With Tesaro Buy" - Scrip, 3 Dec, 2018.)* Then, the day prior to the sales and earnings call, GSK announced a licensing deal with **Merck KGAA**, agreeing to pay £300m ($388m) up front for rights to M7824, which works through two pathways, transforming growth factor-β (TGF- β) trap and an anti-programmed cell death ligand (PD-L1).

Tesaro gives GSK an immediate commercial presence in oncology and a targeted cancer drug to build out, but a lot of investors are intrigued by the opportunity M7824 represents, because the ambition is that the dual mechanism could overcome some of the hurdles that limit the number of patients that respond to PD-1/L1, a potentially enormous commercial opportunity.

Some 70%-75% of patients don't respond to PD-1/L1 drugs or relapse after treatment, Barron said. "If you take a step back and look at the scale of the opportunity, I mean, pembro reported $7bn," he said, referencing Merck's PD-1 inhibitor *Keytruda* (pembrolizumab). "In terms of a relatively modest down payment, this gives us an opportunity, potentially, to disrupt this market."

GSK reviewed data on 700 patients treated in various Phase I settings, including second-line non-small cell lung cancer, that were encouraging. A Phase II trial has already been initiated to investigate M7824 compared to pembrolizumab as a first-line treatment in NSCLC patients with high PD-L1 expression. The company declined to provide a timeline for when data to support registration might be available.

In the near-term, GSK is also focused on indication expansion for Zejula and its B-cell maturation antigen (BCMA) antibody-drug conjugate, which it expects to file for third line or later multiple myeloma in the second half of 2019, after aggressively speeding up the development timeline. *(Also see "J.P. Morgan Notebook Day 2: Biogen, GSK, Bluebird, Roche, Amgen, Biohaven, Lilly And FDA's Gottlieb" - Scrip, 9 Jan, 2019.)*

Meanwhile, the company appears to be de-prioritizing respiratory disease, announcing plans to discontinue three respiratory products due to lack of confidence and portfolio considerations: nemiralisib for chronic obstructive pulmonary disease, TRPV4 for acute respiratory distress syndrome and AVb6 for idiopathic pulmonary fibrosis.

GSK pharmaceuticals sales grew 2% at constant exchange rates to £17.3bn in 2018, while consolidated sales increased 5% at to £30.8bn ($39.8bn). operating profit was £5.5bn ($7.1bn), up 34%. The company guided that 2019 adjusted EPS will decline 5%-9% in 2019, reflecting the generic Advair launch, the impact of the Tesaro acquisition and assuming the consumer healthcare joint venture with Pfizer. *Published online 6 February 2019*

Takeda Says Last Pre-Shire Quarter 'Robust', But Quiet On Divestments

IAN HAYDOCK ian.haydock@informa.com

Takeda Pharmaceutical Co. Ltd. has logged a generally solid last quarter of results before the impact of its acquisition of **Shire PLC** begins to kick in, with mainstay products growing globally and the results of ongoing cost savings driving margin improvement.

While again committing to the general principle of non-core asset sales to pay down debt associated with the acquisition, formally completed on Jan. 8, executives gave little further away at a Feb. 1 third-quarter results briefing in Tokyo.

The newly combined company is "proceeding with non-core asset divestiture negotiations…this continues to be an area of high focus for us as we look to accelerate deleveraging and focus the portfolio," CFO Costa Saroukos said. But he would not comment on speculation around the shape of possible divestments, saying only that "we are actively looking and having conversations on our divestiture strategy."

There has been some media speculation in Japan that selected product lines in emerging markets could be on the block, and CEO Christophe Weber reiterated that the strategic focus would continue to be on gastrointestinal, oncology, neuroscience, rare diseases and plasma-derived therapies, which together account for 75% of the combined business.

"We are looking at simplifying…we can take the opportunity [of the acquisition] to reduce our number of products and simplify our supply chain, for example. We are working in parallel for a couple of groups of products to sell."

Saroukos emphasized that Takeda does not intend to increase its debt load any further, and pointed to recent moves to raise cash to pay for Shire and pay down related debt load, such as the sale of real estate assets in Japan, including its Osaka head office.

