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Joerg Moeller

Moeller Up In Bayer R&D Consolidation, Busch Off To Shire

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In a surprise announcement on the eve of the company's annual pharmaceuticals media day in Berlin, **Bayer AG** unveiled plans to combine all its pharma R&D under a single leader in one unit to be headed by current head of development, Joerg Moeller.

The consolidation comes as Andreas Busch, currently head of drug discovery, leaves "to pursue a new career opportunity at another company," the German group said. However it soon emerged that Busch has been appointed head of R&D at Shire.

Bayer's new unit will cover all of its therapeutic areas of focus, including oncology – for which a strategic business unit headed by **Bristol-Myers Squibb Co.** oncology veteran Robert LaCaze was created in February 2017. That unit, which covers functions from R&D through regulatory affairs and market access to early commercialization, was set up to enable Bayer to move its new cancer treatments to market rapidly in a fast-moving therapeutic area. It is not immediately clear how the oncology unit will be affected by the consolidation of the wider pharma R&D organization. The other therapeutic areas covered are cardiology, gynecology, ophthalmology and hematology.

Moeller, who became head of development for the company's pharmaceuticals division in 2014, will continue to report to Bayer's pharma CEO Dieter Weinand and serve on the pharmaceuticals executive committee. LaCaze also serves on the pharma executive committee.

Busch had been scheduled to present at the Dec. 1 media day, so the timing of his departure to Shire was rather unfortunate for the German group. He was appointed head of Bayer's pharma research in 2006, with his role later extending to cover animal health research.

In a statement Weinand said: "The combined organization will enable us to seamlessly steer all the important activities of research and development […] Joerg has an exceptional track record of bringing new medicines to patients […] and I trust that our team will be even more successful in doing so together under his leadership." He went on to thank Busch for "all his valuable contributions to our company and wish him much success in his future endeavors."

Pharmaceuticals accounts for a minority of the wider Bayer group's sales, but a large portion of its R&D spending.

The new R&D organization comes into effect on Jan. 1, 2018.

XOFIGO TRIAL SAFETY ISSUES

Just hours after the surprise R&D changes were unveiled, Bayer revealed a setback with an 806-patient Phase III trial combining its targeted alpha prostate cancer therapy *Xofigo* (radium-223 dichloride) with abiraterone and prednisone/prednisolone in metastatic castration-resistant, chemotherapy-naïve prostate cancer patients. The trial was unblinded on the recommendation of an independent data monitoring committee because more patients receiving the treatment suffered fractures and deaths than those in the control arm. The company said it would "thoroughly analyze

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How to leverage a top seller (p14)

from the editor

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The lull around Thanksgiving has dissipated and companies are back on the road, signing deals, switching executives and releasing pipeline updates.

Bayer has had a particularly busy time, hastily announcing an R&D restructure just hours before its head of discovery was proclaimed head of R&D at Shire – on the same day Bayer had prepared a press conference to showcase its pharmaceuticals pipeline. An unexpected trial safety issue added to the pressure on the German company (see cover story & p4).

Brexit meanwhile provides myriad reasons for sleepless nights, with the pharma sector seeing more than its fair share of complexity and uncertainty.

As the clock ticks on, industry leaders point out that they need to make contingency plans now. However, contingency planning doesn't usually have to account for such a wide spectrum of outcomes that are not just remotely possible but quite likely, affecting such an extensive array of activities across not one but all industries. To contingency plan around Brexit given the current level of uncertainty would be cripplingly difficult to do well, particularly since there is always the possibility (and the hope) that most of it will prove to have been unnecessary.

Ian Schofield's update on the state of Brexit negotiations and the impact on the pharma industry makes for sobering reading (p8-9). One fears a worst-case scenario just over a year from now, with European drug regulation hamstrung by the chaotic effects of the European Medicines Agency's hasty flight to Amsterdam, while a lack of preparedness for cross-border trade and an overly abrupt Brexit leaves the UK struggling even to procure medicines.

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Melinta Expands Portfolio, TMC Narrows Focus To LDL Reduction With Anti-Infective Deal
http://bit.ly/2nyOHnl
A transaction bringing newly public Melinta three anti-infective products and a related sales force from The Medicines Co. will enable the latter to downsize and focus on its Phase III PCSK9 inhibitor inclisiran.

Can Denmark's ALK-Abello Crack The US Allergy Market?
http://bit.ly/2BAGj99
Increasing patient and doctor awareness of sublingual anti-allergy tablets in the US, while at the same time cutting and rationalizing its product portfolio, are components of a new three-year business strategy aimed at making Denmark's ALK-Abello a less-niche player in the global allergy market.

OPPI Chief Vaidheesh On Burning Industry Issues In India
http://bit.ly/2injOgo
In an interview with *Scrip*, the Organization of Pharmaceutical Producers of India's new chief and GSK vice president (South Asia) and managing director (India) Annaswamy Vaidheesh shares the industry body's take on several critical issues including the Indian government's push for generic medicines and why the effective contract manufacturing model should not be "disrupted" by proposed policy reform.

Glenmark-Celon Generic Seretide DPI On Its Way In Europe
http://bit.ly/2AYEA1l
Glenmark-Celon's generic Seretide Accuhaler dry powder inhaler (DPI) appears on course for a debut in Europe, piling up more pressure on GlaxoSmithKline's respiratory franchise. Substitutability of the generic, however, will be key to driving momentum in uptake.

Finance Watch: Semma Raises $114m As VC Funding Keeps Up Brisk Pace
http://bit.ly/2AD08NR
Semma closed a $114m Series B round to fund development of insulin-producing cells. Also, Tesaro and Catalyst are among recent public company financings, while Otonomy shifted gears, laying off sales staff.

inside:

Shire Tempts Busch From Bayer As It Eyes Top Spot In Rare Diseases

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Having poached Andreas Busch from **Bayer AG** to be his R&D chief days after appointing a new finance head, **Shire PLC** CEO Flemming Ornskov has now put together a strong management team to push the company towards its goal of becoming the leading player in the rare diseases space.

Andreas Busch

Shire

The news that Busch has jumped ship from Bayer, where he was in charge of drug discovery, to become Shire's head of R&D and chief scientific officer in January caused quite a stir not least because the announcement came on the day (Dec. 1) when the German group held a high-profile press meeting to present its own research strategy. It was particularly surprising given that Busch was scheduled to speak at the event in Berlin. *(See front page.)*

For Shire, his appointment is being seen as quite a coup. Busch leads a team of 3,300 researchers at Bayer where he has risen up the ranks over 13 years. His soon-to-be new employer notes that he was responsible for the integration of Schering AG's drug discovery operations (the company was acquired in 2006), "the overall R&D strategy and enforced the improvement of Bayer's research productivity." Prior to joining Bayer, Busch was global head of cardiovascular research at Hoechst and Sanofi-Aventis.

Ornskov is pleased to get his man and said in a statement that "Andy is an outstanding scientist with extensive experience leading R&D functions, and an established track record of building broad portfolios that encompass both biologics and small molecules." He added that Busch's arrival would "further accelerate our ability to discover novel treatments for our innovative rare disease pipeline."

Busch takes over from Howard Mayer, who has been interim R&D chief since Phil Vickers, who earlier this month was named CEO at Canadian start-up **Northern Biologics Inc.**, left the post earlier this year after seven years in charge. Mayer is staying on at Shire as chief medical officer.

So what awaits Busch as he moves into the R&D hot seat? A healthy-looking pipeline for starters as Shire has just shy of 40 programs in the clinic, including 17 in Phase III.

INITIAL FOCUS ON NEW HAE DRUG

Datamonitor Healthare analyst Edward Thomason told *Scrip* that Shire's mid-term R&D efforts would likely concentrate on its hereditary angioedema franchise "and the launch of the much-anticipated SHP643 (lanadelumab) with its best-in-class clinical data set." The company presented hugely positive top-line data in May on the drug, acquired through the $5.90bn purchase of **Dyax Corp.** in late 2015, for $5.9bn - and filings are expected shortly.

Thomason and colleagues forecast that SHP643 could generate global sales of up to $1.80bn given its positive clinical data that have shown the drug has the potential to prevent HAE attacks and significantly improve patient convenience.

Busch's appointment "is a strong addition to Shire's management," Thomason added, saying that experience in cardiovascular, oncology and hematology therapy areas will support the company's rare disease therapy focus and acquired products that came from its $32bn acquisition of **Baxalta Inc.** last year. He also believes that the arrival of Busch also demonstrates Shire's shift away from neuroscience "and further supports that growing likelihood of a potential sell-off" of that business.

Earlier this year, Ornskov said Shire was carrying out a formal evaluation of the full range of strategic options for the neuroscience franchise, including the potential for its independent public listing and an update is expected by year end.

Busch will also be overseeing Shire's plans to consolidate its rare disease research and US commercial operations at a site in Kendall Square, Cambridge. Thomason concluded by saying that growing its rare diseases portfolio will ensure Shire "stays on a high-growth trajectory, as these products enjoy large profit margins due to high prices and a willingness from insurance and healthcare providers to pay for them."

Busch's appointment was announced just over a week after Shire named Thomas Dittrich as its new chief financial officer, starting in early 2018.

Dittrich is currently CFO of Swiss industrial engineering and manufacturing company Sulzer but has plenty of experience in biotech, having spent several years at **Amgen Inc.** where he was head of finance corporate planning and chief accounting officer between 2010 and 2014. He replaces Jeff Poulton, who is joining Indigo Ag, an agricultural start-up.

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Bayer's Weinand Slams Silo Thinking, Short-Termism In Medicines Valuation

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Dieter Weinand, president of Bayer Pharmaceuticals, called on health officials and policy makers involved in decisions about appropriate valuation of new medicines to get out of a short-termist, silo mentality and evaluate therapies for their broader economic impact. Speaking at the **Bayer AG**'s annual pharmaceuticals media day, he warned that as more and more patients demanding access to better and better medicines put an increasing strain on healthcare systems, medicines evaluation needs to take a more holistic, systematic approach, determine the full range of cost components and establish what a justifiable return would be.

DISTRIBUTORS – EXCESSIVE REWARD WITHOUT RISK?

The executive also hit out at the part pharmaceutical distributors have in burdening the healthcare system, claiming that those companies make the same total profit as pharmaceutical developers, but with none of the risk.

