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Enthusiasm For US Biosimilars Wanes For Some, But Not Others

JESSICA MERRILL jessica.merrill@informa.com

What happens next in the US commercial market for biosimilars is being closely watched by drug manufacturers and other health care stakeholders after initial launches have been lackluster.

Three years after the first biosimilar launched in the US – **Sandoz International GMBH**'s *Zarxio* (filgrastim-sndz), a version of **Amgen Inc.**'s *Neupogen* (filgrastim) – the market has failed to deliver eye-opening returns on the first round of investments. If the US biosimilars market were to continue to develop at a similar pace, concern is growing among some in the industry that it could signal a failure for the market and stunt future investment in a category of drugs expected to save the US health care system billions of dollars.

FDA Commissioner Scott Gottlieb has even raised the alarm, warning that commercial barriers today could impact future biosimilar investment.

As Bernstein analyst Ronny Gal put it in a July research note, "This feels like the inflection point for the industry. The investment has been made, but the return – at least in the US market – is delayed."

"Over the next two years, the US biosimilar industry will either get better, on more affordable/predictable US requirements and gradual adoption in the US, or morph into an EU-focused business, without material US presence," Gal said.

Some biosimilar players are going public with similar warnings, calling for new policies to foster the market, particularly around market access.

Biosimilar manufacturers readily acknowledge the commercial challenges in the US, which range from intellectual property barriers that keep FDA-approved biosimilars from reaching the market to rebating and discounting incentives that favor branded products, which benefit from larger volumes. But some players appear less concerned about the slow pace of market formation, taking encouragement from the market development in Europe.

MARKET ACCESS BARRIERS

Mylan NV CEO Heather Bresch is one leader that came out strongly in favor of more policy change during the company's second quarter sales and earnings call Aug. 8, airing frustrations over the slow launch of Mylan's glatiramer (*Copaxone*) generic – a complex generic that faces some of the same challenges as biosimilars. The company simultaneously down-graded expectations for the launch of its first biosimilar in the US, *Fulphila*, which launched in July as the first FDA-approved version of Amgen's Neulasta (pegfilgrastim).

Teva Pharmaceutical Industries Ltd.'s branded Copaxone has been able to hold onto 85% market share, despite the entry of two generics. Teva has taken a hit on price and lost revenues, but the company has been able to effectively block generics by deeply discounting the brand.

The situation is similar to **Pfizer Inc.**'s experience with *Inflectra* (infliximab-dyyb), a biosimilar of **Johnson & Johnson**'s *Remicade* (infliximab), which has held onto 94% market share nearly two years after the launch of the first biosimilar. Sandoz has had more success

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Under The Radar
Small-cap takeover targets (p12-13)

Lenvima's Moment
Competition looms for first-line liver label (p15)

from the managing editor

kevin.grogan@informa.com

The goal of eradicating measles in Europe had been going well and the damage done by Andrew Wakefield's discredited claims in the late 1990s about a link between the MMR vaccine and autism had been countered by science and sensible public health campaigns. But a recent surge in measles cases and a decline in vaccinations shows the battle is far from won.

A new WHO report has revealed there were 37 deaths from measles in Europe in the first six months of 2018, compared with 38 for the whole of last year. 41,000 people were infected, almost double the number in 2017. The figures got scientists clutching their heads with sadness and anger as the 'anti-vax' voice continues to bellow bad science and misinformation.

Alas it is too easy to dismiss the anti-vaccine brigade as buffoons with no influence. News from Italy that the government is pushing for the removal of the legal obligation to vaccinate schoolchildren is truly alarming.

The anti-vax campaigners vilify the pharmaceutical industry, throwing out the line that the sector is only interested in making huge profits. This stance ignores the fact that the vaccines market is small with tight margins – there are much more profitable areas for drug makers to make money.

However, something much more important than economics is public health. Put simply, vaccination saves thousands of lives and the pharmaceutical industry, governments, researchers and health care workers need to counter the anti-vaxxer conspiracy theories and put the evidence for vaccines – one of the great achievements of medicine – firmly in front of the public.

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Phil Jarvis, Mike Ward, Karen Coleman

SUBSCRIPTIONS
Dan Simmons, Ewan Ritchie, Shinbo Hidenaga

ADVERTISING
Christopher Keeling

DESIGN SUPERVISOR
Gayle Rembold Furbert

DESIGN
Paul Wilkinson

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

CUSTOMER SERVICES
US Toll-Free: +1 888 670 8900
US Toll: +1 908 547 2200
UK & Europe: +44 (20) 337 73737
Australia: +61 2 8705 6907
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In Conversation With Novo Nordisk CMO: The Ongoing Fight Against Diabetes
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Stephen Gough has kept his connections with Oxford University and will see collaborations between the two expand next month with the opening of the Novo Nordisk Research Centre Oxford. The executive spoke to *Scrip*.

Interview: Immunocore Gets Ready To Go To Market
https://bit.ly/2wotA8P
The first molecule from its collaboration with GSK has just gone into Phase I trials but Immunocore CEO Andrew Hotchkiss tells Scrip that the UK biotech unicorn is also preparing for the launch of its own lead candidate, IMCgp100 for uveal melanoma.

