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Novo Nordisk's Oral Semaglutide Succeeds, But Prompts Questions

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Novo Nordisk AS's positive top-line data for its oral semaglutide in the Phase III PIONEER 1 study in type 2 diabetes – the first of 10 studies to report – are reassuring in some ways, but raise questions about whether weight loss and compliance are good enough to carry the tablet version of the GLP-1 agonist.

The rest of the trials in the PIONEER development program, which involves more than 9,000 patients, are set to read out this year, putting the company in a position to file for regulatory approval in the first quarter of 2019. A weekly subcutaneous formulation of semaglutide was approved by the US FDA in December and is marketed as *Ozempic*.

Semaglutide has a chance to become the first oral GLP-1 drug on the market, which would remove a major barrier for the injectable class, enabling it to compete against new oral mechanisms like DPP-4 and SGLT-2 for patients with earlier-stage diabetes. Datamonitor Healthcare projected rapid uptake for the drug if approved, with sales of $1.5bn in 2021 and $3.3bn 2025 in the US, Japan and five major European markets.

Novo Nordisk said in its Feb. 22 release of the top-line Phase III findings that the data confirmed the "unprecedented efficacy" reported in Phase II.

Morgan Stanley analyst Patrick Chen pointed out in a same-day note that since the trial compared the drug against placebo, the results are less meaningful than the other PIONEER studies, but valuable in that they confirm Phase II data.

However, while the top-line release showed a positive overall outcome, it arguably presented mixed results, leaving a muddled picture for now.

THREE DOSES TESTED

The PIONEER 1 trial evaluated oral semaglutide once daily in three different doses – 3 mg, 7 mg and 14 mg – versus placebo over 26 weeks in 703 people with type 2 diabetes. Datamonitor analysts expect Novo Nordisk to file for a lower, more tolerable dose in order to compete with the oral anti-diabetes classes, rather than a higher dose with equivalent efficacy to the marketed subcutaneous formulation of semaglutide.

For approval and labeling purposes, the FDA generally prefers clinical trial data from an intent-to-treat population of all comers in a trial, not the number who adhered to treatment. Ozempic's labeling, for example, references the intent-to-treat population.

However, Novo Nordisk reported only minimal data for the intent-to-treat population in PIONEER 1, while offering more details for those who adhered to therapy and did not need rescue medication. The company explained that both methods were used per recent regulatory guidelines.

In the intent-to-treat analysis, all three doses tested showed significant, superior improvement for reducing blood sugar compared to placebo. The highest dose had the added benefit of demonstrating significant and superior weight loss compared with placebo, whereas the other two doses showed only numerical improvements on this measure.

For the intent-to-treat population, oral semaglutide also was generally safe and

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from the editor

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It's interesting to see the new trial report tracking site launched by Ben Goldacre *et al*. Goldacre is viewed by some as the scourge of the pharmaceutical industry, not least for his winningly entitled book *Bad Pharma*, published a few years ago. His new FDAAA.Trialstracker.net site sets out to list all clinical trials that are due to report results on ClinicalTrials.gov under the US FDA Amendments Act Final Rule, which came into force in January last year, meaning that the first fines are falling due around now. The site lists the sponsors of trials due to report, noting whether or not they have done so.

One of the stated aims of this site is to encourage compliance with FDAAA 2007: its creators note that the agency itself is not publicly tracking compliance. It has so far identified 15 trials (as of Feb. 28) whose results are overdue under the new rules, for which their sponsors could be fined around $1.23m (but apparently haven't been). Goldacre reports that some sponsors updated their results after being alerted.

But the bottom line is that the reporting rate is looking surprisingly high: 88.5% of those required to report have done so, and among the 15 in breach, only two are pharma companies and only one is a trial for a drug product. The fact remains that a large body of older trial data is still missing from clinicaltrials.gov, but Goldacre's latest endeavour is so far showing pharma in a much more positive light than various older studies that found a majority of trial results went unreported.

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How Pfizer Warning Letter Tarnished Sandoz/ Momenta's Glatopa Launch

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An FDA warning letter to a **Pfizer Inc.** plant in McPherson, Kansas, where **Sandoz International GMBH** and **Momenta Pharmaceuticals Inc.** had decided to outsource fill/finish operations wound up costing them a first-to-market advantage for their generic of **Teva Pharmaceutical Industries Ltd.**'s *Copaxone* 40 mg (glatiramer acetate) multiple sclerosis treatment.

That warning letter was "our core challenge in 2017," Momenta CEO Craig Wheeler said during a Feb. 21 earnings call. "The delay of getting *Glatopa* 40 mg product to the market due to the warning letter issued to Sandoz's fill/finish contractor … coupled with Mylan's aggressive entry into the market in October, make it clear that the level of revenues we had planned for from this product will most likely not be realized."

The expected reduction in revenues from Glatopa 40 mg is a major reason why Momenta is conducting a strategic review of its business "to live within our means," Wheeler said. This could mean slowing the firm's biosimilars programs and selling assets like the Humira biosimilar it has been developing.

Vasant Narasimhan, who was about to take the reins as CEO of Sandoz's parent **Novartis AG**, told investors during a Jan. 21 earnings call that the delayed launch of the Glatopa 40 mg generic was one of three big risks for 2018 "that are top of mind for me."

THE CHOICE OF CONTRACTOR

The episode strikes home the importance of choosing contract manufacturers that don't have serious, unresolved manufacturing issues like particulates in parenteral drug products, as the warning letter said was the case at the Pfizer **Hospira Inc.** unit's McPherson plant.

It also underscores the possibility that firms can make missteps in outsourcing without turning to low-cost manufacturing facilities in Asia that have sketchy compliance records. In Sandoz/Momenta's case, they were relying on a facility in the US that had been acquired by a global US-based manufacturer with a reputation for quality.

The February 2017 warning letter stemmed from a June 2016 inspection of the McPherson plant that identified issues with investigations into complaints about particulates. The warning letter cited a continuing inability of Hospira to prevent visible particulates from winding up in parenteral drug products despite multiple complaint investigations.

The persistence of the visible particulates showed a loss of control of the plant's manufacturing process that put patients at risk, according to the warning letter. What's more, the FDA noted that it had identified similar violations at other Hospira plants in four warning letters issued over the previous six years. This suggests that in FDA's view, the problem was not specific to the McPherson plant but rather part of a broader, more difficult to correct pattern throughout Hospira's quality system.

The warning letter did not prevent Hospira from continuing to manufacture Glatopa 20 mg for Sandoz/Momenta at the plant, but it did put a hold on approval of the 40 mg formulation, which the firms had expected to launch that month.

When Mylan announced Oct. 3 that the FDA had approved its generic of Copaxone 40 mg, Sandoz/Momenta were still waiting for Pfizer to resolve the issues raised in the warning letter.

During an Oct. 22 earnings call, Momenta CEO Craig Wheeler said Pfizer was reporting significant progress with the remediation and the facility was prepared for reinspection.

In fact, the reinspection was underway.

Wheeler told investors that Momenta and Sandoz had prepared for several possible outcomes of the reinspection: FDA could lift the warning letter or change the facility's status from official action indicated to voluntary action indicated, either of which would allow the agency to grant marketing approval, probably in late 2017 or early 2018. Or FDA could leave the warning letter and OAI status in place.

If the Pfizer manufacturing hold remained in place, Sandoz and Momenta were prepared to switch to another fill-finish contractor they had identified – but this would further delay launch, likely to the second half of 2018.

When three investigators completed the reinspection on Oct. 27, they gave the plant a Form 483 report that described 10 observations, and FDA changed the plant's status to voluntary action indicated, allowing the agency's review of Glatopa 40 mg to resume.

The Form 483 report, which FDA's Office of Regulatory Affairs published Feb. 15, called attention to what it termed inadequate investigations into 139 complaints of ineffective bupivacaine HCl with dextrose, 15 complaints of particulates in hydromorphone HCl that turned out to be silicone-related, and one complaint of a hair partially embedded in a vancomycin HCl vial's stopper section.

The 483 also identified issues with visual inspection training, design of labeling equipment, visual examination of reserve samples, cleaning procedures, field alert reporting, complaint follow-up reporting and complaint handling procedures.

Even though there were still issues with complaints, particulates and investigations, the agency was sufficiently satisfied with the extent to which the firm had taken control of the situation to let it proceed with voluntary corrections, and therefore to release its hold on the Glatopa review.

WHAT NOW

Sandoz and Momenta finally launched Glatopa 40 mg upon receiving FDA approval Feb. 13. What happens next depends on market factors such as how Teva tries to retain Copaxone market share, how Mylan competes and other factors.

"It's going to take some time to really figure out how this market evolves because it is a second generic entry into the marketplace," Wheeler said. "Everything seems to be going well so far from what we're seeing from Sandoz, but it's going to take some time until we're really clear in terms of the total opportunity here."

One thing is clear, though: that opportunity was diminished by an FDA warning letter to the venture's contract manufacturer.

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Allergan's Restasis Defense Falters As PTAB Dismisses Tribal Immunity Ploy

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Allergan PLC went to great lengths to protect its patents for its blockbuster dry eye drug *Restasis* (cyclosporine), but the company's most controversial effort – transferring ownership of its patents to the Saint Regis Mohawk Tribe – was swatted down by the Patent Trial and Appeals Board (PTAB).

The PTAB, which hears patent interference cases filed with the US Patent and Trademark Office, issued a decision on Feb. 23 denying the Tribe's request to dismiss an *inter partes* review (IPR) sought by **Mylan NV** and other generics manufacturers. Allergan transferred its Restasis patent ownership to the Tribe in September so that the Tribe could use its sovereign immunity to seek dismissal of the IPR. However, a district court invalidated the company's patents last year, so Allergan already cut its 2018 revenue guidance and laid off 1,000 employees earlier this year in anticipation of Restasis generics.

Allergan declined to comment on the PTAB decision, but CEO Brent Saunders told *Scrip* in January that a big part of why the company was "tenacious in trying to preserve our intellectual property" was because it was trying to avoid cost cuts and layoffs.

But back in November, after Allergan's Restasis patents were invalidated by the US District Court in the Eastern District of Texas, the company said it expected lower Restasis sales in 2018, which would lead to significant expense reductions to make up for the revenue decline. The cuts pre-announced last year were solidified in early January with the disclosure that Allergan would lay off 1,000 employees and eliminate 400 job openings.

The company now expects Restasis generics to hit the market after the second quarter of 2018. As a result, 2018 revenue is expected to be lower than in 2017 at $15bn to $15.3bn. Non-GAAP revenue totaled $15.94bn last year.

Meanwhile, the district court's invalidation of the Restasis patents is on appeal to the US Court of Appeals for the Federal Circuit, but the US FDA rejected the company's third citizen petition to block Restasis generics.

WHAT WENT WRONG

The PTAB said in denying the Tribe's request to dismiss the IPR that "we determine the Tribe has not established that the doctrine of tribal sovereign immunity should be applied to these proceedings. Furthermore, we determine that these proceedings can continue even without the Tribe's participation in view of Allergan's retained ownership interests in the challenged patents."

Mylan said on Feb. 26 that the PTAB tentatively scheduled a hearing on April 3 to discuss the merits of the IPR with a written decision on the matter expected by June 6.

"The PTAB's ruling reinforces our belief that Allergan's maneuvers to engage the St. Regis Mohawk Tribe for patent protection were a sham," Mylan CEO Heather Bresch said in the company's statement. "We will continue to be steadfast in our efforts on both the legal and regulatory fronts to bring a generic version of Restasis to patients as quickly as possible."