> 'I'm all for outcomes-based contracting but not based on the short-term'

"We need to think about healthcare holistically, how to prevent people having disease that requires long-term care and reduces their productivity, as well as reducing hospitalization," he said, declaring that a large part of the answer, aside from encouraging healthier living, should be medicines – including taking them to prevent or reduce costly outcomes.

Weinand cited a discussion he had had with an unnamed health official to illustrate his point about silo mentality. To his point that assessing the clinical data from Bayer's anticoagulant *Xarelto* demonstrates its ability to reduce costly hospitalization, debility and the need for long term care and nursing, thus offering a large economic benefit to society, the official had responded, "I don't care about any of that. I want to say I got a 5% reduction on the price of the medicine."

"Thinking in siloes is wrong, as is short-term thinking only for the time being and for the relatively short duration of patent protection," Weinand said, pointing out that following patent expiry patients will be able to benefit from medicines for decades "for pennies a day". "For a very short period there should be recuperation of R&D costs," he said, followed by decades of very cheap contribution to patient health. "The way we are structured, somebody is responsible for the drug budget but not the healthcare out-

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Bayer Pharmaceuticals President Dieter Weinand

CONTINUED FROM PAGE 5

comes, and they also take a short-term view. I am all for remuneration for outcomes-based contracting but not based on the short-term."

Weinand also contended that it was appropriate for richer countries to "pay a bit more" to enable patients in poorer countries to access medicines. "You can't charge patients in Nicaragua the same as in Germany or the Netherlands," he said, noting that Bayer aimed to provide its medicines in as many countries as possible whereas "a lot of companies have cherry-picked" their markets.

But on pricing transparency, he said Bayer could not be "completely transparent on cost structures for competitive reasons." Still, "we try to be very socially responsible," he declared. Claiming that "I didn't go into medicine to get rich, and I don't know any colleagues who did either – I did it because I saw my mother suffering from Alzheimer's disease," the pharma CEO said it was "quite a sore spot for me that industry is regarded so poorly." He lamented the fact that industry's attempts to communicate the benefits they bring to society through the development of medicines are thwarted when "one bad example comes along and we are all considered the same."

Joerg Moeller, Bayer Pharma's head of development who is to take the helm of the division's entire R&D organization from the beginning of 2018, added that "as an industry we have to be more up-front about the benefits of what we do." He said that "if we allow discussions always to focus on cost rather than the benefits, it is a very one-sided discussion."

Weinand concurred, noting also that there needed to be wider understanding that "progress in medicine is incremental." He criticized payers that refuse to reimburse new medicines because they only offer, for example, a few weeks' additional survival benefit over existing treatments. "People say, 'Oh, six weeks, it's not worth anything' – but if we'd said that in 1975 we wouldn't have had the progress we've seen in breast cancer survival," he argued, pointing out that over time, incremental improvements add up to real advances, and that after a relatively short time once premium-priced medicines lose market exclusivity and become much cheaper.

"We need to highlight what our work really means for people," he concluded.

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CONTINUED FROM COVER

the data." It said other types of study using this combination had not shown new safety signals. "Based on available data from previous trials as well as real-world use, the benefit-risk profile of Xofigo in its approved indication remains favorable," it stated. No patients were still actively receiving Xofigo since it had been dosed earlier in the program.

The drug is already approved for castration-resistant prostate cancer with symptomatic bone metastases and no known visceral metastases. Bayer sees it as one of its key growth drivers; it is in several additional prostate cancer trials and is also being studied in breast cancer and multiple myeloma. In the third quarter, currency-adjusted sales growth for the product was nearly 25% to €102m.

Bayer has been active in deal making recently, paying $400m upfront to access two TRK inhibitors from Loxo Oncology then signing a peptide drug discovery agreement with Japan's PeptiDream. *(Also see "Loxo's Tissue-Agnostic Approach Brings $400m Upfront From Bayer" Scrip, 14 Nov, 2017.)*

In oncology, Bayer is hoping to build growth through its radiotherapy, targeted small molecule and antibody-drug conjugate products and pipeline, despite having missed the initial PD-1/PD-L1 checkpoint inhibitor immuno-oncology boat that has driven so much activity in oncology in recent times. Bayer's pipeline suffered a setback earlier this year with the Phase II failure of anetumab ravtansine in its lead indication of mesothelioma. *(Also see "Bayer And Morphosys Brush Off ADC Mesothelioma Failure" Scrip, 24 Jul, 2017.)*

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Click here to read *Bayer Shrugs Off Xofigo Sales Pressure From Study Halt*: **http://bit.ly/2Aqtgdb**

Pfizer/Merck KGAA's Bavencio Gastric Cancer Failure Not As Bad As It Seems

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The failure of **Merck KGAA/Pfizer Inc.**'s immuno-oncology latecomer *Bavencio* (avelumab) to significantly improve overall survival in a Phase III third-line gastric cancer study is a blow, but it may not be as bad as it appears, because the market is small and the trial design was more rigorous than competitors' efforts.

The companies reported Nov. 28 that Bavencio as a single agent failed the primary endpoint of the global Phase III JAVELIN Gastric 300 trial, which tested the drug as a single agent against chemotherapy (paclitaxel or irinotecan) in all comers, regardless of PD-L1 expression, in third-line treatment of 371 patients with unresectable, recurrent or metastatic gastric or gastroesophageal junction adenocarcinoma.

The safety profile was consistent with results in prior trials, the companies reported.

"The JAVELIN Gastric 300 data will be further examined in an effort to better understand the results and will also be submitted for presentation at an upcoming medical congress. The outcome of JAVELIN Gastric 300 does not have any impact on current avelumab approvals," the partners said in a statement.

Furthermore, the Phase III JAVELIN Gastric 100 study of Bavencio as a first-line maintenance therapy after induction chemotherapy in advanced gastric cancer is continuing as planned. The primary completion date is March 2019, according to ClinicalTrials.gov.

A latecomer to the immuno-oncology (IO) field, Bavencio was first approved by the US FDA in March for Merkel cell carcinoma, a rare kind of skin cancer and in May for second-line advanced bladder cancer. The companies did not report sales for the drug in the third quarter, but Merck KGaA indicated during its earnings call that it expects €20m ($23.7m) in sales for 2017.

Gastric cancer is a small indication for PD-1/L1 inhibitors relative to others, especially non-small cell lung cancer (NSCLC), but collectively the modest market approvals add up. Morningstar Research has projected that the stomach/esophageal and gastric cancer indications will each be worth $500mn in 2021. Investigators have reported that a number of factors, including high somatic burden and inflammation, suggest that gastric and esophageal cancers might respond to checkpoint inhibitors, but more research is needed to identify responders.

Merck & Co. Inc.'s PD-1 inhibitor *Keytruda* (pembrolizumab) received accelerated approval from FDA for third-line advanced gastric cancer in September, a filing supported by response rate data in a single arm Phase II study. Data from the Phase III KEYNOTE-061 second-line advanced gastric cancer study are expected in July 2019 and the Phase III KEYNOTE-062 first-line gastric cancer study has a primary completion date of June 2020.

Bristol-Myers Squibb Co. reported in November 2016 that *Opdivo* (nivolumab) met the primary endpoint of overall survival (OS) against placebo in the Phase III ONO-4538-12 study of advanced refractory gastric cancer run by its partner **Ono Pharmaceutical Co. Ltd.** But the median OS improvement relative to placebo was small at 1.2 months. Bristol declined to comment on its filing plans in this indication.

Pfizer and Merck KGaA noted in their Nov. 28 statement that JAVELIN 300 was the "first global trial of a checkpoint inhibitor versus an active chemotherapy comparator rather than placebo in this hard-to-treat patient population."

The failure is another sign that despite the success of checkpoint inhibitors over multiple indications to date, unpleasant surprises still happen. It's also a reminder of the value of randomized Phase III trial designs that include an active comparator and use the overall survival gold standard as an endpoint.

Roche's *Tecentriq* (atezolizumab) received accelerated approval from FDA for bladder cancer in May 2016, but the company announced in May of this year that the drug failed to demonstrate a significant improvement in overall survival in Phase III. Merck's Keytruda won accelerated approval for head and neck cancer in August 2016, but failed to improve OS for that indication in a Phase III study reported in July.

NOT-SO-GREAT EXPECTATIONS

BMO Capital Markets analyst Alex Arfaei said in a Nov. 28 note that the failure of avelumab in third-line gastric cancer was disappointing, but that expectations "were very low for this trial."

"In general, immune-oncology (IO) drugs have shown better activity in earlier stages of cancer perhaps because their immune-response effects take some time to manifest. Moreover, gastric cancer is a relatively small market, particularly in later stages (only ~18% of gastric cancer patients receive a 3L therapy, source: Hess et al. Gastric Cancer, 2016)," Arfaei wrote.

Arfaei also suggested that given the differences in gastric cancer trial design – Bavencio was compared to chemotherapy in a Phase III study whereas Merck's successful study of Keytruda was a single arm Phase II trial and Ono tested Opdivo against placebo in Phase III – the failure does not mean avelumab is inferior.

Avelumab is likely to show superior overall survival in the JAVELIN Lung 200 study in PD-L1 positive second-line non-small cell lung cancer, which is due to report in the first quarter of 2018, Arfaei said.

Pfizer also has interesting opportunities in terms of combination studies, including trials testing avelumab with targeted agents, such as the company's own tyrosine kinase inhibitor *Inlyta* (axitinib) in first-line renal cell carcinoma, the analyst said.

Results from the Phase Ib JAVELIN Lung 101 study of avelumab with Pfizer's ALK inhibitor *Xalkori* (crizotinib) or its investigational ALK inhibitor lorlatinib are expected by the end of the year.

"Management believes that the expected activity of IO + targeted treatments is more predictable than IO/IO combos, and is particularly optimistic about Pfizer's Avelumab + Inlyta in 1L-RCC, as well as Avelumab + Lorlatinib in ALK positive NSCLC, and Avelumab + [Pfizer's PARP inhibitor] Talazoparib in ovarian cancer. As for IO combos, Pfizer is quite optimistic about its IO triplet (Avelumab +OX-40+4-1BB; data expected mid-2018), but not about IDO or CTLA-4 +PDx combos," Arfaei said.

"Overall, we agree with Pfizer's IO approach given how far behind the company is," Arfaei concluded.