Pharma Industry Braces For Tough Times In Turkey As Turkish Lira Fluctuates
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In the recent crisis between Turkey and the US, the Turkish lira went down in value against major currencies, including the euro. In Turkey, product prices are determined on the basis of the euro, for which the government applies a fixed rate. As the difference between the two conversion rates grows, companies lose out, forcing the industry to search for ways to cut its losses.

Korea Toughens Corporate Disclosure Rules To Improve R&D Transparency
https://bit.ly/2MI1QWL
Amid a recent stock price rigging scandal involving a local bioventure, and the global push to improve the transparency of clinical trials, Korean financial authorities are pushing for improved public disclosure by pharma/biotech companies of key information on clinical development, such as trial failures or suspensions, to better inform investors.

Deal Watch, Licensing Focus: Roche, Sanofi Exit Ongoing Anticalin Development Efforts With Pieris
https://bit.ly/2BusMES
Sarepta licenses gene therapy candidate from Lacerta, also makes equity investment. Neuren licenses North American rights to rare disease drug trofinetide to Acadia.

Finance Watch: Vaccinex, Aridis Launch August's First US IPOs As The Summer Simmer Slows
https://bit.ly/2N5XDca
The summer slowdown finally seems to have hit the US biopharma IPO market; there were just two during the first half of August. Also, Zogenix leads recent follow-ons with a $312m offering; venture capital in UK biotechs – Orchard and Blueberry.

inside:

with Zarxio, which as an acute treatment for neutropenia doesn't face the same commercial barriers as chronic drugs like Copaxone and Remicade. Amgen said its branded Neupogen only held onto 37% market share coming out of the second quarter.

Given Zarxio's uptake, Amgen management expressed a different view of the biosimilars market compared with some of the company's peers during its July 26 sales and earnings call.

"Some of our competitors and public officials have made statements that the US biosimilar market is not working," Exec VP-Global Commercial Operations Tony Hooper said. "We have a different point of view … The fact that a biosimilar now holds the majority share of this segment less than three years post-launch proves that biosimilars can find a meaningful place in the US market just as they have in Europe."

And in the case of generic Copaxone, Mylan recently announced a steep 60% price cut on its product – hoping to penetrate the market – and it looks like the company is expected to find some success, though a race to the bottom on price will negatively impact margins. Teva responded to Mylan's price cut during its second quarter call, saying that it will be harder for the branded product to retain 85% market share given the competitive pricing in the category.

But Bresch insisted policy changes are needed to fix what she called an "unsustainable" situation and to open market access for biosimilars, which currently are not substitutable or interchangeable. Specialty tiers on formularies are not designed to make biosimilars readily accessible, she said.

"I think we're really going to have to revisit how that works to ensure that access flows," she said. "That's been the feedback we are giving to the President's blueprint, that there has to be that access, or it really ruins the model. "President Trump issued a blueprint on drug pricing in May, which included many ideas to address drug pricing, but will require input and policy development.

Bresch said she's hopeful changes will be implemented, but the company clearly is disappointed that its investment in complex generics and biosimilars – more expensive than generic products to develop with higher barriers to entry – isn't paying off as Mylan anticipated. The company announced the same day that it is exploring strategic alternatives, claiming investors have continued to under-value the stock.

Fulphila will be the fourth biosimilar to launch in the US, though 12 biosimilars have been approved by FDA. A strong launch of Fulphila would be an encouraging signal to other biosimilar manufacturers, while another disappointing launch would signal distress.

STEADY COMMITMENT

Pfizer has run up against early challenges with the launch of its first US biosimilar, Inflectra, which has become something of an unattractive poster child for the US biosimilar market. J&J has successfully blocked Inflectra from the market using stiff rebating tactics following the launch in late 2016.

Inflectra generated $158m in the second quarter, growth of 68%, of which only $63m came from the US. Meanwhile, Remicade generated $1.38bn worldwide in the quarter, $918m of which came from the US in the second quarter.

Pfizer is challenging J&J's rebating practices in court, claiming they are anti-competitive. A district court judge recently determined Pfizer's suit can move forward, denying J&J's motion to dismiss. The outcome of the lawsuit could have implications for the broader uptake of biosimilars in the US, if policy changes don't come first.

As part of a recent business reorganization, Pfizer moved its biosimilar portfolio under the organizational structure of its branded immunology and oncology portfolios. As Chief Operating Officer Albert Bourla said of the restructuring during Pfizer's second quarter sales and earnings call, biosimilars are a "high-risk, high-reward, heavy-in-R&D investment business."

That runs counter to how some in the industry might have viewed biosimilars a few years ago, even taking into account the higher barriers to market. But Pfizer said it remains committed to the biosimilar business and expects to bring five new biosimilars to market in the next two years.

Sandoz CEO Richard Francis seemed encouraged about steady progress in the market during **Novartis AG**'s second quarter conference call July 18. The company was one of the early players in the market with biosimilar launches in Europe, and – with Zarxio – the first sponsor to get a biosimilar to the US market.