However, the PTAB expressly noted that its decision does not make any kind of determination on the legality of Allergan's agreement with the Tribe, under which the company transferred patent ownership to the Tribe and then licensed the patents back for a $13.75m upfront fee and $15m annually.

"In reaching this conclusion, we do not comment on whether the license and the other agreements between the Tribe and Allergan constitute a 'sham' transaction, nor do we need to decide whether the agreements are otherwise improper under the law," the PTAB wrote.

MANY REASONS TO KEEP IPR GOING

The body listed several other reasons, however, for not ending the IPR proceedings. First, the PTAB said that while Native American tribes are immune from state agency proceedings, there's no precedence for upholding sovereign immunity in federal agency proceedings, including the IPR process. It also was determined that tribal immunity does not apply to IPR proceedings, and Allergan remains a party to the current proceeding, because of the terms of its agreement with the Tribe.

The PTAB wrote that "the Federal Circuit has held that the 'party that has been granted all substantial rights under the patent is considered the owner regardless of how the parties characterize the transaction that conveyed those rights," so "based on the terms of the license between Allergan and the Tribe, we determine that the license transferred 'all substantial rights' in the challenged patents back to Allergan."

The PTAB also determined that the Tribe is not an "indispensable party" to the Mylan-initiated IPR as the Tribe had argued.

"For the foregoing reasons, we determine that the Tribe has not established that it is entitled to assert its tribal immunity in these inter partes review proceedings. We further determine that these proceedings may continue with Allergan as the patent owner, and that the Tribe is not an indispensable party to these proceedings," the decision said.

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CONTINUED FROM COVER

well-tolerated, though nausea was a flagged side effect, reported in 5% to 16% of patients on the test drug, depending on the dose, versus 6% for placebo. The drop-out rate for the treatment arms ranged from 2% to 7% for oral semaglutide versus 2% for placebo.

"Whereas all three doses (3/7/14 mg) demonstrated superiority on blood glucose reduction versus placebo (as expected), only the high dose showed superior weight loss. This is weaker than expected as, versus placebo, we would have expected to see superiority across the doses," Societe Generale analyst Florent Cespedescommented in a Feb. 22 note.

The weight loss effect at the highest dose comes at the expense of a 16% nausea rate, the analyst noted.

In the patients who adhered to medication and did not need rescue therapy, the reductions in blood sugar (hemoglobin A1c or HbA1c) from low to highest doses from a baseline of 8% were: 0.8%, 1.3% and 1.5%, respectively. That compares to 0.1% for placebo.

"The American Diabetes Association (ADA) treatment target of HbA1c below 7.0% was achieved by 59%, 72% and 80% of people on treatment with 3, 7 and 14 mg oral semaglutide, respectively, compared to 34% of the people treated with placebo. In addition, from a mean baseline body weight of 88 kg and a BMI of 31.8 kg/m2, people treated with 3, 7 and 14 mg oral semaglutide experienced a weight loss of 1.7 kg, 2.5 kg and 4.1 kg, respectively, compared to a weight loss of 1.5 kg in people treated with placebo," the company reported.

QUESTIONING COMPLIANCE

Cespedes said it was surprising that the company disclosed efficacy only in the second analysis that took into account patients who remained under treatment and who did not require rescue medication, which is a lower bar for semaglutide. "The use of the adherence population suggests that the "adherence to the treatment should not be great," the analyst said.

Adherence may be affected by the dosing regimen. The analyst noted that the drug has to be taken in the morning 30 minutes prior to any meal, which is not very convenient for a chronic treatment.

Cespedes concluded that there are not any strong elements of differentiation for oral semaglutide compared to the oral drugs already on the highly competitive market.

COMPARING GLP-1S

Deutsche Bank's Tim Race acknowledged that the company's release was confusing and raises questions, but saw many positives nevertheless.

Race said in a Feb. 22 note that on the "standardized metrics comparable across GLP-1 studies," oral semaglutide's reductions of 0.8%-1.5% HbA1c from an 8% baseline vs. 0.1% for placebo hold up well against Novo Nordisk's once-daily injectable *Victoza* (liraglutide) and Ozempic, as well as **Eli Lilly & Co.**'s once-weekly GLP-1 *Trulicity* (dulaglutide).

"This is very strong and appears equivalent with best-in-class GLP-1 Ozempic at the top dose and similar to Trulicity at the lower dose (we caveat this though with the usual warnings of cross-trial comparisons). Oral [semaglutide] also got more people below the ADA's 7% treatment target (ranging 59% to 80%, placebo at 34%), which arguably compares better than Victoza, Trulicity and Ozempic in similar studies," Race said.

"Weight loss was only statistically significant at the highest dose, but overall followed the expected pattern with 1.7-4.1 kg reductions [placebo 1.5 kg]. This is broadly in line with Victoza," Race added.

The tolerability profile has been in question, because semaglutide "requires a large amount of protein to be delivered through the gut," but tolerability was actually better in PIONEER 1 than anticipated, Race said.

"One of our main fears was that nausea or high patient discontinuations due to tolerability would be a problem. PIONEER 1 actually saw lower nausea (5%-16%, 6% on placebo) than many GLP-1 drugs and the discontinuation rate due to adverse events was very low (2%-7%, 2% placebo). This is important as it is good to have a drug that is highly effective, but people also need to comply. This data suggests oral semaglutide has a very strong profile that opens it up for use in earlier stage diabetics," Race said.

Morgan Stanley's Chen found the safety to be encouraging – in Phase II the nausea rate for a 10 mg dose was 33% versus 16% for the highest dose (14 mg) in PIONEER 1, Chen said.

Full results from PIONEER 1 will be presented at a medical meeting later this year, which should help clear up lingering questions about the data.

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Pfizer's Mylotarg Finally Gets CHMP Nod

The EU's CHMP has granted a positive opinion to Pfizer Inc.'s targeted anticancer *Mylotarg* (gemtuzumab ozogamicin) for use in acute myeloid leukemia (AML), setting the stage for an arrival in the EU market more than a decade after its first attempt.

Mylotarg is set for approval for the treatment of AML in patients aged 15 years and above, with previously untreated, de novo CD33-positive acute myeloid leukaemia (AML), except acute promyelocytic leukaemia, in combination with daunorubicin and cytarabine, based on the Phase III ALFA-0701 trial. The product has an EU orphan designation.

The EU development follows the decision by the US FDA last year to allow the product back onto the US market for the treatment of adults with newly diagnosed AML whose tumors express the CD33 antigen. That approval also included treatment of patients ages two years and older with CD33-positive AML who have experienced a relapse or who have not responded to initial treatment.

Pfizer acquired Mylotarg when it bought Wyeth in 2009; the drug was first approved in the US in May 2000 as second-line therapy for AML patients 60 years or older under the agency's accelerated approval program on the basis that it had shown improved remission rates. But it never reached the EU market: Wyeth filed it for EU approval in 2005 only to be granted a negative opinion which was later reaffirmed in 2008.

In the US, Mylotarg was withdrawn back in 2010 after a confirmatory, post-approval clinical trial – a randomized trial in de novo CD33-positive AML patients, known as SWOG S0106 – raised new concerns about the product's safety and the drug failed to demonstrate clinical benefit.

Mylotarg was given a new lease of life after new studies using a lower dose and event-free survival as an efficacy endpoint convinced the FDA that the drug demonstrated a favorable risk/benefit profile last July.

alex.shimmings@informa.com, 26 Feb 2018

Novo Nordisk To Target 'New GLP-1 Patients Only' With Weekly Ozempic

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Novo Nordisk AS will not actively try to get existing diabetes patients who currently use human glucagon-like peptide-1 agonists to swap over to its newly approved once-weekly injectable *Ozempic* (semaglutide), "because the GLP-1 market is growing, and it's good to have more options," according to the group's international operations chief Maziar Mike Doustdar.

In an interview with *Scrip*, Doustdar also said the Denmark-based company may have gained a significant edge in a competitive market with the results of its Phase III trial of oral semaglutide. Novo Nordisk Feb. 21 reported positive top-line data for its tablet in the Phase III PIONEER 1 study in type 2 diabetes – the first of 10 studies to report.

OZEMPIC LAUNCH PREPARATIONS

Approved by the EU in February and by the FDA in December, Ozempic is the newest once-weekly GLP-1 agonist to reach the market for type 2 diabetes, and is predicted to be a blockbuster for the Danish diabetes fighter. That will be essential for Novo Nordisk's hopes of offsetting the territory lost by its once-daily GLP-1 *Victoza* (liraglutide) to **Eli Lilly & Co.**'s once weekly GLP-1 *Trulicity* (dulaglutide), which launched in September 2014.

In the US, the group is working to establish value-based contracts for the weekly injectable.

But Doustdar says it will take time for its Ozempic sales to take off in the US. The GLP-1's US launch was officially announced Feb. 5 but will be hindered by limited access during 2018 as contracts are negotiated with pharmacy benefit managers (PBMs), causing a slow take-off.

The European Commission meanwhile granted marketing authorization for Ozempic for the treatment of adults with type 2 diabetes. Doustdar said he was pleased with Ozempic's EU label, indicated as monotherapy when metformin is considered inappropriate due to intolerance or is contraindicated, and as an addition to other medicinal products for the treatment of diabetes. "The EU label helps me position this product basically right after failure of metformin. The broader the label the bigger the pool of potential patients," he told *Scrip*.

He said that label reflects the superior and sustained reductions in HbA1c and body weight achieved with Ozempic relative to comparator treatments, cardiovascular benefits and the statistically significant reduction in diabetic nephropathy with Ozempic relative to standard of care. Novo Nordisk has submitted a variation application to the European Medicines Agency (EMA) for an updated Ozempic pen offering. The new pen offering will help facilitate reimbursement for patients with type 2 diabetes using Ozempic.

The launch of Ozempic is expected to take place in the first EU countries in the second half of 2018 following the approval of the variation application for the updated pen offering.

"Hopefully we'll get the pen okay shortly and as soon as I have the device approved, then we will start launching across Europe," the executive said. He is currently focused on rolling out Ozempic in Japan over the next few months, while at the same time preparing for the European launches. "We aim by the end of 2019 to have Ozempic covered across a good portion of the important markets in Europe, but I can't tell you where we'll first start selling due to competitive reasons."

"Our plan with Ozempic is to focus on GLP-1 new starts rather than switching existing GLP-1 patients, whether they are from Lilly's Trulicity or our own Victoza, or from anyone else; priority number one is to focus on new starts because the GLP-1 market is growing, and it's good to have more options," he said.

"With Victoza, we'll continue focusing on the markets where Ozempic is either not available while also addressing Victoza's proven cardiovascular markers, shown in the LEADER trial results," Doustdar added. Datamonitor Healthcare analyst Richard Veal says the GLP-1 market has been growing strongly since its start in the latter part of the previous decade. "The GLP-1 market has been growing by more than 25% in recent years and this growth can continue if access isn't restricted by payers," he told *Scrip*.

ORAL OPPORTUNITY

Semaglutide also has a chance to become the first oral GLP-1 drug on the market, overcoming a major barrier for the injectable class, enabling it to compete against new oral mechanisms like dipeptidyl peptidase-4 (DPP-4) inhibitors and sodium-glucose cotransporter-2 (SGLT2) inhibitors for patients with earlier-stage diabetes.

If Novo Nordisk's other PIONEER trials provide consistent results, the company says it expects to submit for regulatory approval in 2019 and a possible launch in 2020. The next PIONEER data – from studies 2, 3, 4 and 7 – are to read out in this year's second quarter.