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Time Is Running Out For Industry To Prepare For Brexit, Firms Begin to Feel Staffing Effects

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Stakeholders are worried that a failure to ensure post-Brexit regulatory alignment between the UK and the EU could hit drug approvals, clinical research, trade and many other areas. It could also force the UK to set up its own regulatory regime in parallel with that of the EU.

Brexit negotiations have been proceeding at a snail's pace since the UK triggered Article 50 in March 2017, formally signaling the country's intention to leave the EU. The UK was due to find out in mid-December whether sufficient progress had been made on the "divorce" issues to allow the talks to move onto the post-Brexit UK-EU relationship.

With the continuing uncertainty and some influential politicians still openly pushing for a "no-deal" outcome, concern is mounting over the effects of Brexit on the UK life sciences sector – and particularly the people who work in it.

The implications of limiting the free movement of people for sectors such as the National Health Service and university research have been a concern since the June 2016 EU referendum. The concerns are shared by those working in both the regulatory arena and the life sciences industry. The continuing uncertainty also seems to be leading many EU citizens to consider their future prospects in the UK.

But of course, in life sciences as in many other sectors, Brexit is an EU as well as a UK problem. Just ask the European Medicines Agency, which as a result of Brexit is having to relocate from London to Amsterdam. Also ask national regulators in the other member states, many of whom are taking on new staff to deal with the expected increase in workload when the UK agency, the MHRA, is no longer part of the network.

While Amsterdam was among the top five cities in a survey of EMA staff earlier this year, it could still be some time before it's clear exactly how many of the staff will choose to relocate there. The survey found that for the five cities in group 1 (those most favoured), retention rates would be 65% or above, while for group 2 it would be between 50% and 65%, and for group 3, 30-49%.

The figures are important because they will determine the extent to which the agency is able to carry out its activities during and after the relocation. For the cities in group 1, which included Amsterdam, the agency said that core activities such as new drug approvals and safety monitoring would largely be maintained, albeit with possible delays. However, its ability to carry out strategic activities in areas like antimicrobial resistance, collaboration with HTA bodies, and medicines availability would be significantly affected.

The EMA has already suspended some operations under its business continuity plan, which was published in full on Oct. 13 and set out two scenarios in the face of what the agency calls "this unprecedented situation." These are ensuring a "business as usual" scenario as far as possible during the relocation or, failing that, invoking a range of compensatory measures in the plan such as prioritizing its activities and re-allocating freed-up resources.

> 'The fact that we have no idea what is going to happen is a real, real problem'

INDUSTRY WORRIED

The continuing uncertainty over the Brexit outcome now appears to be starting to cause recruitment problems within the UK pharmaceutical industry. This would be a major headache given that companies operating in the UK rely heavily on talent from across the EU.

Confirmation of this trend came in October when Mene Pangalos, an executive vice president at Anglo-Swedish giant **AstraZeneca PLC**, told a House of Lords Science and Technology Committee hearing that "I had my first conversations where I started to become worried about the impact of Brexit on our employees" – both UK employees in Sweden and elsewhere in Europe, and EU employees working for the company in the UK.

"They are worried about the uncertainty, and obviously we are being as positive as we can be, in terms of saying 'we will look after you', but the fact that we have no idea what is going to happen is a real, real problem, and we are starting to see people turn us down now in the UK because they don't know what the outcome will be in terms of future employment," Pangalos said. "Even though we tell them we have no doubt that great talent is going to be accepted down the road, they haven't got that certainty and so they are saying until we've got it we'd rather go and work somewhere else."

These concerns were echoed by Dave Allen, a senior vice president at **GlaxoSmithKline PLC**, who told the committee it was important to think hard about the effects of Brexit on the science base and the UK's ability to attract talent. "With a population of 65 million,

we cannot expect to have all the talent we need all of the time," Allen said. Companies are asking people to come to the UK to become part of the life science infrastructure "and we need to make it simple for them to do that." The skills they bring are critical, Allen said, and without them "we are not going to compete with countries that are prepared to make it much easier for people to move and thrive in those countries."

FUTURE OF REGULATION

As for the future of the UK and EU regulatory system itself, companies and regulators alike have made it clear that their preferred option is some kind of collaboration agreement that preserves the current alignment of UK and EU regulations over time – and preferably allows the UK to continue its input into the EMA.

In July industry was encouraged by a letter to the *Financial Times* in July from two senior ministers who said the UK "would like to find a way to continue to collaborate with the EU, in the interests of public health and safety." In a return letter, a number of top pharmaceutical company executives said that "patient safety and public health throughout Europe rely on the current pan-European regulations and standards applying to the research, development, manufacture and supply of medicines."

But the ministers also said that if the "desired relationship" with the EU failed to materialize, the UK would have to establish its own regulatory system. Pretty much everything therefore hangs on the final outcome of the Brexit process.

In the event of a "soft" exit – for example, continued membership of the EU single market and customs union, if only for a transitional period – the UK could probably carry on playing a part in the EU regulatory system in some form or other. But if the outcome is "no-deal" and the UK simply crashes out of the EU, the situation would be entirely different. EU centralized drug approvals would no longer be valid in the UK, and the country would have to revamp its regulator, the Medicines and Healthcare Regulatory products Agency, to act as an independent body carrying out its own new drug assessments, with all the resource implications this would entail.

There are risks too for the UK's attractiveness as a location for clinical research. At present the country is routinely included in multinational trials in the EU, but this could change once the UK is no longer a member state. It may also not be able to benefit from the new EU Clinical Trial Regulation, which will streamline the system by offering companies a single submission portal and a central clinical trials database.

As reported in October, the UK is planning to adopt a "Withdrawl Bill" that will transpose all pre-Brexit EU legislation onto the domestic statute books and repeal the European Communities Act of 1972, which gives EU law supremacy over UK domestic law. But because of delays with the portal/database system, the provisions of the CTR will not now apply until the second half of 2019, i.e., after the formal Brexit date of March 29, 2019. According to the Department for Exiting the EU, this means the CTR will not be included in the bill, which would effectively exclude the UK from the proposed system, unless some other regulatory arrangements could be reached.

COMPANIES, BE PREPARED

The longer the negotiations take to move on from the so-called "divorce settlement" that the UK will have to pay as part of Brexit to the nature of the future relationship, the more likely it is that life science companies will need to prepare for a "no-deal" scenario in which the UK abruptly leaves the EU and automatically falls under World Trade Organization rules.

If no reciprocal regulatory arrangements have been agreed, companies in the UK with marketing authorizations or orphan designations for centrally approved drugs will need to transfer them to a license holder established in the EU if they want to carry on marketing them there. Similar transfers of responsibility will be required in the case of the Qualified Person for Pharmacovigilance, and the UK will become a third party as far as exports of APIs and finished products to the EU are concerned.

To help companies plan for these and other eventualities, the EMA has produced a Brexit Q&A document, which was complemented in November with new practical guidance on how to go about transferring their MAs and other functions.

But time is running out, and while the biopharmaceutical industry has called on the negotiators to agree a transitional period after Brexit, companies have been advised to take action now rather than gamble on such a period being agreed. As the EMA's Agnès Saint-Raymond told companies at a Drug Information Association meeting in October: "You will have to decide whether to implement some changes now."

But when is now? Virginia Acha of the UK Association of the British Pharmaceutical Industry pointed out at a TOPRA symposium that same month: "Negotiators have until 2019. We don't… so at what point do we say 'you just passed my no-go'?"

Companies that fail to make their own preparations risk being left behind in the mayhem that a chaotic Brexit could bring.

The nightmare scenario on what's being called "Day 1" is potential drug shortages for patients if drugs are stuck at borders, allowed neither into the UK from the EU or into the EU from the UK. Nobody wants that.

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Outcomes Claim May Help Amgen Make Case For PCSK9 Inhibitor Repatha

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Amgen Inc.'s injectable PCSK9 antibody *Repatha* (evolocumab) has secured the long-sought labeling claim for reducing the risk of cardiovascular events in patients needing greater lowering of LDL cholesterol, but the real-world impact in terms of prescribing and payment remains to be seen.

The company announced on Dec.1 that the US FDA expanded labeling for Repatha to include a claim for preventing heart attacks, strokes and coronary revascularizations in adults with established cardiovascular disease.

The FDA also approved Repatha for use as an adjunct to diet, alone or in combination with other lipid-lowering therapies, such as statins, for the treatment of adults with primary hyperlipidemia to reduce LDL cholesterol. The agency had held off on approving Repatha and **Sanofi/Regeneron Pharmaceuticals Inc.**'s competing PCSK9 inhibitor *Praluent* (alirocumab) for this broader patient population, pending outcomes data.

Repatha was originally approved in August 2015 for use in high-risk patients not achieving goals with "maximally tolerated" available therapies (statins and other lipid lowering therapies) and did not have a claim for CV risk reduction.

Amgen says that following the label change, its focus remains on high-risk cardiovascular patients.

The label change was supported by results from the FOURIER outcomes study, which demonstrated a significant reduction in the risk of heart attack (27%), stroke (21%) and coronary revascularization (22%) with Repatha. There was also a 20% significant reduction in the secondary endpoint related to major adverse cardiovascular events in the study.

However, the reduction for the primary composite endpoint was lower than some expected, at 15%, and there was no significant mortality benefit in the study. Although mortality benefits have not been seen in high intensity LDL lowering trials against moderate statins, the lack of an impact prompted the Institute for Clinical and Economic Review (ICER) to lower its value-based pricing benchmark for Repatha. *(Also see "Amgen Faces New ICER Roadblock To Repatha Reimbursement" Scrip, 15 Jun, 2017.)*

The label change has been expected and analysts see the language as clean. In a Dec. 1 note, Mizuho Securities analyst Salim Sayed pointed out that FDA removed language regarding patients being on a maximally tolerated statin, as the FOURIER study tested Repatha with an "optimized stable lipid-lowering therapy," ideally including a high intensity statin but at least a moderate intensity statin, with or without ezetimibe (**Merck & Co. Inc.**'s *Zetia*).

"While reflective of the trial (69.3% of patients in FOURIER on high-intensity statin, 30.4% on moderate-intensity statin), we believe this language was not exactly expected by Street, is marginally above expectations, and bodes well for the continued increased uptake of Repatha (and the PCSK9 class), especially in high-risk patients who require additional LDL-lowering but may not already be on max-tolerated statin," Sayed said.