Novartis' biosimilars revenues grew 34% to $363m in the second quarter, with growth driven by launches of biosimilar rituximab (*Rixathon*) and etanercept (*Erelzi*) in Europe and continued growth of Zarxio in the US.

Still, Francis cautioned investors that the 34% growth rate in the second quarter could be a high growth rate in a segment that could see more fluctuation. It doesn't necessarily reflect an inflection point, he warned.

Francis said he is encouraged by discussions at FDA to further foster the biosimilar market, but noted that it is still early days. The agency unveiled a Biosimilar Action Plan in July, which includes initiatives to improve biosimilar and interchangeable product development.

"All the guidance, all the discussions, all the comments coming out of the FDA, I think, are extremely positive towards their approach to biosimilars," Francis said. But, he added, Sandoz still is waiting to see what actionable improvements come out of the policy discussions.

BIOSIMILAR STRATEGY

Teva missed the first wave of biosimilar development and was a latecomer to the field, which was largely viewed as a misstep by the world's biggest generic drug maker. The company tried to course-correct in 2016, calling biosimilars a "key ingredient" for growth and signing a commercialization deal with **Celltrion Inc.** for two biosimilar candidates in the US and Canada, versions of Roche's Rituxan and *Herceptin* (trastuzumab).

Now, under the new leadership of CEO Kare Schultz, the company is once again refining its biosimilar strategy and doesn't seem eager to over-invest in the space.

Schultz told investors during an Aug. 2 conference call that Teva will be "targeted and focused" when it comes to biosimilars, pursuing only those biosimilars that tie into the company's commercial footprint.

"We believe that you can only really effectively launch biosimilars if you also have an ongoing commercial presence and a medical presence in the areas you're going for," he said. Schultz pointed to oncology as an area the company could compete in because it has been working in the area.

"We know we are not leaders in biopharmaceuticals, we're not leaders in biosimilars, but we're a reasonably good player and we have some reasonably good medical and commercial footholds that we think we can utilize to generate some really nice businesses."

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Biosimilar Infliximab Success Paves The Way For Adalimumab In Europe

JO SHORTHOUSE joanne.shorthouse@informa.com

"The next big one that comes to the market is adalimumab," says **Napp Pharmaceutical Group Ltd.**'s director of market access and external affairs Andrew Roberts, when discussing the uptake of monoclonal antibody (MAb) biosimilars in the UK. Currently the biosimilar with the widest distribution in the UK is infliximab, with around 600,000 units distributed a year.

"The NHS policy of savings on medicines has been in place for almost a decade so manufacturers were frustrated that the NHS wasn't doing more about biosimilars use," says Roberts. "However, the speed at which policy moved and uptake improved was quite astonishing and over the last 18 months we've started to see far less barriers to uptake in the whole of the UK." Napp distributes **Celltrion Inc.**'s *Remsima* (infliximab), *Truxima* (rituximab), and *Herzuma* (trastuzumab) in the UK.

When Remsima was first launched in Europe, an anti-biosimilar campaign by originator companies threatened to sideswipe commercialization, says HoUng Kim, Celltrion's head of strategy and operations. "They tried to cast doubt on biosimilars to influence prescribing behavior despite the totality of evidence generated to meet the requirement from stakeholders, including the European Medicines Agency," he tells *Scrip*. This tactic failed to work on prescribers. According to the market research firm **IQVIA**, Remsima had 52% of the European market in the fourth quarter of 2017 which, according to Kim, marks the first time a biosimilar has surpassed the market share of originator drugs.

As these figures show, attitudes toward biosimilars have altered drastically in the three years since infliximab was launched onto the European market. In a biosimilars medicines commissioning framework published in September 2017, the UK NHS stated its aim to prescribe 90% of new patients the best value biological medicine within three months of launch of a biosimilar, and at least 80% of existing patients within 12 months, or sooner if possible. Biosimilars have the potential to deliver savings of at least £200m to £300m per year by 2020/21, official numbers state.

Napp Pharmaceuticals' director of market access and external affairs, Andrew Roberts

Since biosimilar infliximab launched in February 2015, it has saved NHS England (NHSE) £99,400,000. This figure dwarfs the savings made by prescribing generic/biosimilar versions of imatinib (£66,333,000), etanercept (£60,300,000), rituximab (£50,430,000) and voriconazole (£15,912,000).

With initial frustrations left behind, Remisima is now the most mature product in Napp's biosimilar portfolio, and growing in use by NHSE by around 12% a year. "The UK has been a huge success story," concurs Paul Clark, director of the biosimilars business unit at Napp. "It took a while to get there, it was a slow start but where we are now is hugely encouraging."

According to figures from NHS England's Regional Medicines Optimisation Committee (RMOC), by May 2018, national uptake of infliximab, in percentage of total treatment days, was 89%; while etanercept was also 89% although it came to the market a year later in April 2016, and rituximab, which came to the market in April 2017, had a 73% uptake.