Sales of real estate and marketable securities generated JPY45.4bn total in cash in the fiscal year to date, while other business divestments brought in JPY27.5bn. The focus will be on boosting profitability and Takeda will "strive to realize top-teen margins in the medium term, with the potential to further accelerate [these] with divestitures," Saroukos told the briefing.

UNDERLYING REVENUE GROWTH

Underlying revenue (excluding the impact of divestments and forex changes) was up by 5% in the fiscal nine months ended Dec. 31 to JPY1,380bn ($12.60bn), representing a modest 1% rise on a reported basis.

Entyvio (vedolizumab) for ulcerative colitis and Crohn's disease continued to power ahead as the Japanese company's top global product, surging 35% on an underlying basis to JPY194.4bn worldwide, helped by an expanded share in biologic therapy-naïve patients. The once-weekly oral proteasome inhibitor for multiple myeloma *Ninlaro* (ixazomib) also grew strongly, up by37% underlying to JPY46.5bn globally. In the same indication, US generic erosion of *Velcade* (bortezomib) continued to be limited, the briefing heard. *Published online 3 February 2019*

For the full story go to: https://bit.ly/2WV0TMV

What GSK's Immunology Chief Did Next

ELEANOR MALONE eleanor.malone@informa.com

From clinical practice to academia to biotech to big pharma: Paul Peter Tak has covered most of the bases when it comes to medicine. Last year he left his role as senior vice president of R&D pipeline, chief immunology officer, development leader and co-chair of the scientific review board at **GlaxoSmithKline PLC** to embrace yet another pillar of the industry: venture investment. He caught up with *Scrip* to talk about his latest endeavor.

In October 2018, after seven years at GSK, Tak joined Cambridge, Massachusetts-based Flagship Pioneering as a venture partner. He readily acknowledges that at GSK he "achieved more than I could have dreamed of and was very lucky that I was so strongly supported to do the right things." So what prompted him to make the leap from big pharma to biotech generator?

Part of it was his interest in combining his varied experience and network across the entire ecosystem "to lead programs in oncology and immunology but also in other therapy areas." Also, he was attracted to the opportunity to do this "at a faster pace than I could do it at a big pharmaceutical company because the process is simpler and it's a very strong organization behind me."

FLAGSHIP'S ALLURE

At Flagship he has already been placed as CEO of an undisclosed biotech start-up operating in stealth mode, and he is starting to take on board positions. He is also helping to identify other senior leaders for Flagship's portfolio companies.

Flagship Pioneering changed its name from Flagship Ventures a couple of years ago to signal its distance from the typical venture capital model of selecting and investing in firms that seek to progress stepwise from existing products, technologies and know-how. Rather, it creates think tanks to build companies from scratch around important unmet challenges, something that is very appealing to Tak. "Flagship's people ask big scientific questions that nobody has answered yet," he explained. "Otherwise, they don't do it." Rather than focusing on specific therapeutic or

Paul Peter Tak

technological areas, the firm is "completely unbiased," following only the biggest areas of need for society and patients and where there is "really exciting very early science."

Tak added: "They are not interested in doing anything other people are doing already: they are looking for what is not only unprecedented, but what is unreasonable, almost. Thinking in a completely new way. They aim to invest in big things in a very novel and extremely smart way."

This chimes with his own approach, which favors following the science rather than committing to a particular condition or commercial opportunity. "That is a very traditional way of thinking that does not necessarily create a lot of value over time, because very often the big opportunities are somewhere other than where you would have predicted." Rather, "you need to start with the pathogenetic mechanisms, the platforms to interfere with human biology in a truly innovative way, and then find out where it is that you can truly make a difference that leads to a beneficial effect on patients' lives. Not the other way round."

Flagship forms prototype companies to address the big questions it has identified and brings together small teams of "super bright people" working both with external laboratories and with Flagship's own laboratories to address the initial hypotheses. "When it looks good Flagship makes a decision on whether to fund a series A. It's all done in stealth mode and these companies are not announced," said Tak.