Roger Longman, president and CEO of the reimbursement intelligence company Real Endpoints, commented that the new label is marginally but not dramatically better.

The change in language regarding statins may help a little bit as some health plans have been insisting on the "letter of the law" in terms of requiring that patients have had a maximally tolerated statin prior to getting a PCSK9 inhibitor. This can significantly increase the burden for potential prescribers in that they need to prove a patient has been adherent to a maximally tolerated statin over a period of time, Longman said.

New labeling could, at least temporarily, give Repatha an edge over Praluent, which is still approved for use in high-risk patients not meeting goals on a maximally approved statin, and does not yet have a claim for reduction of cardiovascular risk. Results from the ODYSSEY CV outcomes study of Praluent are due early in 2018.

Sales of Repatha started to outpace Praluent in the fourth quarter of 2016. *(Also see "PCSK9 Sales Still Slow, But May Get Boost From Label, Guideline Changes" Scrip, 4 Aug, 2017.)* Amgen reported $89m worldwide for Repatha in the third quarter of this year, while Sanofi/Regeneron reported €42m ($49m) during that period.

The CV risk reduction claim also may help boost acceptance with prescribers and payers, although the data from the FOURIER outcomes study supporting the filing have been known for some time and have not had a big impact on sales.

Pricing of PCSK9 inhibitors has proven very controversial. Praluent and Repatha both carry an annual list price of about $14,500. And both have faced challenges breaking into the market due to restrictions on utilization, even for patients who meet the high-risk parameters of labeling.

Many critical cost-effectiveness studies have been published. Some researchers have concluded that relative to adding Zetia on top of statins, the PCSK9 inhibitors would be cost-effective if their list price was cut by 71% to $4,215 annually or less.

Amgen funded its own study that found $9,669 annually is cost-effective. The company has also offered value-based pricing deals to plans, guaranteeing a refund in the case a patient has a heart attack or stroke while on Repatha.

The annual net price nowadays in the US for PCSK9 inhibitors is in the $8,000 to $9,000 annual range, Longman commented.

Following a label change, access may be slightly better but plans will still put significant hurdles in the way of prescribing Repatha until the price comes down to a level equivalent to new branded small molecule cardiovascular drugs, such as **Novartis AG**'s heart failure *Entresto*, and until adherence can be demonstrated, Longman maintained.

A key issue for many plans is they don't see much more adherence to a PCSK9 inhibitor than for a statin, so there is the "twin problem" of price and adherence, he explained.

"If somebody can solve the adherence problem and solve the price problem, that would be a game changer," Longman said.

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The Rebate Debate: Forbes Panelists On How Rebates Trickle Down To Patients

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As the drug industry explores more transparent pricing tactics, one growing question – of the many related to the rebates drug manufacturers provide to payers through contract negotiations – is whether rebates should benefit patients directly at the point of sale instead of going to payers.

The challenge when it comes to navigating the drug pricing system is understanding who benefits throughout the distribution channel. The Pharmaceutical Research & Manufacturers of America has focused on how downstream players contribute to drug cost increases, releasing another report Nov. 30 on how pricing is affected along the supply chain. The industry organization has also targeted pharmacy benefit manager's handling of rebates as part of its efforts on drug pricing, launching the "Share the Savings" campaign earlier this year.

Whether or not the savings payers accrue from rebates trickles down to the patient is getting increasing attention in an era of increasing high-deductible health plans.

Drug manufacturers use rebates as leverage with payers to negotiate a strong position on formularies, at the same time reducing the cost of the drug to the healthcare system. The intention is that the savings are passed onto consumers eventually by payers in the form of lower premiums, but patients with a high-deductible health plan do not get the benefit of the rebate and pay full price for the drug at the pharmacy.

The issue, which is under debate at the Centers for Medicare & Medicaid Services, came up at the Forbes Healthcare Summit Nov. 30, with conflicting ideas about how redirecting rebates to point-of-sale would impact patients.

PhRMA CEO Stephen Ubl said the group's members have saved the healthcare system $100m in rebates in discounts over the last several years.

"The problem is the fruits of those PhRMA negotiations are not making their way to patients at the point of sales. It's a very Byzantine system," he said. "The research shows that patients are too often paying the full list price, even as drug spending has moderated."

Timothy Wentworth, CEO of Express Scripts

He said research PhRMA has done shows 50% to 80% of the rebate could be passed onto consumers at the point-of-sale with a very modest impact on premiums of about 1%.

However, CMS Administrator Seema Verma said point-of-sale rebates could have negative consequences on insurance premiums. "Our data shows that it actually increases premiums so that would be a cost to the tax payer," she said.

Nonetheless, CMS is exploring the idea, she said. The agency issued a proposed rule in November to consider requiring Medicare Part D plans to apply at least a percentage of the manufacturer rebate to reducing beneficiary cost sharing at the point-of-sale. *(Also see "Medicare May Require Part D Plans To Provide Point-of-Sale Rebates" - Scrip, 17 Nov, 2017.)* CMS is seeking public comments on the proposal until Jan. 16.

Express Scripts Holding Co. CEO Timothy Wentworth insisted that pharmacy benefit managers as an industry are open to considering the change and have the ability to precisely administer rebates at the point of sale. "The marketplace has generally not wanted to move in that direction largely because the payers, taking the risk on the overall cost of the overall population, have concluded they still want the rebates to flow through to their overall cost management."

On the drug spending issue, drug manufacturers and PBMs have been on opposite sides of the debate, with drug manufacturers largely pointing a finger at PBMs and other players in the distribution system for taking a cut of the drug's net price and PBMs and payers blaming pharmaceutical manufacturers for high drug prices.

The two opinions were on display during the panel. "Plans and PBMs are pocketing billions in rebates and discounts and it's not making it to the patient," Ubl said. Express Scripts' Wentworth fired back, "The real red herring is the drug company, and they are taking the price up and then that drives everything else."

Wentworth insisted Express Scripts retains 10% of the rebate for its services and that 90% flows through to the plans that then decide how they want to invest the savings. Those decisions usually come down to a choice of reducing out-of-pocket costs for patients that are receiving the drug or lower premiums, he said.

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Congratulations to our Scrip Awards Winners »

2017

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Celebrating the BEST in Health

We would like to thank everyone who attended the 13th Annual Scrip Awards, held on November 29th at the Hilton on Park Lane, London.

The evening, hosted by Alexander Armstrong, was a celebration of excellence across all parts of the value chain and recognized both corporate and individual achievements.

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The winners

Best Technological Development in Clinical Trials – Patient-focused
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Best Technological Development in Clinical Trials – Sponsor-focused
Medidata Synthetic Control Arm

Best Company in an Emerging Market
(Sponsored by ICON)
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Best Partnership Alliance
Cancer Research UK and Bicycle Therapeutics' agreement for BT1718

Financing Deal of the Year
Verona Pharma's NASDAQ listing

Best Contract Research Organization – Specialist Providers (Sponsored by Oracle Health Sciences)
WuXi NextCODE

Best Contract Research Organization – Full-Service Providers (Sponsored by Oracle Health Sciences)
ICON

Licensing Deal of the Year
(Sponsored by Worldwide Clinical Trials)
Crescendo Biologics and Takeda Pharmaceuticals for Humabody-based therapeutics

Executive of the Year (Private companies and those with market cap of <$1BN)
(Sponsored by Lachman Consultants)
Kevin Lee, CEO of Bicycle Therapeutics

Executive of the Year (Companies with market cap >$1BN) (Sponsored by Lachman Consultants)
Elias Zerhouni, president of global R&D at Sanofi

Business Development Team of the Year
EUSA Pharma Business Development Team

IQVIA's Clinical Advance of the Year Award
(Sponsored by IQVIA)
Genmab and Janssen Biotech's CASTOR and POLLUX studies

Community Partnership of the Year
(Sponsored by Medidata)
AstraZeneca's Active Science Program

WuXi AppTec's Biotech Company of the Year Award
(Sponsored by WuXi AppTec)
BioNTech

INC Research/inVentiv Health's Best New Drug Award (Sponsored by INC Research/inVentiv Health)
Roche's Ocrevus

PPD's Pharma Company of the Year Award
(Sponsored by PPD)
Celgene

Scrip's Lifetime Achievement Award
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Rolf Stahel

AbbVie's Post-Humira Strategy Is About Leveraging Its Top Seller

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For **AbbVie Inc.**, Humira (*adalimumab*) is always the elephant in the room – although the pharma has valid reason to believe the immunology powerhouse will continue to drive US sales growth in 2022, it has begun to pump up investor expectations for late-stage candidates that will expand its immunology portfolio and, it believes, leverage Humira's broad utility to launch successfully and grow solidly.

Two AbbVie executives detailed this strategy during the Evercore ISI Biopharma Catalyst/Deep Dive Conference Nov. 29 in Boston, providing rationale for the optimistic guidance presented during the firm's third quarter earnings call on Oct. 28. *(Also see "New AbbVie Guidance Sets High Bar For Post-Humira Pipeline" - Scrip, 28 Oct, 2017.)*

Asked to overview AbbVie's strategy and culture since its spinout from **Abbott Laboratories Inc.** in 2013, Chief Financial Officer Bill Chase acknowledged that Humira eventually going off-patent was seen as an issue the new company would have to address in an ongoing, comprehensive way. The Chicago-area firm recently got some clarity on how long it can stave off biosimilars of adalimumab as a settlement with **Amgen Inc.** determined that a US biosimilar (Amjevita, approved by US FDA in 2016) would not launch until 2023, but that one could hit market in Europe in late 2018. *(Also see "Biosimilar Humira Blocked Until 2023, But Time Could Clear Commercial Path" - Scrip, 28 Sep, 2017.)*

AbbVie now expects Humira to face biosimilar competition in Europe during the latter part of next year's fourth quarter, Chase said, meaning ex-US sales of anti-TNF agent would peak in 2018. But he expects US growth to continue climbing for several more years, led by a strategy to increase penetration in a host of label indications. *(Vice President-Therapeutic Areas & International Development Shao-Lee Lin recently outlined some of this strategy for Scrip during an interview at the American College of Rheumatology (ACR)/Association of Rheumatology Health Professionals (ARHP) annual meeting in San Diego.)*

Chase said that out of the gate in 2013, AbbVie leadership understood that Humira would eventually go off-patent and despite some reason to expect that that would happen "later rather than sooner," the new company needed to develop a strategy for overcoming the related loss of revenue.