Uptake across the UK is not a totally rosy picture for biosimilars. Because it is the decision of regional clinical commissioning groups (CCGs) within the NHS to switch from originator drugs to biosimilars, localized differences can scupper the promised savings. "There is evidence of significant and unwarranted variation between local areas and regions in the use of biosimilar medicines," the NHS stated in its commissioning framework document. "In January 2017, one NHS Trust in central London had an uptake of infliximab of only 25%, whilst another just 16 miles down the Thames had an uptake rate of 99%."

LESSONS STILL TO BE LEARNT

With biosimilar adalimumab about to hit the market, the NHS and other European payers can look to lessons learnt from tried and tested infliximab as a model for biosimilar market access success. "With infliximab we just didn't see the right leadership locally," recalls Roberts. The initiative has got to come from CCGs, who are the budget holders, locally, he explains. "It's just simple project management, if you don't see those plans laid down in advance, and everybody agreed and there are measures in place so everybody is holding each other accountable, you will not get that rapid uptake.

"The areas that did set off like a rocket for infliximab are the areas that had all those plans in place, shared accountability and were measuring what they were doing on a weekly basis. The areas that achieved 99% uptakes are those that micro-managed the change between the NHS Trust and the CCG. If you get areas where you don't have that level of leadership and acceptance of the accountability, you won't get the uptake," he explains. And with the NHS spending more on Humira than any other hospital drug – £333m in 2016/2017 – it needs to get the switch from the originator to biosimilar right at the first time of asking.

While infliximab is undeniably a success story for the biosimilar sector, there are still a few flies in the infliximab ointment, namely the indications where many patients could benefit but cannot access the product. Napp is hoping NHSE will further expand in its prescribing model for the MAb. "There's been an expansion into ulcerative colitis but you haven't seen that

move into arthritis. The health service and patients could see much better long-term outcomes if they did," says Clark. And it is no longer a matter of saving money, says Roberts, as the cost has come down by 90%. "A product that cost almost £1,200 a treatment, is now costing considerably less. There is no justification for withholding treatment for a patient that needs it." Treatment pathways, overseen by the UK's National Institute for Health and Care Excellence (NICE), are "very restrictive" and "have not changed", he says, which is now the main cause for frustration among both the industry and patients. *(Also see "Europe Ripe For Broader Biologic Use In Inflammatory Conditions" - Scrip, 28 Oct, 2015.)*

FUTURE EUROPEAN STRATEGIES

With **Sandoz International GMBH**'s *Zessly* approved earlier this year for use in all indications of the reference drug, the European marketplace for infliximab products is starting to look quite busy, with **Samsung Bioepis Co. Ltd./Biogen Inc.**'s *Flixabi*, **Pfizer Inc.**'s *Inflectra* and Remsima jostling for market share. *(Also see "EU Biosimilar Action: New Competitors For Remicade/Herceptin, Four More Products Await CHMP OK" - Pink Sheet, 30 May, 2018.)* This is healthy for a system such as the UK's NHS that works on tendering, with the ability to choose products encouraging sustainability. While the innovator product normally retains the largest market share, the onus is on the biosimilars to disrupt the market. **Biogen Inc.** markets Flixabi in Europe and this is something it is hoping to do.

"I recognize that I'm third to market and that means it's going to be a much harder and acute business situation but it's still rewarding," Ian Henshaw, head of biosimilars at Biogen, tells *Scrip*. "So, we're going to continue to compete and we're going to continue to work out what it takes to win." The commercialization strategy for Flixabi is the same as for its other branded biosimilar *Benepali* (etanercept) says Henshaw, Europe-wide. "The first response is that we look at every single tender and contract and work out what it takes to compete in that contract, and then what it would take to win. We look at every single opportunity and as a result of that, we're in 11 countries in Europe with Flixabi."

While the general commercialization strategy has the same end goal in sight

Biogen's head of biosimilars, Ian Henshaw

across Europe, the intricacies of the tendering process vary from country to country, with pricing and discounting only one part of the tender, with other considerations such as amount of product, quality of packaging and design, and necessary educational materials. "This is where the sustainability and the evolution of this marketplace is going," says Henshaw.

Celltrion expects a certain limitation for price competition as more and more biosimilar products enter the market, HoUng Kim explains, and because of this the company is focused on a differentiation strategy for each biosimilar product it markets, planning several "value-added features". For Remsima, "we would like to provide a more convenient and accessible treatment administration option to patients with chronic conditions so we are developing a subcutaneous version of infliximab," he explains. Celltrion is also working to improve its production process to maximize supply efficiencies, which will, in turn, lower the price.

BLOCKBUSTER TO BIOSIMILAR

Biosimilar versions of **AbbVie Inc.**'s blockbuster *Humira* (adalimumab) will be launching into a buoyant market of converted payers and patients. Products from **Amgen Inc.**, **Boehringer Ingelheim GMBH**, **Sandoz International GMBH** and **Samsung Bioepis Co. Ltd./Biogen Inc.** will all try to win market share when the doors to Europe open in October. However, AbbVie seems prepared to defend its product.