"We still need to see more PIONEER trial results; we've had one with semaglutide versus placebo and our expectations were both met and exceeded with that," Doustdar said.

"We want to see how this tablet does versus some of the products that it needs to compete with in the marketplace and some of the PIONEER programs will shed light into that. Based on that we'll make decisions on the tablet's positioning and pricing – and a major part of that assessment will be about gauging how enthusiastic patients and their doctors are about oral medication versus injectables."

He noted that oral semaglutide represents "a new scientific path we're walking down – being able to administer a large protein in an oral way."

"Does it really work, and work competitively? The PIONEER trial of semaglutide versus placebo showed that 'sema' had a very high effect of lowering the HbA1c and had significant body weight impact. So 2018 will be an exciting year of PIONEER results," he concluded.

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Guenter Stays Focused After Almirall's Annus Horribilis

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Almirall SA's new CEO is seeking to reassure investors he steadied the ship in 2017 and has positioned it for future growth. Announcing a 16% drop in net sales to €639m last year, Peter Guenter emphasized ongoing cost savings, new control mechanisms and a focus on dermatology growth opportunities as his tools for getting Almirall on course for success. He promised a return to growth in revenues and earnings in 2018, but wouldn't offer any longer-term targets.

Among the challenges he has faced since assuming control at Almirall in October 2017 have been sorting out business irregularities in the US, generic competition to its Aqua Pharmaceuticals subsidiary's oral acne treatment, slowing growth for its ThermiGen aesthetics unit, late-stage discontinuations of nail psoriasis and onychomycosis trials from the PoliGroup business acquired for €365m in 2016, and a delay to the expected EU approval and launch of partnered psoriasis candidate tildrakizumab while heavyweight rivals plough forward.

"The nice thing about a mid-sized company like Almirall is that once you start to take decisions the company follows very quickly, and you can move around in certain directions probably much faster than very big companies," observed Guenter, who was previously in charge of **Sanofi**'s diabetes and cardiovascular business.

INVENTORY DESTOCKING

CFO David Nieto said that the US business challenges that emerged in 2017, notably in relation to inventory destocking, misuse of patient assist cards and the generic erosion of its Aqua unit's *Acticlate* (doxycycline hyclate) business, were behind it after the company booked impairments of €324m in 2017. The Acticlate impairment totalled €246m with the PoliGroup asset impairment adding another €53m. Nieto said that while the Acticlate business had "now stabilized", Aqua would not be a growth driver for Almirall.

Guenter and Nieto pointed to the December in-licensing of the Phase III actinic keratosis asset KX2-391 from **Athenex Inc.**, the successful launch of oral psoriasis treatment *Skilarence* (dimethyl fumarate) in Germany and the UK and the expected launch late in 2018 or early in 2019 of anti-interleukin-23 product tildrakizumab (partnered with **Sun Pharmaceutical Industries Ltd.**) as reasons to be cheerful about Almirall's prospects as a dermatology-focused group.

Nieto noted that the reallocation of resources away from non-core and generic-challenged areas of the business towards product launches and building an EU psoriasis franchise in 2017 would continue with further bolt-on M&A and R&D pipeline strengthening in 2018. Guenter specified that Almirall would spend €30-40m on the European launch and marketing costs for its Skilarence/tildrakizumab psoriasis franchise. He said the firm was shifting 10-15% of its resources from areas suffering from the entry of generic competition into areas of future growth.

> 'If we can have opportunities to increase critical mass in some key markets we will do that – we have the balance sheet to do both'

The company believes KX2-391's apparently improved tolerability and expected short duration of treatment, along with its good effectiveness, should position it well to both expand the actinic keratosis treatment market and gain market share in the class. The product is a new chemical entity with a novel mechanism of action targeting Src kinase and binding alpha tubulin. Almirall's existing actinic keratosis product, *Solaraze* (diclofenac gel), is facing generic competition; it will be hoping that the Athenex deal will enable it to protect and grow its franchise in the US and Europe; the downside is that it will have to pay out launch and sales performance milestones and tiered royalties.

Guenter expressed confidence that Skilarence would exceed €50m in peak sales, after capturing 40% of **Biogen Inc.**'s *Fumaderm* volumes by January and 20% of the value of conventional market share in Germany while also growing albeit from a lower base in the UK; further launches in Finland, Poland, the Netherlands, Spain and Italy are planned for 2018 with additional countries lined up for 2019. The CEO reiterated that the total psoriasis franchise including tildrakizumab would reach peak sales of €250m.

PLAYING CATCH-UP

Still, tildrakizumab will be playing catch-up to **Janssen Pharmaceutical Cos.**'s rival anti-IL-23 *Tremfya* (guselkumab), which got off to a headstart with an EU launch in late 2017. Meanwhile, **AbbVie Inc.**'s risankizumab is also snapping at tildra's heels, although Guenter believes tildrakizumab will still be second to market in Europe, "slightly ahead of risankizumab." He believes recent long-term safety data on tildrakizumab and its three-month dosing regimen (versus every two months Tremfya, although risankizumab will also be every three months) stand in its favor, along with the company's growing position with Skilarence, supporting his overall peak sales forecast for psoriasis.

On M&A, the company will look for late-stage dermatology pipeline assets, although "if we can have opportunities to increase critical mass in some key markets we will do that – we have the balance sheet to do both," said Guenter. Nieto said Almirall would not go above 2.5-3.5X EBITDA leverage.

Investors appeared to be reassured by progress made and plans laid (or at least relieved not be confronted with any more nasty surprises): the stock closed up 3.6% at €8.47 on Feb. 26 following a presentation by Guenter and colleagues.

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Merck & Co's Viralytics Buy Puts Oncolytic Viruses Back In Spotlight

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Merck & Co. Inc. has jumped on the merger and acquisitions merry-go-round to snap up Australia's **Viralytics Ltd.** and broaden its research efforts in oncolytic virus therapy.

The US giant is paying A$502m ($394m), or A$1.75 per share, which represents a premium of 160% to the Sydney-headquartered group's average stock price over the last month. For its money, Merck will gain full rights to *Cavatak*, an immunotherapy based on Viralytics' formulation of an oncolytic virus (Coxsackievirus type A21) that has been shown to preferentially infect and kill cancer cells and is being investigated both as an intratumoral and intravenous agent.

The companies have been partners since November 2015 when they inked an agreement to look at combining Cavatak with Merck's anti-PD-1 blockbuster *Keytruda* (pembrolizumab) and Viralytics provided a progress report at the Society for Immunotherapy and Cancer (SITC) meeting in November last year in National Harbor, MD, about ongoing trials.

PROMISING FOR MELANOMA

Updated results from the Phase Ib CAPRA study in late-stage melanoma patients of the Canatak/Keytruda combination showed good tolerability and a preliminary best overall response rate (ORR) of 61% (14 out of 23 patients) and a disease control rate of 78% (18/23), with very promising durability of response in seven of eleven patients with the most advanced Stage IV disease. These response rates, albeit in the relatively small CAPRA study, exceed the published rates for either agent used alone in patients with late-stage melanoma, Viralytics noted (Cavatak: 28% and Keytruda 33%), adding that there are now 26 of 50 planned patients enrolled in the study. The combo is also in early-stage trials for advanced non-small cell lung cancer and metastatic bladder cancer.

Catavak is also being studied in combination with **Bristol-Myers Squibb Co.**'s CTLA-4 immune checkpoint inhibitor *Yervoy* (ipilimumab) and at SITC, Viralytics gave an update of the MITCI clinical trial, which showed that the combo is well tolerated and has activity in advanced melanoma patients whether or not they have been previously been treated with anti-PD-1 therapies. In the 14 patients who had not been previously treated with Keytruda or other anti-PD-1 therapies, the response rate was 57% and the company noted that in the seven patients who had failed earlier single-line anti-PD-1 treatment, responses have been seen in two of them.

Merck seems to like what it has seen so far and Roy Baynes, head of global clinical development and chief medical officer at Merck Research Laboratories, said in a statement that Viralytics's approach of engaging the innate immune system to target and kill cancer cells "complements our immuno-oncology strategy, which is focused on the rapid advancement of innovative monotherapy approaches and synergistic combinations to help the broadest range of cancer patients."

The purchase of Viralytics is yet another example of a major checkpoint inhibitor company looking to combinations with other immunotherapies which they hope will prove more effective in more patients than their current offerings. Last week, Bristol signed a headline-grabbing deal (involving a $1.85bn upfront payment) with **Nektar Therapeutics** which will look at the combination of the latter's interleukin-2 agonist NKTR-214 with Bristol's PD-1 inhibitor *Opdivo* (nivolumab) and Yervoy.

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The proposed acquisition represents something of a revival of interest in oncolytic viruses. The first such therapy to be approved by the US Food and Drug Administration, back in October 2015 for melanoma, was **Amgen Inc.**'s *Imlygic* (talimogene laherparepvec), but strong competition from the likes of Keytruda, Yervoy and Opdivo has limited its commercial success.

COMBINATIONS THE KEY

Interestingly, Merck R&D chief Roger Perlmutter was research head at Amgen in 2011 when the firm got hold of Imlygic through its $1bn acquisition of Biovex. Merck and Amgen have been working on a Keytruda/Imlygic combo since 2014 and there may be a readout from a Phase III trial, KEYNOTE-034, later this year.

As for the acquisition, the board of directors at Viralytics unanimously recommended the deal, subject to there being no superior proposal and an independent expert concluding that it is in the best interest of shareholders. If all goes well, the transaction should be completed by the second quarter.

The news that Viralytics is likely to be bought will have been noted by other biotechs in the oncolytic virus space. These include the UK's **Psioxus Therapeutics Ltd.**, which is developing enadenotucirev with Bristol and France's Transgene SA, whose *Pexa-Vec* (pexastimogene devacirepvec) is being investigated in combination with Opdivo for liver cancer.

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Gilead Partners With Sangamo For Gene Editing As It Builds Up Kite's Cell Therapy Platform

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Gilead Sciences Inc. chose to invest up to $3.16bn in one of the gene editing field's earliest developers – **Sangamo Therapeutics Inc.** – over emerging players in this area to help Gilead's **Kite Pharma Inc.** subsidiary create better T cell therapies for cancer.

Gilead executives have said since the company acquired chimeric antigen receptor T cell (CAR-T) therapy developer Kite for $11.9bn last year it would invest in additional technologies to expand and improve its new cell therapy platform. Gilead President and CEO John Milligan described Sangamo's zinc finger nuclease (ZFN) technology as "the optimal gene editing platform," in a Feb. 22 statement about the deal, noting that it may be used to develop safer and more effective CAR-T therapies that are available to more patients.

Kite's first approved CAR-T product is the autologous therapy *Yescarta* (axicabtagene ciloleucel) for certain advanced lymphoma patients, which is comprised of reengineered T cells derived from each treated patient. The Gilead company plans to use Sangamo's ZFN technology to develop off-the-shelf allogeneic CAR-T, T cell receptor (TCR) and natural killer (NK) cell therapies.

The partners, which have identified some initial oncology targets for specific therapeutic programs, also will attempt to develop CAR-T therapies for solid tumors – a sort of holy grail for the field, which to date has been successful primarily in hematological malignancies.

RICH DEAL TERMS

Gilead will pay Sangamo $150m up front for an exclusive license to the ZFN technology for oncology indications and up to $3.01bn in fees related to research, development, regulatory and commercial milestones for 10 or more products – up to $300m per program – plus single-digit royalties on any commercialized products. Kite will be responsible for all development, manufacturing and commercialization costs and, it will fund all of Sangamo's work under the collaboration.