The firms are initially headed by a senior leader from Flagship. Should things progress positively, the decision will be made to transition the firm into a "growthco", with an external CEO appointed who further builds the leadership team and seeks additional funding through a series B round in which Flagship will co-invest.

"Flagship builds discovery platform companies and invests broadly in multiple programs. This is a fantastic way to de-risk the organization," said Tak. "And you can increase the probability of success of every medicine by being extremely thoughtful about the therapeutic target. You need to design relatively small clinical trials that will yield a high density of data to find out early on whether hitting the mechanism will lead to you hitting pathways downstream that are known to be associated with clinical effect."

Flagship's successes include messenger RNA therapeutics and vaccine developer Moderna, which became the largest biotech IPO in December 2018, raising $604m with a valuation of $8.1bn, and cellular therapy developer Rubius Therapeutics, which raised $277m and had a total valuation of $2bn in its July 2018 IPO.

MUTUAL BENEFITS

Tak pointed out that with $2.5bn in committed capital in 2018, more than 15 IPOs over the past five years, more than 40 therapeutics in development and around $1.2bn being spent on discovery each year, the Flagship ecosystem "could compete with any pharmaceutical company in terms of discovery investment." He sees his new role as a chance to "accelerate what I tried to achieve, which is basically getting into the clinic to make medicines that could be transformational for patients."

For its part, Flagship gains from Tak's understanding of "what a medicine looks like," his insight into patient needs – thanks to his decades of clinical practice (he has received an award from the minister of health in his native country the Netherlands for being the best rheumatologist in the country), his existing network in the UK and continental Europe, and his experience in experimental medicine and leadership.

CONTINUED ON PAGE 23

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

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

PIPELINE WATCH, 1–7 FEBRUARY 2019

Event Stage	Lead Company/Partner	Drug Name	Indication	Comments	Change To LOA (%)	LOA (%)
Phase IIIb Published Results	ViiV Healthcare	Tivicay (dolutegravir)	HIV/AIDS	DAWNING (vs. Lopinavir/Ritonavir); The Lancet Infectious Diseases, Online Feb. 4, 2019	0	100
Phase III Published Results	Paratek Pharmaceuticals, Inc.	Nuzyra (omadacycline)	Skin Infections And Pneumonia	OASIS-1, Optic; NEJM, Feb. 6, 2019	0	100
Phase III Updated Results	Eisai/Purdue Pharma	lemborexant	Insomnia	SUNRISE 2; Improved Sleep	0	90
Phase III Top-Line Results	Sanofi/Immunogen	isatuximab	Multiple Myeloma	ICARIA-MM (w/PomDex); Met Primary PFS Endpoint	3	38
Phase III Top-Line Results	Protalix BioTherapeutics/Chiesi	pegunigalsidase alfa	Fabry's Disease	BRIGHT; Positive Renal Function Data	1	66
Phase III Top-Line Results	MacroGenics, Inc.	margetuximab	Breast Cancer, HER2-Positive	SOPHIA; Positive Results	7	43
Phase III Top-Line Results	Eli Lilly/Incyte	Olumiant (baricitinib)	Atopic Dermatitis	BREEZE-AD1,2; Met Primary Endpoint	3	71
Phase III Top-Line Results	GenSight Biologics S.A.	GS010	Leber's Hereditary Optic Neuropathy	RESCUE: Promising Results	0	45
Phase III Trial Initiation	Ardelyx Inc.	tenapanor	Hyperphosphatemia	AMPLIFY; As Adjunctive Therapy	0	64
Phase III Trial Announcement	Eisai/BioArtic AB	BAN2401	Alzheimer's Disease	Confirmatory Study In Early Alzheimer´s Disease	0	20
Phase III Trial Announcement	Acadia Pharmaceuticals/Neuren	trofinetide	Rett Syndrome	In Girls, In 2H 2019	0	17
Phase III Trial Announcement	Orion Pharma	Simdax (levosimendan)	Amyotrophic Lateral Sclerosis	REFALS-ES; Extension Study	0	52

Source: Biomedtracker | Informa, 2019

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Under Tak's steerage of GSK's immuno-inflammation therapy area unit, development programs included:

- GSK3196165, a granulocyte-macrophage colony-stimulating factor licensed from **MorphoSys AG** which has yielded positive Phase II results in rheumatoid arthritis;
- the interleukin-6 inhibitor sirukumab, which GSK handed back to partner **Janssen Biotech Inc.** in 2017 as part of an R&D cull shortly before the product's rejection by the FDA for rheumatoid arthritis;
- and a subcutaneous formulation of the lupus drug Benlysta (belimumab), which was approved by the FDA in 2017.