"Commercially, this is going to be interesting," stated Ronny Gal in a Bernstein analyst note. AbbVie is expecting 20% decline in product sales in Europe in year one, and has the capabilities to deal with 30%. As Humira is not a hospital product, patients know if they are being prescribed a biosimilar, and AbbVie has an unpublicized "different strategy" from that of the Remicade and Rituxan (rituximab) innovators. "In our view, AbbVie appears much more prepared than prior defenders and their key objective is to prevent the creation of large patient databases ahead of US biosimilar introduction. AbbVie is much more likely to give up price than volume," says Gal.

Gal states that additional tactics used by AbbVie will include arguing that there's a change in formulation so that there is no proof of biosimilarity against the current version, arguing for access to new, less painful formulation through patient advocacy groups, contracting to block the biosimilar, introducing rebates for major payers, and using late-patented indications to threaten legal action, which works in conjunction with discounts.

While the price of Humira will inevitably fall, market share is not so cut and dry. "Adoption of biosimilars may be a bit slower than Enbrel," says Gal, "but there is material animosity to AbbVie among EU payers, after what they see as price gouging. And the biosimilars are competing with each other, as well as AbbVie."

Goldman Sachs has looked to **Amgen Inc./Pfizer Inc.**'s Enbrel and **Janssen Pharmaceuticals Inc.**'s Remicade for pricing guidance but note two meaningful differences between them and Humira. Firstly, Humira has a dominant and growing market share outside the US, in terms of sales, heading into biosimilar competition, while both Enbrel and Remicade were losing share at the same point; although this could be offset by the fact that Humira is expected to see three to four biosimilars in the first year, while Enbrel and Remicade saw only one or two.

"Our Humira decline curve is steeper in the first year with -18% growth while Enbrel was down 8% and Remicade down 10%. Over the three years post biosimilar competition, our Humira decline is a cumulative 32%, which is less aggressive than what we expect for Enbrel (-37%) and Remicade (-48%); we do not expect Humira's long-term OUS erosion to be as steep due to the drug's best-in-class profile and strong, growing market share even before any anti-TNF biosimilars were on the market," it stated in an equity research note.

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CVS Sees Growing Use Of Real-Time Drug Price Data

MANDY JACKSON mandy.jackson@informausa.com

CVS Caremark has found that real-time price transparency data tools are seeing increasing use by both physicians and patients, often translating into a switch to lower-cost competing products.

For example, **CVS Health Corp.** noted this month that when doctors are presented with information about available therapeutic options for a given disease or condition, they choose a drug with lower out-of-pocket costs 40% of the time. They may select either a generic or a brand with better placement on the CVS Caremark formulary instead.

With not only doctors and pharmacists, but also patients accessing real-time data and actively choosing generics or brands with lower out-of-pocket costs at the pharmacy counter, biopharmaceutical companies may face more pressure to negotiate favorable placement on the pharmacy benefit manager (PBM) formulary, and perhaps keep tabs on how they stack up versus the competition.

CVS said in a recent report titled "Current and New Approaches to Making Drugs More Affordable" that its PBM CVS Caremark is looking to reduce costs with strategies beyond standard approaches, such as encouraging the use of generics, requiring prior authorization for newly prescribed brands, and negotiating rebates from biopharma companies in exchange for favorable formulary placement.

One new initiative that CVS Caremark has implemented with an eye on cutting patients' out-of-pocket costs is using cost-effectiveness data from the Institute for Clinical and Economic Review (ICER) to deny formulary coverage for newly launched drugs.

In another initiative, the PBM is encouraging member health plans to offer zero-dollar co-pays for medicines that treat chronic diseases, and advocating for policy changes to broaden the definition of therapies that can be covered in this way.

REAL-TIME DATA USE GROWING QUICKLY

But CVS has already seen encouraging responses to ongoing efforts to offer real-time data on prescription drugs costs and other information.

For example, prescribers may connect with the CVS Caremark database via the patient's electronic health record (EHR), allowing the doctor to stick with the originally prescribed brand or choose a lower-cost option before the patient leaves the physician's office.

In those 40% of instances where a doctor chooses a drug with a lower out-of-pocket cost, patients save an average of $130 when they fill their prescription, according to the PBM. It did not provide estimates on its own savings when preferred or generic drugs are swapped in.

Second, the pharmacist – at a CVS store or any other pharmacy in CVS Caremark's network – can review the patient's prescription and access the PBM's Rx Savings Finder. The pharmacist can then recommend a lower-cost alternative to the doctor based on the patient's CVS Caremark-administrated pharmacy benefits.

Third, patients whose pharmacy benefits are covered by the PBM can access CVS Caremark's app or online portal and use the Check Drug Cost tool available there. When this happens, the PBM says that 20% request a switch to a lower-cost option and save $120 per prescription fill. "As we rapidly onboard EHRs to include real-time benefits information, prescribers are accessing it for our PBM members approximately 280,000 times per week. As additional EHRs are on-boarded this year and the prescriber population who can access real-time benefit information exponentially increases, we expect this to significantly increase," CVS told *Scrip*.