"That was the first rallying cry," he noted. "And frankly, before we even spun out of Abbott, we were laser-focused on building out pipeline because we recognized at some point, we would need to have a portfolio of assets that would allow us to continue to grow. That's the first issue. The second issue is coming out of Abbott, we were suddenly free to pursue a management of the company that was in line with what a biotech or biopharma investor wanted."

RESPONSIBILITY, FREEDOM FOR CHOOSING

Along with the responsibility for replacing Humira's revenue, this gave AbbVie the freedom to ask itself what it wanted to be and how it wanted to get there, Chase said. An emphasis on specialty indications with high unmet need emerged as a strategic focus.

"We gave ourselves a mandate to only bring forward disease therapies that were highly differentiated. And we were just laser-focused on that. And we went from having a very broad portfolio of areas that we were interested in [and] narrowed it down," Chase said. The spinout resulted in a new engagement for the team running AbbVie, he added. "There is something to be said to wake up one day and suddenly realize you're out on your own and you control your own destiny. And that was driven through the entire organization. We gave ourselves very long-range goals."

While EU Humira business will fall into a "manageable decline" of between 15%-20% by 2020, Chase predicted, US sales growth in the range of $1.5bn-$2bn per year should continue. But the product's ultimate longer-term role is to help drive AbbVie's future business, he said.

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"Humira is an absolutely important asset for many reasons, right? But at the end of the day, Humira … is going to lose exclusivity," Chase told the conference. "And so the role of Humira in our portfolio is to ultimately generate cash, to fund the pipeline in the near term and ultimately to allow us to leverage our other immuno assets and allow those to grow to their maximum potential."

"Over and above Humira, there is something that we refer to as the AbbVie growth platform, which is a book of business that has phenomenal growth prospects," he continued. "It's a business that's going to go from about $9.5bn in sales this year to an estimate that we have in our long-range plan … of $35bn risk-adjusted by 2025."

Several qualities helped AbbVie to focus and executive developing differentiated products that could better serve existing needs or meet unmet needs, Scott Brun, divisional VP of infectious diseases and immunology development said. Some of that derived from an ability to remain "local" in decision-making despite operating a company with big pharma scale.

"Our discovery, our development, our business development teams are all close enough in terms of our location at headquarters with our leadership that we're able to collaborate on a real-time basis and make sure that everything that we are thinking about and doing is aligned," Brun told the conference. "Now I think the other thing is a previous mentor of mine said, 'Good medicine is good business.' And the way we think about that is [to ask] what exactly is it that the patient is looking for out there? And it comes to the whole point of differentiation."

That was an important departure in thinking for the spinout, he added, because Abbott had had a focus on "fast follower" products that provided perhaps just an incremental benefit over a competitor's established product.

"[Now], we're trying to build molecules right up front to say, 'How can we really make a difference which makes late-stage development potentially more streamlined and efficient?'," Brun said. "With our selective JAK1 inhibitor [upadacitinib], for example, [we're] doing a Phase II study early on in TNF-inadequate responders, realizing, speaking with our commercial group, that this indeed is a growing group."

AbbVie also employs what Brun calls a "cradle-to-grave development model" that provides continuity in drug development, so that what is envisioned early on hopefully is what is brought to the finish line.

"So you don't get these kind of discontinuities, where someone might have done a very clever proof-of-concept experiment, but then that transition to the group that ultimately has to translate it to regulatory approval and then market access considerations may have a different vision," he explained. "Now, again, those teams evolved, they have the proper expertise. But I think that continuity of vision really helps us a lot."

Additionally, AbbVie takes a somewhat flexible budgetary approach to R&D, which enables it to act nimbly when a new opportunity appears, Brun said. "We can really follow the science," he said. "R&D is no longer a zero-sum game, where we have an absolute allocation. And if we want to do something new, we've [don't have] to slow down or stop something else. If we see something that we're excited about, we can come to [Chase], we can make our case and know that if we can make a strong argument, there's the potential to add that to our portfolio."

HEAD-TO-HEAD TESTING IN PHASE III

Central to the post-Humira plans are a pair of Phase III candidates, upadacitinib anti-IL23 risankizumab. AbbVie has upadacitinib in six Phase III trials just in rheumatoid arthritis to learn where it may offer treatment advantages over both Humira and competitor products, Brun said. *(Also see "AbbVie's New Generation JAK inhibitor Looks Good But CV Specter Looms" - Scrip, 12 Sep, 2017.)*

Rizankizumab, meanwhile, is being tested head-to-head against both Humira and **Johnson & Johnson**'s *Stelara* (ustekinumab) in psoriasis. *(Also see "Is Triple Phase III Triumph for AbbVie's Risankizumab In Psoriasis Good Enough?" - Scrip, 27 Oct, 2017.)* Although some safety issues have been seen with both candidates, Brun pointed out that in one-year data risankizumab is outperforming Stelara in PASI 100 (Psoriasis Area and Severity Index) scores. These head-to-head studies will help AbbVie build a case for adoption of its new therapies for harder-to-treat patients, he said. *(Also see "Safety Issues Not Dampening AbbVie Optimism For Humira Successors" - Scrip, 2 Aug, 2017.)*

"At one year, we're seeing PASI 100 scores complete clearance of 55% to 60% compared to Stelara within the same studies running 20% to 30%," Brun said. "Also importantly, we've seen that in patients with inadequate response to Humira at week 16 within a head-to-head study, [by] is switching to risankizumab at week 52, you've got, I think, close to 66% of patients at a PASI 90 score versus only [about 20%] who remained on Humira. So again, [these studies are] demonstrating the power of this agent in patients who've not been successful with prior biologics."

AbbVie projects those two drugs to combine for $11bn in annual sales by 2025, meaning they are seen as playing crucial roles in picking up where Humira will leave off as biosimilar competition erodes that product's sales. When AbbVie unveiled its new long-term guidance on Oct. 28, BMO Capital Markets analyst Alex Arfaei called the projections overly optimistic, saying they appeared to be based on assumptions of not much change occurring in pricing, access and biosimilar competition within immunology. He said AbbVie's growth prospects through 2021 seemed excellent, but reserved judgment on prospects beyond that.

GETTING ITS PART OF AN $89BN MARKET

Chase pointed to the huge overall market these products will be targeting by the middle of the next decade. The 2025 sales guidance also incorporates third-party projections, the exec added.

"[If] you look at the autoimmune segments that we're going to be competing in by 2025, we're looking at an $89bn billion market," Chase said. "If you take these assets … and look at the aspirational market share that we've placed on them, it's high single digits, right? Yes, they're large numbers, but recognize Humira only has 32% of the market, [yet] It's a $20bn product."

Risankizumab and upadacitinib could meet AbbVie's guidance in 2025 by achieving market penetration in the high single digits, he said. To achieve this, AbbVie will need to continue with one of the values it brought from parent Abbott, Chase noted, which is the importance of execution. While AbbVie from the start decided to focus tightly on differentiated products targeting unmet medical needs, it also saw value in leveraging a corporate structure with clinical operations in 60 countries and commercial operations in 100, he explained.

"The final part of the story will be commercial execution," Chase said. "And recognize when these products come to market in 2020 – in 2019, Humira will still be a very important, growing product for the company."

"We will go from a company that is offering Humira across a broad array of indications to a company that is offering a portfolio of assets that we feel will have differentiated capabilities in hard-to-treat patients and the ability to marry that entire product offering, wrap it in our patient programs, which we absolutely believe are best-in-class and also tie it to Humira, where at this point, Humira's new patient share [still] far exceeds any of its competitors," he added. "We feel that that will enable us to get quicker uptake of the new brands and put them on a course to ultimately realizing that potential."

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Sublocade Approval Grows Indivior's Opioid Addiction Franchise In Competitive Market

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FDA approval of **Indivior PLC**'s *Sublocade* (buprenorphine extended-release) gives healthcare professionals another weapon to fight the growing opioid addiction epidemic in the US. It also gives the UK-based company another product in the battle to maintain its dominant share of the opioid use disorder (OUD) market.

Indivior has seen the market share for its blockbuster OUD treatment *Suboxone* (buprenorphine/naloxone) sublingual film dip slightly as price-sensitive payers cut back on brand-name drugs to reduce opioid use and as sales have increased for **Alkermes PLC**'s competing product *Vivitrol* (naloxone). Sublocade could give Indivior's OUD franchise the boost it needs as Suboxone and the company's sublingual tablet *Subutex* (buprenorphine) are challenged by generic versions of buprenorphine and Vivitrol. However, it also faces new competition from another long-acting buprenorphine injection – **Braeburn Pharmaceuticals Inc.**'s CAM2038, which has a Jan. 19 user fee date.

Buprenorphine is a partial agonist of mu-opioid receptors in the brain, which mediate the drug-liking, or pleasure, associated with opioids. Indivior's depot product Sublocade delivers sustained plasma levels of buprenorphine. It was approved on Nov. 30 and Indivior will make it available in the US during the first quarter of 2018.

Jefferies analyst James Vane-Tempest projected peak annual sales of $1.3bn by 2025 versus Indivior's guidance of more than $1bn in peak sales. In a Nov. 30 note, Vane-Tempest said that "we expect the ramp-up in demand to be relatively protracted as we expect initially the depot will primarily be used to treat those with severe cases."

Indivior set the Sublocade wholesale acquisition cost (WAC) at $1,580 per month, or $18,960 per year, for both the 100 mg and 300 mg monthly doses. Vane Tempest previously estimated the cost at $8,000 per year after discounts. The $1,580 monthly WAC price – before rebates or discounts – falls in the middle of a $1,000 to $2,000 range that company officials discussed on Nov. 2 during Indivior's third quarter earnings call.

CEO Shaun Thaxter said then that "we believe that the right price for this technology lies somewhere in the range of the pricing that is already established and accepted for injectable depot technologies. So if we look to the schizophrenia category, and indeed our own addiction category where there's already a monthly depot, you would say, 'Well, if I look around, surely you guys must be thinking somewhere in the $1,000 to $2,000 a month range,' and we would say, 'Yes, we are."