SILO BREAKER

But it was arguably earlier in the pipeline that he really made his mark. Tak's passion for "breaking down silos" saw him foster the application of immunology research beyond autoimmune conditions to include other disease areas, most notably oncology.

For example, GSK's initial research into the RIP1 kinase, which regulates inflammatory cell death and inflammation, in autoimmune conditions like rheumatoid arthritis and inflammatory bowel disease was expanded to include pancreatic cancer after the researchers saw a scientific publication on a possible link between inflammatory cell death and pancreatic ductal adenocarcinoma. Similarly, the company expanded its systemic stimulator of interferon genes protein (STING) agonist development program into cancer.

Tak also established GSK's Immunology Network to bring together pharma, biotech and academic scientists, which led to the establishment of Sitryx Therapeutics to develop treatments based on the emerging area of immunometabolics. Validating Tak's approach, GSK's chief scientific officer and president of R&D Hal Barron last year announced the company's new R&D strategy, which will focus heavily on the immune system and genetic science, as well as external collaboration and fostering a culture "of truth-seeking versus progression-seeking."

It is apparent that Tak has an enthusiasm for shaking up science as well as organizations that is underpinned by an impatience to advance medical science. His diverse career is indicative of a focus on the end – creating transformational treatments for patients – rather than any one means of getting there, whether that be academia, medical practice, big pharma or biotech. Right now, like quite a few other émigré executives from big pharma, he's attracted to the nimble, risk-taking, entrepreneurial spirit of biotech.

"I led a very significant part of the R&D at GSK over the past few years, including oncology, immuno-inflammation and infectious diseases, and after looking at other global head of R&D jobs in big pharma, as well as venture jobs and senior roles in academia, I came to the conclusion that I wanted to lead a biotech company, to develop medicines for patients and create value for the investors and for the company," he explained. In fact, it's not his first foray into biotech: in 2005 he founded gene therapy firm Arthrogen, to target rheumatic diseases, and for a few years he was CEO of the GSK spin-out Tempero Pharmaceuticals, which was re-acquired by its originator in 2015.

For Tak, it is very much a case of right place, right time. "I think this is the best time ever: it's a privilege to be able to work in this era in history on biomedical science, because we are seeing an explosion of knowledge at the moment, at the same time as enormous unmet need to address many diseases where we don't have therapeutic options that are good enough, and it all comes together with the whole tech revolution, including the digital revolution. Being at this interface is an incredibly exciting opportunity."

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APPOINTMENTS

Executive	To Company	New Role	From Company	Previous Role	Effective Date
Stefan Mueller	CureVac AG	Vice President, Preclinical	Sandoz Biopharmaceuticals	Global Program Leader	1-Feb-19
Aleksandra Rizo	Geron Corp	Chief Medical Officer	Celgene Corp	Executive Director, Strategy and Clinical Lead	30-Jan-19
Robert Friesen	Kiadis Pharma	Chief Scientific Officer	Ablynx	Chief Scientific Officer	1-Feb-19
Timothy Simon	Melinta Therapeutics Inc	Chief Commercial Officer	Pfizer Inc	Commercial Lead, RCC, Lung and Immuno-oncology	28-Jan-19
David R. Trexler	MorphoSys AG	President and Director	EMD Serono	Senior Vice President, US Oncology Commercial	6-Feb-19
Paul Willems	Osivax	Chief Medical Officer		Consultant	30-Jan-19
Patricia Malarkey	Royal DSM NV	Chief Innovation Officer	Syngenta	Head, Research and Development	15-Mar-19

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