The PBM also noted that patients using the Check Drug Cost tool on Caremark.com initiate about 250,000 searches each month.

In relation to the Rx Savings Finder tool, CVS noted in a June 26 blog post that it "will help our pharmacists quickly identify if there are any available savings opportunities for individual patients at the pharmacy counter. This tool is expected to produce an average of $420 in additional annual savings for the patient."

CVS additionally told *Scrip* that "savings methods for the Rx Savings Finder tool help the CVS Pharmacy customer maximize their pharmacy benefit first. This includes helping to identify lower-cost options covered under the patient's pharmacy benefit, such as a generic medication or [a] therapeutic alternative or if the patient could save money by filling a 90-day prescription rather than a 30-day prescription. Other potential savings options for eligible or uninsured patients are then applied where allowed by applicable laws and regulations," such as co-pay assistance programs.

ZERO-DOLLAR CO-PAYS FOR CHRONIC DISEASES

The third of CVS Caremark's more recent efforts to cut out-of-pocket costs for patients – encouraging member health plans to cover the cost of medicines so that patients have no co-pays for drugs that treat chronic diseases – is most relevant for individuals that have high-deductible health plans (HDHPs).

CVS notes that those patients have higher out-of-pocket (OOP) costs – 2.5% of the PBM's individual members have more than $1,000 in annual OOP expenses – making them less likely to fill prescriptions. Prescription non-compliance often translates to more use of other kinds of health services down the road and higher overall health care costs.

"Recognizing this, the federal government allowed HDHPs associated with health savings accounts (HSAs) under Internal Revenue Service (IRS) rules to create a preventive drug list, which enables plans to have zero-dollar co-pay for drugs that prevent disease," CVS explained in its report issued this month. "The definition of 'preventable' is somewhat flexible – CVS Caremark encourages clients to cover all generic medications for chronic diseases as well as some key branded drugs, like insulin, under this category."

The PBM believes the IRS should broaden the definition of preventive medicines and cited its own recent research, which "indicates that expanding preventive drug lists to the five most chronic diseases – diabetes, hypertension, hyperlipidemia, asthma/COPD and depression – could substantially improve care and lower costs." The report points out that rebates issued at the point of sale on top of standard formulary recommendations enable zero-dollar co-pays.

"The rules governing HSAs should also be changed to give HDHPs the option to cover all prescription drugs – including generic and brand drugs – outside the deductible, so patients can access these drugs for little or no co-pay if that is how the plans want to structure their benefit," CVS added.

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How Big A Blow To Biogen Is NICE 'No' For Spinraza?

KEVIN GROGAN kevin.grogan@informa.com

The spinal muscular atrophy (SMA) drug *Spinraza* (nusinersen) continues to drive revenue growth at **Biogen Inc.**, but a likely rejection from NICE means that any contributions to sales from the countries covered by the cost effectiveness watchdog will be a long time coming.

'To date, 20 European markets, including Scotland, have already made Spinraza available'

The company and patients who suffer from the rare neurodegenerative disease have expressed disappointment over NICE's draft guidance which does not recommend Spinraza, the only drug approved for SMA. The committee issued a statement claiming that "the evidence showed a substantial benefit for nusinersen," but highlighted "significant uncertainties, particularly around its long-term benefits," adding that the cost is "extremely high."

NICE concluded that, based on its list price of £75,000 per dose excluding VAT, the cost-effectiveness estimates for nusinersen ranged between £400,000-£600,000 per year of quality adjusted life (QALY) gained. Even with the proposed confidential discount, that is "too high for it to be considered a cost-effective use of NHS resources."

It is estimated there are there are 1,200-2,500 children and adults in the UK with SMA. Spinraza, which is approved specifically for the treatment of 5q spinal muscular atrophy, is injected directly into the spine and is a lifelong treatment.

NICE went on to note that it is aware Biogen intends to engage with stakeholders to develop a proposal for a managed access arrangement, which is aimed at "addressing uncertainties in the evidence" and reducing the financial risk to the NHS. However, the committee noted that these arrangements "are extremely unusual outside of the Cancer Drugs Fund and NICE's highly specialized technologies program."

Terry O'Regan, managing director of Biogen UK and Ireland, said in a statement that while the company is very disappointed that NICE has issued a 'minded no,' "we are not surprised given the challenges of assessing rare disease medicines via the standard technology appraisal (STA) route, and our expressed reservation of the suitability of this route for evaluating medicines such as nusinersen." He went on to say that "sadly, this decision and the lengthy timeframe of the whole process highlights the UK challenge in providing access to rare disease medicines in a timely manner, similar to other leading economies."

O'Regan noted that to date, 20 European countries, including Scotland, have already made Spinraza available. He urged NICE and NHS England "to continue to work with us on agreeing the terms of a managed access agreement so that patients in England, Wales and Northern Ireland can share equality in access compared to other countries across Europe and the world."

Spinraza, which was approved by the European Commission in June 2017, having got the green light in the US in December 2016, is a key growth driver for Biogen. Second-quarter sales more than doubled versus the year-earlier period in 2017 to $423m and were up 16.2% over first-quarter 2018, driven by penetration into the adult SMA population in the US and international expansion.