"Sangamo will be primarily responsible for developing and optimizing the cell therapy genome-editing process, including levering ZFNs to knock out specific target genes and [adeno-associated viral vectors (AAVs)] to deliver CARs, TCRs and NKRs for autologous and allogeneic T-cell and NK cell products," Sangamo Senior Vice President and Chief Business Officer Curt Herberts said during the company's Feb. 22 conference call to discuss the deal and its fourth quarter 2017 financial performance.

Sangamo reported a $13.1m net loss for the quarter and ended 2017 with $244.6m in cash – a balance that has grown significantly in 2018 via the upfront fee from Gilead/Kite and through a second collaboration with **Pfizer Inc.** The deal announced in January brought in $12m in upfront cash and the promise of up to $150m in milestone fees for the development of a gene therapy to treat neurodegenerative disorders, including amyotrophic lateral sclerosis (ALS) and frontotemporal lobar degeneration (FTLD), both of which are caused by a mutated C9ORF72 gene.

Sangamo Senior Vice President and Chief Financial Officer Kathy Yi said during the conference call that the company expects its cash resources will last into the second half of 2020. The cash will fund four Phase I/II programs for the treatment of hemophilia A and B and lysosomal disorders, and myriad preclinical and research-stage programs. Its wholly-owned and partnered assets include genome editing, gene therapy, gene regulation and cell therapy programs. Besides Gilead/Kite and Pfizer, Sangamo is working with **Shire PLC** and **Bioverativ Inc.**, in a deal inked before the latter company was spun out of Biogen.

WHY NOT CRISPR?

Analysts were somewhat surprised that Gilead chose Sangamo over other gene editing pioneers, such as **CRISPR Therapeutics AG**, but BMO Capital Markets analyst Iain Somaiya surmised that the decision was based largely on Sangamo's experience with its ZFN technology since the 1990s, versus firms founded within the past five years to work on CRISPR/Cas9-based technologies.

"Gilead seems to be prioritizing experience over novelty by selecting ZFNs (in development since the '90s) over CRISPR/Cas9 or Cpf1 (~five years old)," BMO Capital Markets analyst Iain Somaiya wrote on Feb. 22. "We think improvement in ZFNs in recent years resulting in faster lead product generation (~100 ZFNs can be generated and screened against a particular gene sequence in ~10 days), efficiency (~99.5% on-target gene editing efficiency and off-target editing below limit-of-detection), and ability to multiplex (putative advantage for CRISPR, but ZFNs can achieve ~76% efficiency for four same-cell edits) made this collaboration possible."

Investors appeared to be impressed with Gilead's endorsement of Sangamo's ZFN technology, sending the Richmond, Calif.-based company's stock up 14.4% to close at $25.40 on Feb. 22.

"The deal unlocks substantial potential for Sangamo, validating and leveraging ZFN tech, while leaving several immune cell types/indication paths unencumbered," Jefferies analyst Maury Raycroft wrote in a Feb. 22 note. "For Gilead, the potential to create next-gen autologous and broad off-the-shelf therapies should provide a competitive advantage."

Raycroft said the deal terms "could be the best yet for a gene editing program" and cited four prior deals in the CAR-T space:

- **Johnson & Johnson**'s agreement to pay **Transposagen Biopharmaceuticals Inc.** up to $292m per CAR-T under a 2014 agreement;
- Pfizer's 2014 deal with **Cellectis SA** worth $80m up front and $185m per product;
- **Juno Therapeutics Inc.**'s 2015 deal to pay **Editas Medicine Inc.** $25m up front and $230m per product for three programs; and
- A 2015 transaction in which **Novartis AG** agreed to pay **Intellia Therapeutics Inc.**

$10m up front and $230m per product over a five-year term.

"We find it interesting that Gilead chose zinc finger technology over CRISPR technologies; we had speculated CRISPR Therapeutics as a potential partner candidate, since it is the last company that has an unencumbered oncology vertical using CRISPR technology," William Blair analyst Katherine Xu said in a Feb. 22 note.

"However, we believe it is likely that Gilead chose Sangamo's ZFN platform, because it is a more established technology with a good degree of flexibility in gene sequence target design and apparent lower risk of off-target effects, as well as some demonstrated success in human gene-editing, both *in vivo* and *ex vivo*," Xu continued. "Further, Sangamo is the single-largest holder of zinc finger protein-related patents and exclusive licenses, which should provide Gilead with a cleaner [intellectual property (IP)] landscape in which to develop and commercialize novel therapies."

Sangamo Vice President of Research Michael Holmes explained during the company's call that "multiplex editing is the ability to make multiple genetic changes in a single step and is critical for the development of next-generation cell therapies to treat liquid and solid tumors in cancer. It enables simultaneous knockout of certain genes to prevent the body from rejecting the treatment and knock in a new gene to equip the modified T-cells with targeted anti-tumor functions."

MORE DEALS FOR SANGAMO

While working with Kite to accelerate the development of its next-generation therapies for cancer, Holmes said Sangamo will use its technology to explore the use of gene-edited cell therapies in indications outside oncology, including autoimmune diseases. The agreement with Gilead does not preclude the company from using its technology to develop treatments in non-cancer indications on its own or with additional partners.

For Gilead, the deal continues the company's promised strategy of investing in technologies that can improve upon the CAR-T and TCR technology that Kite developed prior to its acquisition last year. The company acquired **Cell Design Labs Inc.**, which already was working with Kite, for $567m in December. Many in the cell and gene therapy sector believed that Gilead's Kite acquisition validated these technologies and would catalyze investment in the CAR-T sector. Although, as Jefferies' Raycroft pointed out, many players already were partnering with smaller firms to boost their internal programs.

"We view this Sangamo partnership as building on the scientific expertise and access to technology Gilead has, but we would expect Gilead to continue to pursue external opportunities in the cellular therapy space," Credit Suisse analyst Alethia Young said in a Feb. 22 note. "With ~$37bn in cash, we view the $150m upfront to Sangamo as incremental compared to the amount of technology the company has the ability to acquire with its resources. We think CRISPR and gene therapy (particularly for diseases outside of oncology) remain on the table."

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OPTIMIZING ENROLLMENT:

The need for broad, timely data and powerful, yet simple analytics

Access to data and the ability to mine it for insights into patient availability are key drivers of efficient clinical trial enrollment. The explosion in healthcare data means the raw material needed to generate insights is available in huge quantities. The problem is study teams have limited ability to standardize, aggregate and analyze these vast datasets. Addressing these shortcomings will optimize enrollment by empowering teams to be more effective at bringing awareness of relevant clinical trials to patients and considering how to bring patients to the clinical trials that can potentially offer life-saving treatment options.

Today, many trials struggle to efficiently identify, recruit and retain participants. A significant minority of trial sites never enroll a single patient, which results in significant recruiting challenges and adds time and cost to the study lifecycle. This has a downstream commercial impact for sponsors and, more importantly, means patients must wait longer for potentially life-saving new treatments.

The recruitment conundrum remains unsolved despite concerted efforts to improve feasibility and design clinical trials around the needs of sites and the patients they enroll. These efforts have yielded many benefits, but predicting the true availability of patients at the time of enrollment is still beyond their reach. Organizations have responded by sourcing data to improve their predictions, with often mixed results.

Why early data initiatives have struggled

The modern healthcare system is rich in data, including a wide breadth of sources like electronic medical records and laboratory results. Equally, data depth is provided by large private payers and integrated systems in the United States and national single payers in Europe. These organizations have records on tens of millions of patient lives.

Large pharmaceutical companies have accessed some of these networks to help predict where they will find patients eligible to participate in clinical trials. Yet the effect on the bottom line of recruitment rates has been mixed, and enrollment rates in many trials remain suboptimal.

The struggles of early data initiatives reflect the need for access to broader, more real-time data. Although an abundance of data is available, most sponsors have relatively few affiliations to the networks that control it. Thus, decisions intended to optimize enrollment are made on the basis of a narrow subsection of all the data that could inform those choices.

A study team with access to real-world evidence from payers, prescribers, diagnostic testing laboratories and hospital patient records is better placed to predict subject availability than one equipped with data from a single network. Getting access to very robust, extensive records from multiple organizations in multiple geographies will give sponsors a global data pool capable of getting trials to patients, and getting patients to the physicians running those trials.

The need for competitive intelligence

Access to such broad data gives study teams a good idea of where to locate trial sites. What it cannot do is say whether those sites will be able to enroll patients when the study goes live. Historic data, however broad and deep, can be rendered ineffective by changes on the ground, such as targeting the same patient population as a competitive trial. To fully optimize enrollment, companies need competitive intelligence that factors the geographic distribution and inclusion/exclusion criteria of rival clinical trials into forecasts of patient availability.

Study teams look for early competitive intelligence while building country strategies and coming up with lists of potential investigators in their targeted geographies. The need for intelligence becomes more pressing when the team is pre-qualifying sites during the site assessment phase. If, for example, 40% of a study's top 30 potential investigators are actively involved in a competitor's clinical trial, it is vital that the study team is aware and mitigates the risk of a protracted site selection process.

That level of understanding can only be achieved through intelligence that illuminates similarities between trials that are competing for the same population of patients. Minor differences in inclusion/exclusion criteria will influence which studies recruit patients in droves and which struggle to enroll at all. Study teams that explore these nuances in protocol design can better anticipate challenges in the site selection process and offset the potential effect of a competitor's trial on recruitment rates.

These factors are crucial to the optimization of enrollment. Competitive intelligence and an intelligent trial design will move study teams closer to the ideal scenario: being able to view patient availability across the entire clinical trial process, from protocol feasibility up to actual recruitment by sites.

A significant minority of trial sites never enroll a single patient

What end users need to glean insights

Pools of broad, timely data incorporating competitive intelligence will give companies a far more accurate picture of patient availability than they have today. Accessing the data is just the first step; the multitude of data sources must also be standardized, aggregated and analyzed in a simple and consumable format.

Housing data from a large number of networks in a single platform will enable powerful, predictive enrollment modelling. Tools that ingest and use real-time electronic patient data to make predictions about enrollment are available in the market today. Expanding the data available to these models will result in more accurate predictions about where patients are, and their potential for inclusion in a clinical trial.

It is important to ensure the system mines the breadth of the data. Applying analytics that are too targeted to the resource will undermine efforts to create broad datasets through affiliations with global networks. Conversely, such overly-targeted analytics subset the repository to the point where it effectively covers only a narrow spectrum of information.

Analytic platforms must also consider the user experience. End users will be clinical development professionals—not data scientists. The system must be easy to access, navigate and use within the context of existing processes while also providing powerful analytics, predictive models and visualizations. Failing to meet this user experience standard will lead to a significant failure rate.

Developing effective analytics based on broad and timely datasets are big challenges, but they will also yield big rewards. By rising to these challenges, the industry can unlock the potential of data-driven insights that connect patients to clinical trials and clinical trials to the patients who want to take control of the full scope of their healthcare options.

About Medidata Solutions

medidata

Medidata Solutions is the leading global provider of cloud-based solutions for clinical research in life sciences, transforming clinical development through its advanced applications and intelligent data analytics. The Medidata Clinical Cloud™ brings new levels of productivity and quality to the clinical testing of promising medical treatments, from study design and planning through execution, management and reporting. We are committed to advancing the competitive and scientific goals of global customers, which include over 90% of the top 25 global pharmaceutical companies; innovative biotech, diagnostic and device firms; leading academic medical centers; and contract research organizations.