Later in the call, Thaxter noted "the feedback that we're getting from payers is [a] very high degree of comfort within this range" based on the value Sublocade provides.

BETTER ADHERENCE, LESS ABUSE

Sublocade offers multiple potential benefits over Suboxone and other oral buprenorphine products. The once-monthly injection could improve patient adherence with OUD therapy compared with daily self-administered treatment, which would be especially attractive to payers who want to make sure patients are taking medicines as prescribed to get the full effect of costly new drugs.

Since Sublocade must be administered by a health care professional, it's also less likely that patients could misuse the product and that the drug could be diverted for illegal sales and use.

The Sublocade label has a black box warning against self-administration of an intravenous injection, because the drug quickly forms a solid mass – the slow-release depot that enables once-monthly administration – that can cause a blockage, tissue damage or an embolus, which can lead to a blood clot.

FDA approved the drug with a Risk Evaluation and Mitigation Strategy (REMS) that requires pharmacies and health care professionals to undergo special training regarding dispensing and administration of Sublocade, which will be provided to health care professionals under a restricted distribution program. The REMS is designed to prohibit distribution directly to patients for self-administration, misuse or illicit distribution of the product.

Indivior's product is the first once-monthly injectable buprenorphine product approved to treat moderate-to-severe OUD in adults who've initiated treatment with a transmucosal buprenorphine-containing product and have been on a stable dose for at least seven days. Sublocade is intended for administration by a health care professional in combination with counseling and psychosocial support.

The FDA's statement on the approval notes that regular adherence to medication-assisted treatment with buprenorphine reduces opioid withdrawal symptoms and the desire to use opioids. It also decreases the pleasurable effects of opioids when those drugs are used while individuals are taking buprenorphine, which can make continued opioid abuse less attractive.

Sublocade's approval was supported by two clinical trials, including a randomized trial and an open-label study, that enrolled a total of 848 adults who achieved a stabilized dose on Suboxone film. Response to medication-assisted treatment in both studies was measured by urine drug screening and self-reporting of illicit opioid use during a six-month treatment period. Sublocade-treated patients had more weeks without positive urine tests or self-reported opioid use, and more patients had no evidence of illicit opioid use compared with the placebo group.

BETTER EFFICACY THAN CAM2038?

Indivior is highlighting that Sublocade completely blocked drug-liking effects for a full month in most patients, with a steady state of delivery of at least 2 ng/mL of buprenorphine over a month.

Numis Securities Ltd. analyst Paul Cuddon noted in a Dec. 1 report that the Sublocade approval and label "reinforces a key competitive advantage (vs [Braeburn's] CAM2038) of the product's 'bloc(k)ade' of drug-liking given the high circulating levels of buprenorphine in the blood over an entire month," which he said is unlike the Braeburn candidate.

Braeburn is seeking approval for both once-weekly and once-monthly injections

of its CAM2038 for the initiation, stabilization and maintenance treatment of OUD without any kind of lead-in treatment with Suboxone or other oral buprenorphine products.

Analysts noted the significance of FDA's approval for both doses of Sublocade; the label calls for initial dosing at 300 mg for the first two months and 100 mg monthly doses thereafter with the possibility to go back up to 300 mg as needed. During the FDA advisory committee review at the end of October, some of the panelists questioned whether or not prescribers should be allowed to increase the maintenance dose to 300 mg.

"We are particularly encouraged that not only was the higher dose approved, but the recommended dose is '300 mg monthly for the first two months followed by a maintenance dose of 100 mg monthly,' and that 'the maintenance dose may be increased to 300 mg monthly for patients who tolerate the 100 mg dose, but do not demonstrate a satisfactory clinical response,'" Jefferies' Vane-Tempest wrote.

Indivior does have a challenging marketing task ahead, since the company acknowledged during its third quarter call that branded OUD treatments are losing favor among managed Medicaid health care plans.

COMPETITIVE RISK, OPTIMISTIC EXPECTATIONS

CEO Thaxter said "our Suboxone film business has remained resilient, ending the year-to-date period with an average share of 58%. Although this was down three percentage points from the previous year, I'll remind you that this was achieved in the face of intense competition from generic and branded competitors. Where we have lost this share has been largely concentrated in the most price-sensitive payers – and for us, less profitable payers – that prioritize generic offerings."

Indivior does not break out individual product sales in its earnings statements, but noted that Suboxone accounts for the majority of its revenue, which increased 4% to $828m for the first three quarters of 2017 versus $799m for the prior year's first three quarters. Billion-dollar-plus projections for Sublocade would appear to put the new product on par with Suboxone.

Competitor Alkermes has a long way to go with Vivitrol to catch up with Suboxone, but sales of the mu-opioid receptor antagonist – a once-monthly injection approved for the treatment of alcohol dependence and for the prevention of opioid dependence relapse – rose 24% to $69.2m in the third quarter versus $55.8m for the same quarter in 2016. Total 2017 sales are projected at $265m to $275m.

Alkermes CEO Richard Pops said during the company's third quarter call that Vivitrol has about a 5% share of the OUD market, but the number of prescribers is growing at about 30% per year. He indicated that the company is not worried about competition from Sublocade, because approval of long-acting buprenorphine injections should boost Vivitrol's use as well.

"On the long-acting injectable BUPs, we think those are important medicines," Pops said on Oct. 26. "And I think it has a salutary effect in the market that if more doctors are trained to access branded medicines from specialty pharmacies and give injections and monitor patients on a monthly basis, that's exactly the type of medicalization of this treatment paradigm that is necessary for more expanded use of Vivitrol."

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Sanofi's Dengue Vaccine Health Warning Seen Hitting Product's Sales

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Sales prospects for **Sanofi**'s dengue vaccine Dengvaxia took a big hit when the French group admitted that use of the world's first approved shot against the mosquito-borne virus will be curbed due to evidence it can worsen the disease in people who have not previously been exposed to the infection.

Sanofi said in a statement Nov 29 that a new analysis of long-term clinical trial data on the vaccine showed "Dengvaxia provides persistent protective benefit against dengue fever in those who had prior infection. For those not previously infected by dengue virus, however, the analysis found that in the longer term, more cases of severe disease could occur following vaccination upon a subsequent dengue infection."

Sanofi is requesting a label update to highlight that the vaccination should not be recommended in patients not previously infected with Dengue.

The company is booking an after-tax charge in its fourth-quarter results of around €100m ($118.6m) due to the likely impact on sales. But Sanofi said the announcement did not affect its full-year guidance of broadly stable earnings per share at constant exchange rates.

The Paris-based company had had high expectations for Dengvaxia when it was launched two years ago. At the time, Sanofi described it as a potential blockbuster, but the dengue fever jab had a slow start and sales in 2016 were a paltry €55m.

Its performance has dropped even more steeply this year: Dengvaxia sales for this year's third quarter were only €4m, a 90% slide from the €30m registered for the same 2016 period, bringing its sales so far this year to just €22m ($25.5m).

The slide is expected to get worse after the latest health warning. Analysts at Credit Suisse called the development "a major negative" for Dengvaxia.

"We believe that this will seriously impact the potential for the vaccine in nationwide vaccination programs, even in high-risk countries. We also believe that this eliminates the potential of Dengue as a traveler vaccine in the developed world," analysts at Credit Suisse said in a reaction note on Nov. 30.

They slashed their peak sales forecast for Dengvaxia from $300m to $10m.

But Dengvaxia's troubles should offer an opportunity for Japan's **Takeda Pharmaceutical Co. Ltd.**, which is developing a rival vaccine that it hopes will perform better.

Called TAK-003, Takeda's candidate prophylactic vaccine for dengue is in Phase III testing and data has shown activity across all serotypes.

Published online 30 Nov 2017

More Vaccine Disappointment For Sanofi As First C Diff Toxoid Vaccine Fails

ALEX SHIMMINGS alex.shimmings@informa.com

The failure of **Sanofi**'s investigational vaccine against *Clostridium difficile* after a planned interim analysis of a Phase III study showed it was unlikely to meet its primary endpoint raises some questions over the therapeutic approach of targeting a vaccine against *C. difficile* toxins, and will delay development of one of its rivals.

The interim analysis and decision to terminate development also comes just days after new data reduced the commercial potential of Sanofi's pioneering dengue fever vaccine, *Dengvaxia*.

The failed Cdiffense study was designed to test the vaccine, known as ACAM-CDIFF, in a subpopulation at risk of *C. difficile* infection. It assessed its efficacy in preventing the onset of symptomatic primary CDI confirmed by polymerase chain reaction in adult subjects aged ≥50 years who are at risk for CDI and have received at least one injection. Planned enrollment was 16,500 patients.

C. difficile is a spore-forming pathogen that typically causes symptoms in individuals with altered gut microbial flora, releasing toxins – the main ones are known as A and B – that can result in a range of disease manifestations from asymptomatic colonization to diarrhea, pseudomembranous colitis, toxic megacolon, intestinal perforation, or death.

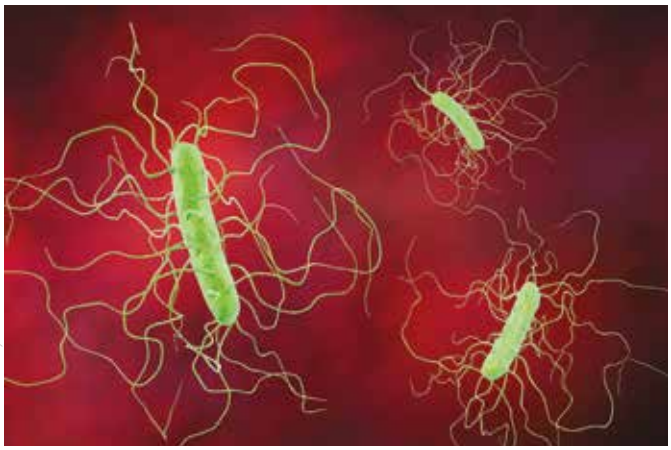
ACAM-DIFF is one of a number of candidates designed to target the toxins produced by *C. difficile* rather than the bacterium itself and thereby confer active immunity. This contrasts with the only approved *C. difficile* vaccine, **Merck & Co. Inc.**'s *Zinplava* (bezlotoxumab), which consists of a fully human monoclonal antibody that binds to and neutralizes the B toxin and so confers passive immunity. Zinplava was approved late last year in its first market, the US, despite some concerns at the advisory committee stage; the EU followed suit in January.