It begs the question as to how vital in commercial terms reimbursement in the UK (excluding Scotland, which has made Spinraza routinely available to patients with type 1 SMA and will consider the medicine for types 2 and 3) is for Biogen. Edward Thomason, an analyst at Pharma Central, believes it still is important.

He told *Scrip* that despite the small number of SMA patients in the UK, the high cost of therapy would have driven significant value and on the rejected list price, Spinraza could have reached over $170m after three years. He added that "the initial rebuff is not surprising given the high cost and the unclear durability and long-term effects of Spinraza treatment. Nevertheless, it is likely that a final agreement will be agreed in the future, opening Biogen to a significant pool of SMA patients."

Thomason went on to say that "whilst NICE is notoriously difficult for rare disease companies to agree reimbursement with, the significant UK population means it is still extremely profitable for companies to persevere particularly regarding the influence NICE has over other regulatory and reimbursement bodies in Europe."

Biogen's battle with NICE echoes the struggles that another US biotech – **Vertex Pharmaceuticals Inc.** – has had with the agency. Earlier this week, Vertex said it will not file data for its latest cystic fibrosis combination therapy *Symkevi* (tezacaftor and ivacaftor) until NICE changes how it assesses the cost-effectiveness of its drug – the two sides are currently deadlocked over the price of the company's *Orkambi* (ivacaftor/lumacaftor). *(Also see "Stand-Off: Vertex Refuses NICE Data on CF Drug Symkevi, HTA Body Awaits Next Move" - Pink Sheet, 14 Aug, 2018.)*

Thomason told *Scrip* that "despite Vertex' bluster, the situation is unlikely to change just yet. However, NICE's influence is undoubtedly under threat, primarily from the Brexit decision. It is likely that once the UK has left the European Union, separate regulatory processes will be installed and it's possible that companies will deem the UK market less appetizing, preferring to prioritize European submissions."

He concluded by saying that with access to new medicines in UK likely to be further delayed, "it's possible that NICE's resilience against rare diseases might wilt in order to secure medicines earlier."

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BioNTech And Pfizer Explore mRNA Flu Vaccines In $120m+ Deal

KEVIN GROGAN kevin.grogan@informa.com

Expanding from its personalized cancer immunotherapy area of expertise, Europe's largest private biotech **BioNTech AG** has signed a collaboration with **Pfizer Inc.** to develop messenger RNA (mRNA)-based vaccines for the prevention of influenza.

The cash terms that the German group has negotiated are impressive. BioNTech will receive $120m in upfront, equity and near-term research payments from the US drugs behemoth and is eligible for up to $305m in development, regulatory and commercial milestones, plus royalties.

In an interview with *Scrip*, CBO and CCO Sean Marett said the move represents the first time BioNTech has moved into infectious disease in humans, having inked an agreement in May 2016 to develop novel, first-in-class mRNA vaccines and therapeutics specifically for animal health applications. He added that the Pfizer deal is also the first in a number of collaborations planned to expand the firm's R&D presence in infectious disease.

Ugur Sahin, co-founder and CEO of BioNTech, stated that building a significant presence in infectious disease "supports our goal of building a global immunotherapy company." The flu collaboration "will combine our deep understanding of the immune system to treat disease with the cutting-edge technologies and significant infrastructure that we have built-up over many years to develop immunotherapy treatments," he said.

The Pfizer collaboration is the first equity deal with big pharma that BioNTech has concluded, Marett said, and while he would not disclose what size stake the company has taken, he noted that the sums involved show Pfizer's commitment to the flu alliance. The latter will assume sole responsibility for further clinical development and commercialization of mRNA-based flu vaccines, following BioNTech's completion of a first in human clinical study.

Marett did not put a timeline on the studies but BioNTech's work on potential flu vaccines is well advanced and the company has developed a variety of technologies which have impressed Pfizer. Its head of vaccine R&D, Kathrin Jansen, said in a statement that "innovative vaccine approaches are urgently needed to provide improved protection against seasonal flu, and to respond rapidly and in quantity to pandemic influenza threats."

She added that mRNA vaccines "offer a novel approach to code for any protein or multiple proteins, and the potential to manufacture higher potency flu vaccines more rapidly and at a lower cost than contemporary flu vaccines. BioNTech is one of the industry leaders in mRNA technology and we are looking forward to working closely with them."

The rationale behind the deal looks compelling. Developing an mRNA-based universal flu vaccine could protect against a broad variety of strains, possibly replacing seasonal vaccine and eliminating the need to develop a new one every year. The current approach of producing vaccines from chicken eggs based on the previous flu season's viral strains is antiquated, and Marett pointed out that as it usually takes several months to create the vaccine using eggs, the virus can dramatically change – these virus changes in eggs would not be an issue using an mRNA approach.