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Jobs Go At Shield Therapeutics As Failed Study Fallout Hits

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Shield Therapeutics PLC is to make significant cuts to its workforce while its board considers the firm's future in light of the recent failure of a key new study of its only marketed drug *Feraccru* (ST10, ferric maltol) that would have opened it up to the US market.

The news comes just as the CHMP has voted to broaden the product's label in the EU, but as the job cuts will be focused on its sales staff, Shield will be unable to take much advantage of the expanded indication.

Feraccru was first approved in the EU for the treatment of iron deficiency anemia (IDA) in patients with inflammatory bowel disease (IBD) in early 2016, and first marketed in the UK and Germany. It will remain commercially available through Shield, and will still marketed by its commercial partners in Scandinavia, Switzerland and central eastern Europe.

SHARES LOSE VALUE

But the plan has always been to extend its use in other anemia populations. A key plank in this ambition was the US Phase III study AEGIS-CKD study which evaluated hemoglobin response to Feraccru (30 mg twice daily) compared with placebo in the treatment of IDA in patients with chronic kidney disease (CKD). Since top-line news of its failure on Feb. 5, shares in the firm listed on the AIM have lost more than 80% of their value, and were trading on Feb. 23 at around 22.50 pence.

The "unexpected and disappointing" results are now being analyzed more fully by the company and the outcome expected by the end of March. These, together with discussions with the US FDA, will largely inform the board's strategy.

In the meantime, "significant" job cuts and a reduction in promotional activities related to Feraccru will preserve resources, with "identification of further cost containment remaining an ongoing priority". Shield currently employs around 80 people and it seems probable well over half of these will go; further details are likely to come in the next week or so.

The headcount reduction will give the firm sufficient cash resources to fund the business until at least the end of Q4 2018; it had previously had a cash runway until the end of the second quarter.

This should give it time to "think about what is doable and what can get the best value for shareholders," CFO Karl Keegan told *Scrip*. "The board want to fully understand what had gone on in the trial as it came as a big surprise to everyone, and they want to extend the cash run as long as possible into Q4; it may slip into 2019 depending on other decisions that are made."

ADDED VALUE?

Shield CEO Carl Sterritt said in a statement that there was significant value in Shield's assets "not least because of the frequent positive feedback we continue to receive from prescribers and patients who use Feraccru." This value has been augmented, at least to some extent, by the CHMP opinion announced on Feb. 23 which recommends that the label be changed to include all patients with iron deficiency.

> The negative is that we have a failed trial in the US but we do have a drug approved in Europe and the other positive is getting this broader label

Keegan said this added a theoretical value to the asset. While the IDA in IBD population is attractive commercially it is relatively small compared (300,000 patients in Europe) with the far wider "iron deficiency" indication which runs into many millions.

"The negative is that we have a failed trial in the US but we do have a drug approved in Europe and the other positive is getting this broader label. The downside is that we will not have our own means of exploiting that broader label."

As a result of a change in focus for Shield's finance team since the AEGIS-CKD initial trial results, the company said it would now announce its results for the year ended Dec. 31 2017 on April 11 and not as previously announced on Feb. 28.

It did say trading for FY 2017 was in line with board expectations and 2018 trading started positively. Revenues for the 12 months ended Dec. 31 are expected to be £637,000 (up from £304,000 in 2016).

At the year end the company's unaudited cash position was £13.3m (2016: £21.0m).

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ABAC Chief Calls For Better Antibiotic R&D Incentives In Europe

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European biotechs in the antimicrobial resistance space are being hurt by the funding hurdles in schemes such as the Horizon 2020 research and innovation program, and are turning to the US for financial support.

So noted Albert Palomer, CEO of **ABAC Therapeutics**, speaking to *Scrip* days after the Spanish company announced it had closed a €16m Series A round. In an interview, he spoke about the different approaches on each side of the Atlantic for novel antibiotics to both 'push' incentives (those designed to support R&D directly) and 'pull' incentives (those that reward successful outcomes) and why the US offers a better deal for small biotechs.

Albert Palomer

PULL AND PUSH

Looking at push incentives in particular, Palomer spoke glowingly about CARB-X (Combating Antibiotic Resistant Bacteria Pharmaceutical Accelerator), the $450m global initiative backed by the US government and the UK's Wellcome Trust. Describing it as the holy grail, he said CARB-X is "very practical and if you pass the exams, you get the money, that's it," while in Europe, "the system is exactly the opposite."

Palomer said that Horizon 2020 is not practical, noting that "the money is there and the commitment to antibiotics is there" but the process is flawed. "You have to compete with thousands of projects," he noted and "the management is extremely complex and small companies can't afford that, you won't see many small biotechs applying to Horizon 2020, it is not helping us."

It is a frustrating situation especially as the European firms involved in antibiotics research are themselves well-organized, Palomer added, citing the BEAM (Biotech companies in Europe combating Anti-Microbial Resistance) Alliance, which has 45 members which are collectively developing over 120 R&D projects focused upon the cure and prevention of bacterial infections. "We are much better organized than our US counterparts but most of us are asking for money from the US: it is a paradox."

What the sector needs, he said, is "a European CARB-X, something practical but for biotech, not big pharma. That would be helpful, especially as we have so many leading companies in this field in Europe."

As for ABAC, its financing round announced Feb. 16 was led by Israel-based healthcare fund Pontifax and the Global Health Science Fund (jointly established by Quark Venture and GF Securities). There was also backing from Caixa Capital Risc, Debiopharm Innovation Fund (part of the venture arm of the Switzerland-based infectious diseases specialist) and existing investor Ferrer, the Spanish company that ABAC was spun out of in 2013.

Palomer told *Scrip* that "it has been quite an experience, but we've learnt a lot – we are scientists!" He added that the firm only contacted a few backers, "people who really understand what we are doing and we have a good balanced group of investors who add value scientifically as well as financially."

What ABAC is doing is applying precision medicine to the treatment of infectious diseases. The firm has developed a discovery platform called PasNas to identify novel pathogen-specific antibiotics designed to selectively kill multi-drug resistant bacteria.

PasNas, developed by Palomer and fellow ABAC co-founder Domingo Gargallo-Viola (the firm's chief scientific officer), maximizes the likelihood of success for the hits found in the screening phase process, resulting in more artificial intelligence-type decision-making. It has generated a series of promising molecules and ABAC's lead program will target multi-drug resistant *Acinetobacter baumannii*.

Palomer said the latter is a rare but increasingly fatal pathogen recently nominated by the World Health Organization as the most urgent bacterial threat for which new drugs are needed. The Series A funds will be used to advance the *Acinetobacter* program into the clinic.

As well as Acinetobacter, ABAC is also targeting the other three infections caused by the 'big four' Gram-negative bacteria – *Pseudomonas aeruginosa*, *Klebsiella pneumoniae* and *Escherichia coli* – which have been tackled previously by broad spectrum antibiotics. Palomer stressed that the pathogen-specific principle applies to all bacteria species, saying the strategy of the company is to have one drug per pathogen.

As for the future, he said the next two years will be dedicated to increasing the value of the company and then "not just selling to big pharma but collaborating with them, a joint venture." In an area of such unmet medical need, there is room for smaller players to make a difference, Palomar claimed.

He concluded by returning to financing, but this time 'pull' incentives. The main one would be getting a realistic price for antibiotics, which Palomer says is vital for the innovative companies in this field to flourish. As for market entry rewards of €1-2bn for new antibiotics mentioned in some circles as a possible incentive, he was skeptical about such schemes ever seeing the light of day, as "I have never seen any healthcare system release €1-2bn for a new drug and our investors don't believe it either."

However, it is possible that for therapies tackling very dangerous pathogens, a higher price may be achievable, with antibiotics being seen in a similar light to rare disease treatments, Palomer added.

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AbbVie's Got A Competitive Edge With Elagolix

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The first positive Phase III data from **AbbVie Inc.** and partner **Neurocrine Biosciences Inc.** for elagolix for the treatment of heavy menstrual bleeding in women with uterine fibroids puts pressure on competitors also looking to break into the emerging new drug treatment category. AbbVie announced data from the first of two Phase III studies testing elagolix in women with uterine fibroids Feb 21.

There are currently limited non-surgical treatments for heavy bleeding associated with uterine fibroids, but **Allergan PLC** and the **Roivant Sciences GMBH**-backed women's health start up **Myovant Sciences Ltd.** are also looking to break into the category. Thus far, Allergan and partner

Gedeon Richter PLC have appeared to have a lead in the race with the selective progesterone receptor modulator (SERM) ulipristal, which is pending at the US FDA for uterine fibroids with action expected in May. But the drug, which is approved in Europe as *Esmya*, ran into a potential safety snag that could impact the US review.

Myovant, meanwhile, is further behind AbbVie with relugolix, which like elagolix is a gonadotropin-releasing hormone (GnRH) receptor antagonist. Myovant initiated two Phase III trials testing relugolix in women with uterine fibroids and two Phase III trials in women with endometriosis last year, with data expected in 2019.

AbbVie and Neurocrine have another advantage. They already filed elagolix with the FDA for approval for the management of endometriosis with associated pain and received a priority review. With FDA action expected in the second quarter, they are poised to have a substantial head start in terms of commercializing the drug.

Uterine fibroids are a common type of abnormal growth in a women's pelvis. Up to 80% of women can have fibroids by the age of 50, though most are asymptomatic. About 25% of women have fibroids that cause heavy menstrual bleeding, painful periods and unexpected vaginal bleeding, and the condition can affect African American women more often. Existing treatment options include invasive and non-invasive procedures including surgery (hysterectomy, myomectomy), as well as oral contraceptives, progestins, and occasionally GnRH agonists that are not specifically indicated for the treatment of uterine fibroids, according to AbbVie.

In the Phase III ELARIS UF-1 study of elagolix, AbbVie and Neurocrine tested the drug in combination with low-dose hormone, or "add-back" therapy (estradiol/norethindrone acetate). The study met its primary endpoint of reduced heavy menstrual bleeding, with 68.5% of women with uterine fibroids achieving clinical response compared to placebo (8.7%) as measured by the alkaline hematin method. Clinical response was defined as menstrual blood loss volume of less than 80mL during month six and a 50% greater reduction in menstrual blood loss volume from baseline to month six.

One of the challenges of treating with GnRH antagonists is managing the side effects, which include hot flashes and reduction in bone mineral density. AbbVie said those effects were seen in the Phase III data but did not provide any details. The full results will be presented at an upcoming medical meeting. The company said the data do support a regulatory filing for elagolix and believes it is poised for a commercial launch in uterine fibroids in 2020.

GnRH antagonists work by blocking GnRH signaling, inhibiting luteinizing hormone and follicle-stimulating hormone secretion, which leads to reduced ovarian production of the hormones estradiol and progesterone. That's why adding back some hormone can help mitigate side effects.

ROOM FOR MORE THAN ONE

Elagolix and relugolix could end up having some differences, particularly depending on how the Phase III trials are designed and how the side effects are mitigated with add-back therapy. Myovant CEO Lynn Seely talked to *Scrip* about the competitive dynamics at the J.P. Morgan Healthcare conference in January. She mentioned that maximizing the benefits while managing the tolerability and side effects could potentially differentiate the therapies, and pointed out that relugolix has a longer half-life. But Seely also said she believes the market opportunity is large enough to support more than one product.

"Millions of women are suffering and it's highly unusual to have so few treatments," she said. "It's actually great that AbbVie is getting out there and starting to change the landscape from surgical procedures to oral medication."

Seely likened the experience to the one she went through at her former company, **Medivation Inc.**, where she was chief medical officer and helped develop and launch the prostate cancer blockbuster *Xtandi* (enzalutamide) after **Johnson & Johnson** successfully developed a drug for the same indication, *Zytiga* (abiraterone).