Sanofi Pasteur had already flagged *C. difficile* as one of its more difficult vaccine targets, together with cytomegalovirus and Staphylococcus. Apparently managing expectations about ACAM-CDIFF's prospects, R&D chief John Shiver recently told *Scrip*, "I have a lot of optimism that we will get to an endpoint soon with this study, which is a difficult trial to conduct, and hopefully that endpoint is favorable."

Analysts, too, have been circumspect. Those at Bryan Garnier said in a Dec. 4 research note, "We were cautious about this development and more specifically on the target population to be vaccinated in the end, also considering other approaches to the condition." They had only had peak sales for the product at €300m.

PFIZER MOVES INTO POLE POSITION

ACAM-CDIFF's demise leaves **Pfizer Inc.** pretty much in possession of the development field in a market that has been estimated at more than $1bn; its candidate PF-06425090 moved into Phase III in March and also targets both A and B toxins. Pfizer is aiming for a universal recommendation for use in adults 60 and older. The product was recently highlighted by Pfizer's vaccines leadership team, together with another Phase IIb vaccine candidate for *Staphylococcus aureus*, as representing significant long-term commercial potential in the vein of its pneumococcal blockbuster vaccine *Prevnar*.



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> ACAM-CDIFF's demise leaves Pfizer pretty much in possession of the development field

Another contender, the French biotech **Valneva SE**, recently announced a change to the development strategy for its product, VLA 84, that makes it dependent upon its rivals' success – a role that will now fall to Pfizer.

During its third quarter results presentation on Nov. 9, Valneva said that VLA 84 had completed Phase II and was Phase III-ready with immunogenicity and safety data "not inferior" to other vaccines being developed, with the possibility of "distinct competitive advantages in industrialization and future manufacturing".

Nevertheless, potential partners were hesitant about the level of investment required to fund a Phase III clinical trial, and as a result the company has changed its strategy. It will now wait until a first competitor achieves approval, and then conduct a head-to-head, non-inferiority Phase III based on an immunological correlate. This, Valneva hopes, will "substantially improve the investment-risk profile of an in-house, or partnered, final development to take the product to market."

Analysts at First Berlin Equity Research noted to investors on Nov. 24 that this approach would be comparable to a biosimilar registration process for biologic drugs. "This registration path is particular to vaccines and it requires demonstrating non-inferiority to an approved similar vaccine based on immunogenicity. Such a Phase III trial is significantly less risky and may cut the required investment level for the development by up to 50%," they wrote. "In our view, the market is large enough for three players. Therefore, this scenario can still be very advantageous for the company despite the time delay of some 2-5 years."

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Regeneron Deal Puts Decibel In The Driver's Seat

JESSICA MERRILL & MANDY JACKSON

Regeneron Pharmaceuticals Inc. is looking for ways to put its vast drug discovery and development machinery to work on behalf of start-ups that don't have the resources to build those capabilities on their own. Through that effort, it negotiated a novel collaboration with hearing-focused **Decibel Therapeutics**.

The deal's structure is unique: Regeneron will make an equity investment in Decibel and provide financial support for research and development, but the two-year-old biotech will retain full worldwide commercial rights to any therapeutics discovered under the collaboration that are designed to protect, repair and restore hearing. The arrangement announced Nov. 28 is unusual, because young biopharma firms generally have to concede some commercial rights in exchange for an investment from a larger partner.

Specific financial terms were not disclosed, but the companies said that in exchange for access to Regeneron's technology and capital contributions, Decibel will pay Regeneron tiered royalties based on net sales for therapies developed via the partnership. Decibel President and CEO Steven Holtzman told *Scrip* that the financial arrangement was designed to approximate a 50/50 split of potential revenue.

"Regeneron gets economics in a couple ways: first, through equity appreciation on the position they've taken in Decibel; and second, through royalties that they will earn on products that we discover and develop together," Holtzman said. "The deal approximates a 50/50 splitting of economics for anything we collaborate on all the way through, but allows Decibel to remain in the driver's seat for development and commercialization."

Decibel will have access to Regeneron's R&D technologies, including genetics research, drug discovery capabilities and antibody development and manufacturing, which the company said should significantly reduce its time and investment to develop new drugs. Regeneron established a large genetic database through the Regeneron Genetics Center (RGC), and recently hit a milestone of 250,000 patients sequenced.

"The foundation of this collaboration is grounded in Regeneron's commitment to great science, and the field of hearing is an area where we can make a real change in people's lives with a comprehensive scientific approach," Holtzman said. "Decibel was founded with a belief that developing clinically meaningful therapeutics for hearing will require the establishment of a fully integrated platform of drug discovery, delivery and development capabilities tailored to the unique biology of the ear."

REACHING OUT TO START-UPS

The two partners came together after Regeneron approached Decibel investor Third Rock Ventures about meeting with its portfolio companies to establish these kinds of collaborations. Decibel executives realized quickly during their first meeting with Regeneron's representatives that the companies' scientific approaches were closely aligned, the start-up's CEO said. Decibel and Regeneron let their scientists shape an R&D plan combining the firms' resources with the aim of accelerating the discovery and development of therapeutics in the field of hearing. Regeneron, for its part, said in the companies' joint announcement that it sees "creative collaborations" like the deal with Decibel as a way to extend the impact of its technologies. "We're excited to invest in new discoveries coming not only from our labs, but also from young biotechnology companies with whom we believe we can synergize," Regeneron said.

Holtzman noted that other small biopharma firms should be interested in arrangements like this because the spirit of the Regeneron-Decibel deal "is a true collaboration between our scientists, working shoulder-to-shoulder on project teams." Also, he said, this collaboration "allows the small company to remain in the driver's seat from early research through clinical development and commercialization."

He continued: "If you think about it, biopharmas have done this for years on the commercial side, leveraging their large-scale investments in global commercialization capabilities by in-licensing pipeline candidates. Regeneron has made significant investments in its research capabilities and is looking to get a different kind of leverage based on that. It's a highly attractive model for younger start-ups to be able to tap into those broader capabilities while focusing the investment they build in-house on the aspects that are truly bespoke to their own strategic model."

Regeneron itself has flourished into a big biotech with investment from a big pharma partner, **Sanofi**, through a long-term collaboration that has resulted in new drugs like *Praluent* (alirocumab), *Dupixent* (dupilumab) and *Kevzara* (sarilumab). The drug development portion of the partnership (excluding oncology) is largely winding down this year.

TAPPING INTO GENETICS RESEARCH

Decibel is particularly interested in tapping into Regeneron's RGC to find drug targets for monogenic hearing disorders and to identify commonalities among broader populations with noise- or age-related hearing loss. Regeneron's contributions to Decibel's discovery and development efforts will involve target identification and validation tools, including the big biotech's proprietary *VelociSuite* technologies, as well as antibody engineering and manufacturing capabilities.

"World leadership in hearing therapeutics will require us to build – virtually from scratch – industrial-scale and quality expertise and capabilities in all relevant aspects of hearing drug discovery, translational medicine and clinical development. We will have neither the bandwidth nor financial resources to build in-house technologies of a broader nature in such areas as human genetics, mouse genetics, informatics, monoclonal antibody technology, etc.," Holtzman said. "This collaboration allows us to leverage that broader set of capabilities within Regeneron, while enabling us to focus on developing our hearing expertise."

Decibel's development programs still are preclinical, so the company is not disclosing specifics about its development timelines nor will it describe the particular R&D focus of its collaboration with Regeneron. However, the CEO said Decibel's initial areas of interest under the agreement include "monogenic hearing loss disorders as well as ototoxicity and noise-induced hearing loss and tinnitus."

Boston-based Decibel was established in October 2015 with the sole aim of filling the white space in drug development for new therapies to address hearing loss and other hearing disorders.

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CVS/Aetna To Merge In Defensive Play To Reshape Healthcare Delivery

JESSICA MERRILL jessica.merrill@informa.com

The pharmacy retail giant **CVS Health Corp.**'s purchase of health insurer **Aetna Inc.** in a $69bn merger will shake up the way drugs and healthcare are delivered. The companies say a more integrated healthcare management and delivery platform will help eliminate waste and make healthcare more affordable, while also presenting new opportunities through CVS' walk-in clinics to bring expanding healthcare options to patients.

The combination of two heavyweights working in different areas of the healthcare spectrum could present speed bumps in the near-term, but the move announced Dec. 3 could be a smart long-term defensive play to position CVS to compete in a dramatically changing healthcare market by reducing its dependence on dispensing prescriptions.

> 'We see the healthcare marketplace evolving into a more value-based system'

No one mentioned Amazon during a conference call hosted by both companies Dec. 4 to lay out the strategic rationale for the merger, but investors and other healthcare stakeholders are very aware of the potential disruption posed by the online retailer if it decides to move into drug distribution. Amazon hasn't announced any plans to move into the pharmacy business, but rumors have been percolating.

CVS' pharmacy benefit manager (PBM) CVS Caremark is already partnered with Aetna for pharmacy distribution services, so the deal isn't expected to present massive changes on that front. The arrangement could present some risk to the PBM side of CVS' business if rival insurers are uneasy about working with a competitor and change their contracts. **Anthem Inc.** recently announced a new five-year contract with CVS for some PBM services beginning in 2020 after their contract with **Express Scripts Holding Co.** ends, while Anthem builds its own internal PBM.

Much of the merit for the CVS/Aetna deal is around the opportunity to diversify CVS's business, eliminate waste and drive efficiencies in the system that CVS says will make healthcare more affordable for patients and lower costs for payers. The companies expect to generate synergies of $750m by the second year after the close of the deal.

The retailer and insurer also see opportunities to use data analytics to drive more value-based decisions around healthcare decisions.

"We see the healthcare marketplace evolving into a more value-based system, where premium is placed on the efficiency with which care is delivered and we will become a leader in driving further adoption of value-based care models through our combined assets, promoting lower cost sites of care, eliminating unnecessary spending, and enhancing our clinical programs by integrating data across our enterprise assets," CVS CEO Larry Merlo said during the call.

CVS would be able to leverage Aetna's massive claims data for making-value-based decisions. Aetna insures roughly 22m people in the US, people Aetna could push into CVS to receive more healthcare services.