"We were second but we brought a differentiated product to market in a very under-served marketplace and both have done very well, and I suspect you may see something similar here," Seely said. Myovant licensed the drug from **Takeda Pharmaceuticals International GMBH** for markets outside of Japan, but Takeda already announced the results of Phase III trials for the Japanese market that turned out positively.

AbbVie expects elagolix will be a blockbuster with sales potentially surpassing $2bn. BMO Capital Markets analyst Alex Arfaei agreed, guiding to sales of $2.2bn in 2025. "We believe elagolix is a promising assets for endometriosis and uterine fibroids," he said in a same-day research note. "We fully acknowledge that AbbVie has a promising pipeline. Our concern is that it is not strong enough to offset headwinds facing the immunology franchise with interchangeable biosimilars and drive growth after 2022." The company is hoping its pipeline will help offset lower sales of *Humira* (adalimumab) ahead of biosimilar competition.

One uncertainty is Allergan/Gideon's ulipristal. In Europe, the EMA has put restrictions on use of Esmya for the treatment of uterine fibroids after several reports of serious liver injury and hepatic failure in women taking the product. It seems likely the safety issue will need to be explored before FDA grants approval. *Published online 23 Feb 2018*

Richter Expects Esmya Sales To Drop 50% Following EU Restrictions Over Liver Concerns: **http://bit.ly/2Cq1dwf**

AbbVie's Alzheimer's Efforts Voyage Into AAV-Targeted Tau Antibodies

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AbbVie Inc. and **Voyager Therapeutics Inc.** are collaborating on an Alzheimer's disease program that would create a single-administration gene therapy delivering a monoclonal antibody targeting tau protein into the patient's central nervous system via a targeting mechanism using adeno-associated vector (AAV) technology.

Announced Feb. 20, the agreement brings Voyager $69m up front with the potential for up to $155m in preclinical and Phase I option payments, up to $895m in development and regulatory milestones for each candidate ultimately licensed by AbbVie and tiered royalties on global sales of any product reaching the market. Cambridge, Mass.-based Voyager will be responsible for the research, preclinical and Phase I work, with AbbVie holding options to take over and advance three of five target programs.

Voyager said the partnership will begin with discovery work, and will not build upon any previous R&D either company has undertaken in Alzheimer's. Therefore, it will not affect nor incorporate AbbVie's tau-targeting antibody candidate ABBV-8E12 for Alzheimer's, which is currently being tested in a 400-patient Phase II study.

The Chicago-area pharma also is investigating that candidate in Phase II for progressive supranuclear palsy (PSP), mirroring a **Biogen Inc.** effort which is studying a tau-targeted antibody licensed from **Bristol-Myers Squibb Co.** in the same two indications.

According to Biomedtracker, there are 10 clinical candidates for Alzheimer's disease that target tau protein, whose deposits or "tangles" are implicated in the neurodegenerative disease. Five of the candidates solely target tau, while five others include tau in a multiple-target approach. The most advanced, according to Biomedtracker, is **TauRx Pharmaceuticals Ltd.**'s small-molecule tau integration inhibitor LMTX, which is in Phase III.

The deal is AbbVie's second partnership in recent months in neurodegenerative disease, following October's tie-up with **Alector LLC** to investigate an immuno-neurological approach to Alzheimer's and other neurodegenerative disorders. It is Voyager's second big pharma partnership, following its ongoing 2015 collaboration into CNS disorders with **Sanofi.** That agreement, however, was revised in late 2017, when the French pharma gave up its ex-US rights to Voyager's lead clinical candidate, VY-AADC01 for Parkinson's disease.

ENCODING ANTIBODIES

Voyager said the partnership with AbbVie will attempt a novel therapeutic approach, in creating "vectorized" gene therapy that would more or less teach the brain to fight Alzheimer's disease.

"That's the nature of the program, that the two parties will combine their efforts to create new monoclonal antibodies that can be vectorized," Matt Osborne, Voyager's VP of investor relations, told *Scrip*. "It's a newer concept to take not just the antibody but the genes that encode the monoclonal antibody and deliver them with a one-time infusion to the brain so that then there can be production of the monoclonal antibody directed against tau."

The partners are not disclosing what specific type of vector will be used, although Voyager said capsid AAV technology in-licensed from **California Institute of Technology** in 2016 will be considered for the program. The capsid technology, being tested in some of Voyager's other pipeline programs, can affect the way a gene therapy penetrates certain cell types or tissues, he said. The two companies also aren't providing much detail on timelines, although Voyager said AbbVie should have the opportunity to select the three targets to take forward within two to three years.

Morgan Stanley analyst Matthew Harrison, in a Feb. 20 note, called the agreement with AbbVie "a positive for Voyager, as it provides the company with non-dilutive capital to progress its efforts with Alzheimer's disease, a therapeutic area known for its complexity and burdensome trial costs."

"Additionally, many investors may see AbbVie's involvement as a sign of validation for Voyager's gene therapy platform," he said. BTIG analyst Dane Leone also offered a positive take on the partnership Feb. 20, calling it "highly strategic" for Voyager as it allows the biotech to maintain its primary focus on its lead candidate in Parkinson's disease. AbbVie clearly was encouraged by Voyager's preclinical findings related to the delivery of vectorized tau antibodies, Leone added.

While the early work will fall to Voyager, the company pointed to AbbVie's longtime expertise in antibody development, particularly its ongoing success with multi-blockbuster drug *Humira* (adalimumab), as an advantage. "They have tremendous, deep experience in preclinical and clinical development and then global commercialization of antibodies," the company said.

The R&D effort's goal is to use vector technology to both penetrate the blood-brain barrier to deliver an Alzheimer's therapy directly to the brain – using either intravenous or intrathecal administration, Osborne noted – but also then target the therapy to the desired locations once it passes that barrier.

"The challenge with current antibodies that are systemically administered [is that] they have to be dosed weekly or bi-weekly," Osborne explained. "And not enough of that antibody crosses the blood-brain barrier – only about 0.1% of the antibody gets into the brain and crosses the blood-brain barrier. But then it's also important which cells in the brain you are targeting and whether the antibody can get into those certain cell types."

Much of the R&D work, therefore, will involve optimizing the delivery method, the capsid, the uptake and ultimately the expression of the genetic material included in the therapy, Osborne added.

Voyager's lead program VY-AADC01 is currently wrapping up the third cohort of its Phase Ib trial, with plans for a pivotal Phase II/III study to launch by the middle of 2018. The biotech intentionally withheld US rights to the candidate from its agreement with Sanofi, which is why the pharma said it decided to cede its ex-US rights to the therapy, while continuing to participate in two other programs begun under the 2015 collaboration.

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Lilly Halts Hanmi BTK Inhibitor Trial For RA, Mulls Other Indications

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Eli Lilly & Co. has suspended Phase II clinical trials in rheumatoid arthritis of its novel oral Bruton's tyrosine kinase (BTK) inhibitor HM71224/LY3337641, which was licensed in from **Hanmi Pharmaceutical Co. Ltd.** in 2015, but the two companies are continuing to discuss development of the small molecule for other indications, Hanmi said.

"Lilly has informed us on Feb. 14 that it will suspend clinical trials of the molecule as interim results of its Phase II study [in RA] have increased the possibility of not meeting the efficacy as targeted," said Hanmi.

However, there are no changes to its license deal with Lilly on HM71224/LY3337641 and Hanmi isn't obligated to return its upfront payment and does not have other financial cost obligations because of this, explained the South Korean pharma firm.

"After a scheduled review of the data, it was determined that the difference between the placebo and active treatment arms of the study was not sufficient enough to support the continuation of the trial," Nicole Hebert, advisor, Lilly Research Laboratories Communications, told *Scrip*. "Lilly and Hanmi are in discussions about the next steps for the molecule."

According to clinicaltrials.gov, Lilly's two part Phase II study to evaluate the safety and efficacy of LY3337641 in adult subjects with RA, the RAjuvenate Study, had begun in August 2016 with an estimated enrollment of 276 participants. It was slated to be primarily completed in May 2018.

"Lilly has had difficulty in getting its JAK inhibitor *Olumiant* (baricitinib) approved for use in RA by the FDA. This, together with uncertainty around HM71224/LY3337641's efficacy, may have driven Lilly's decision to terminate the Phase II study for the BTK inhibitor," Christina Vasiliou, an analyst at Datamonitor Healthcare, told *Scrip*.

Lilly initially filed for US regulatory approval of Olumiant for moderate to severe RA in January 2016. In April 2017, the FDA issued a complete response letter for Olumiant's NDA, indicating that additional clinical data are required to determine the most appropriate doses and further assess the drug's safety profile across treatment arms. Following discussions with the FDA, Lilly resubmitted Olumiant's NDA with new safety and efficacy data, in the fourth quarter of 2017, the analyst noted.

However, Lilly's Hebert said that there is no connection between suspending the Phase II BTK inhibitor and baricitinib.

"Autoimmune disease is indeed a focus area for Lilly. Our goal is to transform autoimmune disease and to improve lives with leading-edge science, and we are exploring creative clinical approaches and multiple pathways in hopes of identifying new ways to deliver better outcomes," he added.

Hanmi pointed out that clinical trial suspension is frequently seen in novel drug development and stressed that it will further speed up the development of its global innovative drugs with international pharma partners. Hanmi has experienced both setbacks and positive progress since it reached several major licensing out deals with global pharmas in 2015 and 2016.

Boehringer Ingelheim GMBH returned rights to olmutinib, the EGFR inhibitor it licensed from Hanmi in 2015. Meanwhile, Rolontis, a novel, long-acting granulocyte colony-stimulating factor (G-CSF) licensed out to Spectrum Pharmaceuticals Inc., has become Hanmi's first drug developed with its proprietary platform to approach the regulatory filing stage in global markets.

SHARES FALL ON NEWS

Hanmi shares sank 8.5% on Feb. 19, the first trading day after the news was released late Feb. 14; South Korean stock markets were closed Feb. 15-16 due to Lunar New Year holidays.

KB Securities said in a research note that Lilly's clinical trial suspension of may have a negative impact on the South Korean pharma sector as a whole, although it is different from Boehringer Ingelheim's return of rights to olmutinib.

It can't rule out the possibility of Lilly returning its rights to the molecule to Hanmi, but given other global pharmas like AbbVie, AstraZeneca, Merck and Gilead Science's development of BTK inhibitors for the treatment of diseases such as blood cancer and lupus, Lilly is likely to begin clinical trials of the molecule in new indications, the brokerage predicted. According to Biomedtracker, Bristol-Myers Squibb has also initiated a Phase II study on the BTK inhibitor BMS-986142 for RA, while AbbVie Inc.'s BTK inhibitor, acquired via its acquisition of Pharmacyclics, is in a Phase I study.

Samsung Securities also said HM71224 has potential to be developed for other indications given that AbbVie's Imbruvica (ibrutinib), the world's first approved BTK inhibitor, has various uses including in chronic lymphocytic leukemia/small lymphocytic lymphoma and mantle cell lymphoma.

In the March 2015 deal, Lilly inked a license and collaboration agreement with Hanmi for HM71224 under which the partners intended to develop it for RA, lupus, Sjogren's syndrome and other related autoimmune conditions.

Lilly agreed to pay $50m up front and up to $640m in potential milestones for the drug plus double-digit royalties. Lilly is responsible for development, regulatory, manufacturing and commercialization in all indications for all territories outside of Asia (South Korea, China, Taiwan, Hong Kong) where the company operates.

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Aimmune Accelerates Commercial Planning For Peanut Allergy Drug

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Aimmune Therapeutics Inc. says it is planning to "significantly accelerate" its launch planning for the oral peanut protein capsule AR101 now that it has positive data in hand from the Phase III PALISADE study in allergic children and adolescents aged 4 to 17.

More than 2.2m children in the US have a peanut allergy and nothing is approved to prevent severe reactions, though epinephrine is available to reverse potentially deadly reactions. With that in mind, the US FDA granted AR101 breakthrough therapy and fast track designations for desensitization of peanut-allergic patients ages 4-17, and now Aimmune plans to submit a biologic license application (BLA) to the agency before the end of 2018 based on PALISADE's positive results announced Feb. 20.

The company's candidate was developed using its proprietary *Characterized Oral Desensitization ImmunoTherapy* technology platform, created with the help of partner **Nestle Health Science SA**, which made a $145m equity investment in the biotech in late 2016.

Individuals in the 496-patient Phase III PALISADE study were gradually exposed to higher doses of peanut protein. Results were compared to placebo and AR101 hit primary and secondary endpoints, and had an attractive safety profile. Aimmune's BLA filing in the US will be followed by a filing in Europe in the first half of 2019.

The company will release results from a safety study of AR101 called RAMSEY in the third quarter and at the time of its BLA filing AR101 will have a clinical database just over 1,000 exposed patients overall, 600 of whom completed up-dosing with around 500 who had a full year of treatment.

"It should be a robust database by the end of this year," CEO Stephen Dilly said during a Feb. 20 investor call.

ACCELERATING COMMERCIAL LAUNCH

Chief Operating Officer Jeffrey Knapp said that the company has been planning for an accelerated launch in the US due to the breakthrough therapy designation. All of the leadership in marketing and market access is in place and now that the company has PALISADE data it will begin to significantly fill out the organization on the commercial side, including medical affairs and medical science liaisons. As Aimmune gets closer to launch, it will implement a robust plan that has already been drafted for hiring field staff, including field management and sales reps, and then bring on professionals who can help with payer education and getting the drug included on formularies.

"We have had these plans in place now for many months and can't wait to get into exercising them now," Knapp said.

Aimmune plans to target 5,000 allergy specialists at 2,000 to 3,000 offices and will have a robust program ready at the time of launch, Knapp said. The demand is very significant, but the company is focused on having a "smooth and safe start," the exec told the call.

STRONG DATASET

The PALISADE study included 496 highly allergic patients , most of whom were aged 4-17. After about one year of treatment, patients completed a double-blind, placebo-controlled food challenge (DB-PCFC) which involved exposure to increasingly higher doses of peanut protein. At the study start, patients could not tolerate more than 30 mg of peanut protein and 72.2% had a history of anaphylaxis.

In an intention-to-treat analysis, 67.2% of those on AR101 tolerated at least a 600 mg dose of peanut protein in the food challenge, compared with 4% for placebo, a highly significant result that satisfied the primary endpoint ($p<0.00001$).

"The lower-bound of the 95% confidence interval (CI) of the difference between treatment arms at the primary endpoint was 53%, greatly exceeding the pre-specified threshold of 15% ($p<0.00001$)," the company noted in a statement.

Furthermore, 50.3% of AR101 patients aged 4–17 tolerated a 1,000 mg dose of peanut protein in the exit food challenge versus 2.4% for placebo, also a highly statistically significant result.

The company will be marketing the drug as a tool for managing accidental exposure, so the data for different doses will provide reassurance of protection – having that buffer is clinically important, Chief Medical Officer Daniel Adelman said during the call.

The breakdown by dose was part of a pre-specified, hierarchical statistical analysis and likely will ultimately be incorporated into labeling, though Dilly said that exactly how that will be done is "open to discussion."

EXAMINING SAFETY

Of those on the treatment arm, 20.4% discontinued treatment, with 12.4% withdrawing due to treatment-related adverse events. In the placebo arm, the dropout rate was 6.5%, 2.4% due to adverse events.

The serious adverse event rate (based on 372 evaluable patients) was 2.4% (n=9) in the AR101 arm versus 0.8% (n=1) for placebo. In the treatment arm, there were two severe adverse events related to treatment – one patient experienced anaphylaxis, and the other had wheezing on the first day of treatment. Both patients had elevated baseline peanut-specific IgE levels greater than 100 kU/L and both dropped out of the study, the company reported.

Causes of dropouts included one case of biopsy-confirmed eosinophilic esophagitis (EoE), which resolved upon treatment termination; anaphylaxis events, one of which was severe and required hospitalization; acute viral illness and eye pruritis. The case of EoE is what would be expected for a population getting no treatment, the company said.

The overall rate of systemic hypersensitivity reactions in the treatment arm was 14.5%, but the vast majority (98%) were mild or moderate.

Aimune also reported data for a small study cohort of 55 adults aged 18-49. In this group, 21 dropped out of treatment, but the company explained this largely wasn't due to adverse events, but more

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typically due to things like scheduling. The drug showed borderline statistical significance in the intent-to-treat analysis of the older patients and highly significant efficacy for completers in an exploratory analysis (85% of completers tolerated at least a 600 mg dose of peanut protein).

That result is very respectable and will allow the company to discuss with regulators what the upper age limit for this treatment should be and the company is also looking into how it can make it easier for college-aged students, a target population, to complete a course of treatment, Dilly said.

Results for the patients aged 4-17 will be presented at the American Academy of Allergy, Asthma and Immunology annual meeting in Orlando in March followed by an abstract release for the adults in May at the European Academy of Allergy and Clinical Immunology meeting in Munich.

DATA MOSTLY WELL RECEIVED

Aimmune's data were well received by analysts. Strong efficacy and safety data "de-risks shares and bodes well for approval," JMP Securities analyst Liisa Bayko, who projects peak revenue of about $1.2bn, said in a Feb. 20 note.

The data is even stronger than Phase II data, which is not the norm in drug development, Bayko said.

Bayko also said that she was impressed with the proportion of patients able to tolerate greater exposure to peanut and the high rates in those who completed treatment, which could reassure patients that they have achieved some protection.

Commenting on adverse events, Bayko noted that the safety profile was "quite clean" as the dropout rate was lower than expected.

Most dropouts happened during up-dosing and overall the safety profile in the study improves on the "already positive risk-benefit profile from the Phase II data," Bayko said.

Credit Suisse analyst Vamil Divan said in a Feb. 20 note that the efficacy and safety results were better than in Phase II and highlighted the efficacy relative to placebo far exceeded the level proposed by the FDA.

Commenting on the two patients who had severe side effects related to treatment, the analyst noted that both had peanut-specific IgE > 100kUA/L, "which reinforces the idea that peanut-specific IgE could be an important biomarker," Divan said.

The upcoming presentations may feature more information on biomarkers.

Jefferies analyst Eun Yang commented in a Feb. 20 note on **DBV Technologies SA** – Aimmune's closest competitor – that overall efficacy was strong and safety and tolerability in PALISADE were in line with expectations.

In the fall of 2017, DBV Technologies announced that its Viaskin Peanut patch therapy failed the primary endpoint for significant response for treated versus placebo in its Phase III PETITES study, per the statistical analysis plan agreed with the FDA. However, the company guided that it would be discussing data with regulators and said on Feb. 14 that it was going ahead with a filing for peanut allergy in children aged four to 11, based on the agency's feedback.

DBV is slated to file a BLA in the second half of this year.

Yang said that it is difficult to directly compare the data for the two investigational peanut allergy candidates, given the difference in primary outcomes, but that Aimmune's oral immunotherapy shows stronger efficacy whereas DBV's patch looks safer, so the latter would be a preferred option for children in Jefferies' view.

Yang expects FDA will approve both in the first half of 2019.

Although sell-side analysts reacted positively to PALISADE, the market sent Aimmune's stock price down by about 6% on the news to a close of $34.96.

Credit Suisse's Divan expressed surprise at the sell-off, noting that this may reflect the large stock movement over the last 12-18 months and the lack of meaningful catalysts over the next several months until potential approval of AR101 in 2H19.

"We also agree that there are still questions regarding the commercial attractiveness and execution of AR101, however we have previously stated that we see potential for both AR101 and DBVT's Viaskin Peanut to succeed in the peanut allergy market. Taking their efficacy and tolerability profiles into account, we expect AR101 to be used in patients who are more focused on building up a strong level of protection against peanut protein while Viaskin Peanut may be used more by patients who are less focused on the level of tolerance they obtain, but more focused on doing something to manage their situation and doing so in the most convenient way possible. We maintain our 80% probability of success of AR101 and our Outperform rating," Divan said.

DBV's stock closed down by 3.21% on Feb. 20 at $25.03.

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Takeda Catches Rising Tide Of Antisense Neuroscience R&D

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Early-stage antisense products targeting Huntington's disease and amyotrophic lateral sclerosis are attracting the attention of big pharma companies, and are the first targets of a just announced broad collaboration between Japan's **Takeda Pharmaceutical Co. Ltd.** and the US's **Wave Life Sciences Ltd.**, designed to develop therapies for genetically defined neurological diseases.

The deal announced on Feb. 20 is multi-faceted and could see Cambridge, Mass.-based Wave Life Sciences receiving at least $230m in funds initially, with the potential to receive up to $1bn in pre-commercial milestones.

The potentially large size of the collaboration in monetary terms is indicative of the growing competitiveness of the neuroscience sector, and the growing interest in nucleic acid-based technologies. For example, another big pharma company, **Roche**, recently took up an option on an antisense neuroscience compound for Huntington's disease on the strength of early clinical-stage results.

The Takeda/Wave Life Sciences deal announcement was unexpected, but acts to validate Wave Life Sciences' technology and its stereopure approach, commented Leerink analysts in a same-day note on the collaboration. Wave Life Sciences says its oligonucleotides are stereopure and allele-specific, thereby reducing the potential for off-target side effects and giving greater control over the products' therapeutic effects.

The US company's technology can be designed to act via antisense, RNA interference or exon skipping mechanisms, and the arrangement with Takeda is expected to hasten Wave Life Sciences' emergence as a global commercial neurology company, remarked analysts at JMP Securities.

The arrangement is in Takeda's sweet spot for new collaborations – the Japanese big pharma company has been restructuring its research effort over the past several years, narrowing its scope to three main areas.

OPTION AGREEMENTS

The collaboration between Takeda and Wave Life Sciences foresees the two companies collaborating not only on neuroscience antisense R&D but also on commercial activities, and allows Takeda to have options on various CNS research programs. Wave Life Sciences will receive an upfront payment of $110m under the collaboration, and Takeda will also buy $60m of the US company's shares, at $54.70 per share, and provide at least $60m in funding over four years to advance multiple preclinical targets that it selects and licenses.

The arrangement is in Takeda's sweet spot for new collaborations – the Japanese big pharma company has been restructuring its research effort over the past several years, narrowing its scope to three main areas, neuroscience, gastrointestinal disorders and cancer, and pursuing an externalization strategy focused on signing deals that complement its internal product pipeline.

The first batch of Wave Life Sciences's investigational oligonucleotide antisense products to be evaluated in the collaboration, with Takeda having an option to co-develop and co-commercialize after the demonstration of clinical proof-of-mechanism are: WVE-120101 and WVE-120102, which selectively target the mutant huntingtin gene and are in Phase Ib/IIa clinical trials for Huntington's disease; and WVE-3972-01, which targets the C9ORF72 gene and is expected to enter clinical studies in the fourth quarter of 2018 for the treatment of amyotrophic lateral sclerosis and frontotemporal dementia (FTD).