Value-based decisions involve every aspect of healthcare, but on the pharmaceutical side, Aetna has been proactively working with manufacturers on select value-based reimbursement agreements. What's needed for pharmacies and pharmacy benefit managers to make value-based reimbursement decisions is access to health outcomes data from insurers. A fully integrated system is becoming increasingly important as the drug industry slowly moves towards more value-based reimbursement, and it's one of the reasons Anthem is opting to build its own internal PBM.

BUILDING HEALTHCARE HUBS

The companies view CVS' 9,700 pharmacy stores and 1,100 MinuteClinic walk-in clinics as an opportunity to establish healthcare hubs patients can go to for vision, hearing and nutrition services as well as clinical and pharmacy services. CVS said it plans to pilot many different programs as the combined company evolves.

As one example, CVS said it envisions welcoming diabetes patients in stores for counseling on weight loss programs, medication adherence and glucose monitoring in between doctor visits. Keeping diabetes patients on a solid healthcare program could save the US healthcare system billions of dollars, according to the companies.

"Whether it's the role of the pharmacist, the role of the nurse practitioner at MinuteClinic, the expansion of services at Minute Clinic that could include blood draws, or the role that a nutritionist can play in CVS … those are all things that in addition to what already exists today that we're going to be piloting," Merlo said.

Under the terms of the agreement, CVS will acquire all outstanding shares of Aetna for a combination of cash and stock, with each Aetna shareholder receiving $145 per share in cash and 0.8378 shares of CVS for each Aetna share. The transaction values Aetna at approximately $207 per share, or $69bn. Including the assumption of Aetna's debt, the total value of the deal is $77bn.

Analysts were largely pleased with the acquisition, understanding the challenging dynamics ahead for CVS, though they view the near-term execution as high-risk.

"We would be supportive of the company's long-term strategic decision to vertically integrate into the managed care business, and believe that once fully integrated, the combined entity will be in an enviable competitive position," Deutsche Bank analyst Glen Santangelo said in a Dec. 3 note.

Jefferies analyst Brian Tanquilut, in a Dec. 4 note, said, "We share management's views on the need for a more integrated and community based healthcare approach and believe that CVS is a strategic asset that has the ability to position itself as a unique player that can provide a solution to this void the US healthcare system," he said. But he pointed out the changes needed across the 9,000+ retail stores "poses meaningful operational risk to the combined entity."

Published online 4 December 2017

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

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

Selected clinical trial developments for the week 24–30 November 2017

LEAD COMPANY/PARTNER	COMPOUND	INDICATION	COMMENTS
Phase III Results Published			
Amgen Inc./Novartis AG	*Aimovig* (erenumab)	episodic migraine	STRIVE; the *NEJM*, Nov. 30, 2017.
Teva Pharmaceutical Industries Ltd.	fremanezumab	chronic migraine	HALO; the *NEJM*, Nov. 30, 2017.
Ipsen	*Dysport* (abobotulinumtoxinA)	lower limb spasticity after a stroke or traumatic brain injury	*Neurology*, Nov. 1, 2017
Phase III Interim/Top-line Results			
Merck KGAA/Pfizer Inc.	*Bavencio* (avelumab)	gastric cancer, third line	JAVELIN Gastric 300; missed primary endpoint, other studies underway.
Auris Medical Holding AG	brimapitide	sudden deafness	HEALOS; missed primary endpoint, but some improvement noted in subpopulation.
Bayer AG/Nektar Therapeutics	*Amikacin Inhale*	hospital acquired pneumonia	INHALE 1, 2; missed primary endpoints.
Egalet Corp.	*Egalet-002* (oxycodone) abuse deterrent formulation	moderate to severe pain	Effective pain relief in second Phase III study.
Catalyst Pharmaceuticals Inc.	*Firdapse* (amifampridine phosphate)	Lambert-Easton myasthenic syndrome	Positive results, the second Phase III study.
Updated Phase III Results			
Novartis AG	*Cosentyx* (secukinumab)	psoriasis, nail and palmoplantar	GESTURE; long term efficacy confirmed.
Phase III Initiated			
ViiV Healthcare	cabotegravir, two-monthly injections	HIV prevention in women	HPTN084; In sub-Saharan Africa.
ViiV Healthcare	cabotegravir plus rilpivirine injections	HIV/AIDS infection	ATLAS-2M; two-drug regimen every eight weeks.
Two Cells Co. Ltd./ Chugai Pharmaceutical Co. Ltd.	gMSC1 cells	chrondrogenesis in knee surgery	Versus microfracture.
Zogenix Inc.	ZX008	Lennox-Gastaut syndrome	Adjunctive therapy.
Phase III Announced			
Shire PLC	maralixibat (SHP625)	progressive familial intrahepatic cholestasis	A placebo controlled study.
Iterum Therapeutics Ltd.	sulopenem etzadroxil	urinary and reproductive tract infections	In adult women.
Deciphera Pharmaceuticals Inc.	DCC-2618	gastrointestinal stromal tumors	Invictus; in previously treated patients.
Phase II Suspended			
Regeneron Pharmaceuticals Inc./ Bayer AG	*Eylea* (aflibercept) plus nesvacumab	diabetic macular edema, wet age-related macular degeneration	RUBY, ONYX; Lack of additional benefit.

Source: Biomedtracker

First Efficacy Study for Janssen's Mosaic HIV-1 Vaccine

STEN STOVALL sten.stovall@informa.com

Following encouraging trials in monkeys and healthy humans, J&J subsidiary **Janssen Pharmaceutical Cos.** feels confident enough to enter its investigational mosaic HIV-1 preventive vaccine in proof-of-concept Phase IIb testing, in collaboration with the Gates Foundation and the National Institutes of Health (NIH).

"Based on the immune response in trials with monkeys and subsequently in healthy human volunteers we are optimistic that this vaccine could also protect in humans and that's why we now start this efficacy trial and we hope it can be demonstrated to really protect healthy people against infection with the HIV virus," Johan Van Hoof, global vaccines R&D head at Janssen Pharmaceuticals, told *Scrip* in an interview.

Mosaic-based vaccines contain immunogens created using genes from different HIV subtypes responsible for HIV-1 infections worldwide. These immunogens are delivered through viral vectors which combine with other components such as soluble proteins to form mosaic-based prime-boost vaccine regimens that first prime and then boost the immune system, with the aim of producing stronger and longer-lasting immunity to HIV.

The new HVTN 705/HPX2008 study, also known as 'Imbokodo', will evaluate whether the investigational Janssen vaccine regimen is safe and able to reduce the incidence of HIV infection among 2,600 women in sub-Saharan Africa.

"Ultimately the goal is to deliver a global vaccine that could be deployed in any geographic region to help protect vulnerable populations at risk of infection," Van Hoof explained, adding: "a preventive vaccine would be a vital tool in a comprehensive global strategy to end the HIV pandemic."

He said the mosaic HIV-1 preventive has already shown significant immune protection in monkeys and identified promising biomarkers. "This gives you some sort of benchmark when you go into humans with the hope of inducing similar immune profiles and immune response in human populations."

Phase I and Phase IIa trials using this vaccine in healthy volunteer humans have already been conducted. "We were very pleased to see that in one of the best regimens from those that we achieved immunogenicity profiles very similar to ones seen in protected monkeys. Based on that, there seem good reasons to believe that this vaccine could be protective in humans, so the time has come to test the vaccine in a Phase IIb proof-of-concept study."

He noted that the search for an HIV vaccine is made difficult in part by the unique properties of the virus – including its ability to mutate quickly and its global genetic diversity with multiple strains and subtypes prevalent in different parts of the world.

The new Imbokodo study is part of Janssen's long-standing collaboration with the NIH and the relatively recent addition of the Gates Foundation to the project.

If the vaccine proves successful, he said manufacturing could be conducted in the Netherlands.

But he said it was too early to discuss when the vaccine might be launched.

"It's premature to say when this might be on the market. In a perfect world - and if all goes well - it would still take at least four to five years for that to occur. First we need to see whether it works or not."

Published online 30 November 2017

APPOINTMENTS

EMD Serono Inc., Merck KGAA's biopharma business in the US and Canada, has appointed ***Zhen Su*** as chief medical officer for North America. Su most recently was global head of medical affairs, oncology, at EMD Serono, having previously held leadership roles at Sanofi and GlaxoSmithKline.

Joining CAR-T immunotherapy company **Cellectis SA** are ***Elsy Boglioli*** and ***Stéphane Depil***. Boglioli has been appointed executive vice president, strategy and corporate development; she joins from Boston Consulting Group where she served as partner and managing director, and leader of BCG's biotech-focused business in Europe. Depil, adjunct Professor at Léon Bérard Cancer Center & University Claude Bernard Lyon 1, France, becomes senior vice president research and development and chief medical officer. He will retain his academic role. Previously, he was CEO of oncology start-up Netris Pharma, and before that worked at Servier, where he directed oncology R&D.

Biogen Inc. has appointed ***Mark Hernon*** as senior vice president, chief information officer. Hernon joins from Takeda Pharmaceuticals, where most recently he was global head of R&D site strategy and operations, leading the global transformation of Takeda's R&D activities.

Lund, Sweden-headquartered **Alligator Bioscience AB**, which is developing antibody-based pharmaceuticals for tumor-directed immunotherapy, has expanded its management team. ***Charlotte Russell*** has been appointed chief medical officer and ***Peter Ellmark*** vice president discovery. She was previously senior medical director at Genmab AS, of Denmark. Dr Ellmark has been promoted from principal scientist at the firm. Both assume their new positions on Jan. 1, 2018. In addition, Cecilia Hofvander has been recruited as director investor relations and communications.

Shao-Lee Lin has been appointed executive vice president research and development and chief scientific officer at ***Horizon Pharma PLC***. She will join in early January from AbbVie Inc., where she was a corporate officer and vice-president, therapeutic areas, development excellence and international development. She previously held leadership roles at Gilead Sciences Inc. and Amgen Inc., She will join Horizon in early January 2018.

Juhana Heinonen has been appointed chief commercial officer at **Faron Pharmaceuticals Oy**. Heinonen joins Faron in early January 2018 from AstraZeneca PLC, where he served as global marketing director for the biological asthma drug *Fasenra*. At the Finnish firm he will be responsible for the launch strategy for its Phase III candidate *Traumakine* for acute respiratory distress syndrome.

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