Huntington's disease is a hot therapeutic area for antisense products right now. At the end of last year, Roche decided to exercise its option on **Ionis Pharmaceuticals Inc.**'s antisense compound IONIS-HTT-Rx, after it reported favorable results in Phase I/IIa studies in patients with Huntington's disease. And the successful launch of the first antisense oligonucleotide for the treatment of spinal muscular atrophy, **Biogen Inc.**'s *Spinraza* (nusinersen, developed in collaboration with partner Ionis Pharmaceuticals), has attracted attention. As part of the first component of the collaboration, Takeda also has an option to co-develop and co-commercialize products arising from a research program in spinocerebellar ataxia type 3 (SCA3), targeting the ATXN3 gene, also after the demonstration of clinical proof of mechanism.

If Takeda exercises its option on any of the programs, Wave Life Sciences will receive an opt-in payment and will lead manufacturing and joint clinical co-development activities, with Takeda leading joint co-commercial activities in the US and leading commercial activities ex-US. Global costs and profits will be shared 50:50 and Wave Life Sciences will receive development and commercial milestone payments.

One potential talking point is how much "target knockdown" will be sufficient to prove the mechanism of action works, Leerink analysts remarked.

In a second component of the collaboration, Takeda will have rights to exclusively license multiple preclinical programs targeting other neurological disorders including Alzheimer's disease and Parkinson's disease. During its four-year term, the companies will evaluate up to six preclinical targets at any one time.

Takeda will fund at least $60m of Wave Life Science's preclinical activities and pay the US company for agreed additional expenses, and if Takeda advances six programs through regulatory and commercial milestones, Wave Life Sciences would be eligible for more than $2bn in cash milestone payments, of which more than $1bn would be in pre-commercial milestone payments. Wave Life Sciences would also receive tiered high single-digit to mid-teen royalty payments on global commercial sales of each licensed program.

TIED TO OUTCOMES

The Japanese company may be paying significant amounts under the collaboration, but neuroscience is a difficult therapeutic category in which to develop new therapies. And Takeda is certainly familiar with the risks involved in developing new neuroscience therapies – the company and another US partner, **Zinfandel Pharmaceuticals Inc.**, have just terminated the global TOMMORROW Phase III study of the PPAR-gamma agonist *Actos* (pioglitazone) because it failed to delay the onset of mild cognitive impairment due to Alzheimer's disease.

Takeda notes that it has similar collaborations in neuroscience including the recently signed deal with **Mindstrong Health** to explore the development of digital biomarkers for selected mental health conditions, and a deal with **Denali Therapeutics Inc.** to use that company's technology for transporting antibodies into the brain to develop and commercialize therapies for neurodegenerative diseases.

Wave Life Sciences' lead product, an antisense product for the treatment of Duchenne muscular dystrophy, WVE-210201, which targets exon 51, is not part of the Takeda deal. That compound is in Phase I trials, and a second non-partnered potential Duchenne muscular dystrophy program, targeting exon 53, is expected to enter Phase I studies in the first quarter of 2019.

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

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

Selected clinical trial developments for the week 16–22 February 2018

LEAD COMPANY/PARTNER	COMPOUND	INDICATION	COMMENTS
Phase III Suspended			
Merck & Co. Inc.	verubecestat	Alzheimers disease, prodromal	APECS; unlikely to show positive benefit/risk profile.
Phase III Results Published			
Gilead Sciences Inc.	*Descovy* (tenofovir alafenamide plus emtricitabine)	HIV/AIDS	ABC/3TS Switch; *The Lancet* online, Feb. 20, 2018.
Roche	*Zelboraf* (vemurafenib)	melanoma	BRIM8; *The Lancet Oncology* online, Feb. 21, 2018.
Phase III Interim/Top-line Results			
Novo Nordisk AS	semaglutide, oral	diabetes, type 2	PIONEER 1; effective and well tolerated.
AbbVie Inc./Neurocrine Biosciences Inc.	elagolix	uterine fibroids	ELARIS UF-I; met efficacy endpoints.
Eli Lilly & Co.	*Taltz* (ixekizumab)	genital psoriasis	IXORA-Q; reduced impact on sexual activity.
Evolus Inc.	prabotulinumtoxinA	glabellar lines	EVB-003; met primary endpoint.
Mesoblast Ltd.	Prochymal	graft vs host disease	Met primary endpoint.
Updated Phase III Results			
Aimmune Therapeutics Inc.	AR101	peanut allergy	PALISADE; met primary efficacy endpoint.
CytoDyn Inc.	PRO 140 (CCR5 MAb)	HIV/AIDS, refractory	Reduced HIV-1 viral load.
Dermira Inc.	glycopyrronium tosylate, topical	primary axillary hyperhidrosis	ATMOS-1, -2; improved disease symptoms, well tolerated in extension study.
AbbVie Inc./Boehringer Ingelheim GMBH	risankizumab	psoriasis, moderate to severe	ultima-1; ultima-2; high levels of clear skin.
Celgene Corp.	*Otezla* (apremilast)	Behcet syndrome	RELIEF; reduced oral ulcers.
Eli Lilly & Co.	*Taltz* (ixekizumab)	psoriasis, moderate to severe	UNCOVER-3; efficacy sustained for three years.
Eli Lilly & Co.	*Taltz* (ixekizumab)	psoriatic arthritis	SPIRIT-2; sustained efficacy for one year.
Novartis AG	*Cosentyx* (secukinumab)	psoriasis, moderate to severe	SCULPTURE; efficacy sustained at five years.
Janssen Pharmaceutical Cos./ MorphoSys AG	*Tremfya* (guselkumab)	psoriasis, moderate to severe	VOYAGE 2; sustained responses at 72 weeks.
Leo Pharma AS	*Kyntheum* (brodalumab)	psoriasis, nail	AMAGINE-2, -3; sustained symptom improvement.
Phase III Initiated			
Roche	*Tecentriq* (atezolizumab)	liver cancer, untreated advanced	IMbrave150; combined with bevacizumab.
Centrexion Therapeutics Corp.	CNTX-4975	arthritis pain	VICTORY-1; a trans capsaicin non-opioid injection.
Vertex Pharmaceuticals Inc.	VX-659, tezacaftor and ivacaftor	cystic fibrosis	Triple combination therapy.
Wilson Therapeutics AB	WTX101	Wilson's disease	FOCuS; a copper-binding-protein.

Source: Biomedtracker

EU Delays For Portola CHMP Trend Votes

ALEX SHIMMINGS alex.shimmings@informa.com

Portola Pharmaceuticals Inc.'s Factor Xa inhibitor betrixaban's future in the EU is looking dicey after the EMA's CHMP issued a negative trend vote on the product's marketing application at its meeting this week. On the plus side, it also communicated a positive trend vote on the MAA for its universal Factor Xa inhibitor reversal agent, *AndexXa* (andexanet alfa), but this too represents a slight delay.

Betrixaban's negative trend vote means it is unlikely the committee will adopt a positive opinion on the company's MAA at the formal CHMP decision vote scheduled for March. The committee said that additional steps would be needed to gain marketing approval in Europe, and analysts are calling time on the product in this market.

Portola CEO William Lis said during a conference call that the CHMP had acknowledged betrixaban's efficacy in the APEX study but said uncertainties remained regarding a positive benefit risk.

"Specifically, the CHMP was seeking support from either a second confirmatory study; biological plausibility for betrixaban in another approved indication; or interestingly, external support within the class from other Factor Xa inhibitors, which none of which have gained approval in the US or Europe in the acute medically-ill population at this time," he told investors.

This was "particularly disappointing" given the broad label that the product received from the US FDA in June as *Bevyxxa* for hospital and extended duration prophylaxis (35 to 42 days) of venous thromboembolism in patients hospitalized for an acute medical illness and at risk for thromboembolic complications, a large population; this followed a priority review by FDA with no advisory committee panel. Launch however was delayed to early this year due to manufacturing issues.

The US approval set it apart from its predecessors on the market as it is the only one to have an indication for the population with acute medical illness. Portola estimates that some 100,000 patients hospitalized with an acute illness die from VTE events each year in the US, typically after discharge.

But in the EU, Lis said the company would consider its next steps for a potential path forward, but until then it will be concentrating on the US. "We're going to remain really focused on the US launch of Bevyxxa. We're going to be pouring our resources into the US."

ANDEXXA MORE POSITIVE

For AndexXa, the position is a little better, with the positive trend vote, but still the committee has asked for more data that will delay the CHMP opinion until the fourth quarter. Portola is seeking conditional approval for andexanet alfa for the reversal of the anticoagulant effects of apixaban and rivaroxaban in patients experiencing uncontrolled or life-threatening bleeding.

This product too has been held up by manufacturing issues: these among other things led to a complete response letter back in August 2016 and a revised application was accepted last August with a PDUFA date of Feb. 2. The date was pushed back to May 4 after Portola submitted additional data requested by the agency for the ongoing Phase IIIb/IV ANNEXA-4 study as part of the continuing review process, and this constituted an amendment to the submission.

Lis said that the CHMP also wanted a little more information on the Generation 2 manufacturing scale-up process as well as more details on the ANNEXA-4 data for AndexXa.

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Belgium-based **Bone Therapeutics SA** appointed ***Jean Stéphenne*** Chairman of the board of directors with immediate effect, replacing Steve Swinson who had informed the board of his intention to step down. Stéphenne's experience in life sciences include senior leadership roles at many biotechnology and pharmaceutical companies, most recently as chairman of TiGenix NV. Stéphenne was also previously a member of the corporate executive team of GlaxoSmithKline PLC and chief executive of GlaxoSmithKline Biologicals SA (now GSK Vaccines).

Sotio AS has appointed ***Radek Špíšek*** as CEO effective March 1, replacing ***Ladislav Bartoníček***, whohas been CEO since early 2014 and will stay active within SOTIO's top management, replacing Špíšek on the company's supervisory board. Špíšek's appointment of as CEO will ensure continuity in the company's management and strategic goals.

Family-owned **Helsinn Group** of Switzerland appointed ***Paul Rittman*** CEO of its US subsidiary, Helsinn Therapeutics (US) Inc., replacing William Mann, who steps down on February 28. Rittman, who takes up his position on March 5, most recently was senior vice president and general manager of US oncology at Teva Pharmaceuticals USA Inc. where he also previously held other senior commercial roles. Before that, he worked in a number of roles at Intrabiotics, Aventis/Hoechst Marion Roussel Pharmaceuticals and its predecessor companies.

Swedish **Orphan Biovitrum AB** (Sobi) has appointed ***Henrik Stenqvist*** chief financial officer effective in the "late spring" and replacing current CFO ***Mats-Olof Wallin***, who will support the transition process and retire by year-end 2018. Stenqvist joins the Swedish rare disease specialist from a position as CFO of Recipharm AB. Prior to that, Henrik Stenqvist served as the CFO of Meda AB.

Privately-held **Blade Therapeutics Inc.** has appointed ***Ryan Maynard*** CFO. He joins Blade from Rigel Pharmaceuticals Inc. where he most recently was executive vice president and CFO. In his new role, Maynard will lead Blade's finance and accounting functions, as well as investor and public relations.. During his tenure at Rigel, Maynard raised over $700m through numerous follow-on public offerings, which supported Rigel's research and development of small molecules inhibitors for auto-immune diseases and oncology. Maynard currently serves on the board of directors for Iovance Biotherapeutics Inc., which is focused on autologous cellular immunotherapies for oncology indications.

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