BioNTech is not the only company looking at mRNA vaccines for flu. The most high-profile rival is **Moderna Therapeutics LLC** while in February, fellow Germany-headquartered biotech **CureVac AG** and the Bill & Melinda Gates Foundation, which bought a stake in the firm for $52m in 2015, agreed to develop mRNA-based vaccines designed to prevent both influenza and malaria infection. Marett told *Scrip* that the mRNA space needs more companies like his, Moderna and CureVac, noting that "it is good for the field and good for each other." He explained that mRNA as an area of research is still very young and it will take a while to explore its applications. In order to do so, "you need critical mass," he added.

BioNTech itself has advanced a lot since its formation 10 years ago, Marett said, noting that it is not that long ago that the Mainz-based group did not even have a website. Earlier this year the company raised $270m in a Series A round, having previously secured a number of lucrative oncology deals with top-tier partners such as **Genentech Inc.**, **Genmab AS**, **Eli Lilly & Co.** and **Sanofi**.

Marett noted that the partnerships inked thus far – the first was signed in 2015 and the Pfizer pact is BioNTech's seventh – have been 50/50 deals in terms of costs and future rights, "so we work to pharma budgets, not biotech budgets." As such, the possibility of an initial public offering is often raised and he told *Scrip* that at some stage a listing is inevitable, given the capital-intensive demands of the business, which now employs some 750 staff.

An IPO has its pros and cons, he stressed, noting that the last decade of having the Struengmann family as owners (the brothers Andreas and Thomas sold their generic drug firm Hexal to **Novartis AG** for $7.5bn in 2005) "has allowed us to do the deep science and validate our technologies."

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Novo Nordisk Makes Long-Term Bet On GBM Technology With Ziylo Buy

STEN STOVALL sten.stovall@informa.com

Novo Nordisk AS says development of glucose responsive insulins is a key strategic goal and is underscoring that commitment by buying **Ziylo Ltd**, a move that gives the Danish diabetes specialist full rights to the university spin-out's early-stage synthetic glucose binding molecule technology.

The transaction is potentially worth more than $800m. Its terms see Novo Nordisk paying an undisclosed upfront payment while other pay-outs depend on achieving certain development, regulatory and sales milestones.

Ziylo is a University of Bristol spin-out company which is pioneering development of synthetic glucose binding molecules which the parties believe could lead to safer and more effective insulin therapy.

GLUCOSE RESPONSIVE INSULIN

A glucose-responsive insulin would help eliminate the risk of hypoglycemia, the biggest risk associated with insulin therapy and one of the main barriers for achieving optimal glucose control. A glucose responsive insulin could also lead to better metabolic control and thus overall reduce the burden of diabetes for people living with the disease, the duo said.

> 'We're in effect creating is a hybrid form of insulin that contains insulin itself connected to a glucose 'switch' and when a patient's sugar level plummets, where ever it is in the body, it can deactivate that insulin and therefore stop a hypoglycemic episode'

"What Ziylo's technology brings to the table is a class of molecules that broadly speaking can bind and thus 'sense' glucose," explained Marcus Schindler, senior vice president, global drug discovery at Novo Nordisk.

"Our aim is to couple these glucose binding molecules to an insulin, and we at Novo Nordisk are leaders in engineering insulin molecules, so you'd have a totally novel insulin molecule that would produce a smart insulin that would be activated only when glucose levels are high and when insulin is needed and which would be inert or inactive when glucose levels are at a normal level," he told *Scrip*.

For diabetic patients, that would alleviate the concern about hypoglycemia and help them reduce and hopefully eventually abandon the need for glucose monitoring, he added.

Ziylo's CEO Harry Destecroix told *Scrip*: "We're in effect creating a hybrid form of insulin that contains insulin itself connected to a glucose 'switch' and when a patient's sugar level plummets, whereever it is in the body, it can deactivate that insulin and therefore stop a hypoglycemic episode." The biotech CEO believes this novel therapy could offer a new market that bridges type 2 and type 1 diabetes care.

MARKET POTENTIAL SEEN

"If it works well, then it offers the potential to increase market share because a lot of type 2 diabetics are on the verge of requiring insulin therapy, but because of the risks associated with moving them on to insulin due, for example to the risk a mistake might be made administering it, this new smart insulin could make it much simpler for patients and offer much more tolerance because even if one over-injects it wouldn't matter that much because the insulin will just deactivate."

There have been numerous attempts at trying to 'sense' insulin. One such ill-fated attempt was seen after the 2010 purchase by **Merck & Co. Inc.** of **SmartCells Inc.** in the hope of developing glucose-responsive insulin formulation for treating diabetes, an R&D effort that didn't pan out. But Schindler believes that Ziylo and Novo Nordisk might just crack it.

"We've done research in this field for around two decades. Ziylo's molecules really seems to be able to sense and react to glucose concentrations in the blood, and combing that with insulin could really be cutting edge. That said, it is a research project which requires further work and preclinical proof of concept before it can be turned into reality and apply it to patients and hopefully one day launch it."

BUT TEN YEARS AWAY AT LEAST

Still, such an innovative therapy looks to be at least a decade out in the future. "We are in a preclinical setting … so I think ten years is a reasonable time frame for this if things go well," Schindler said.

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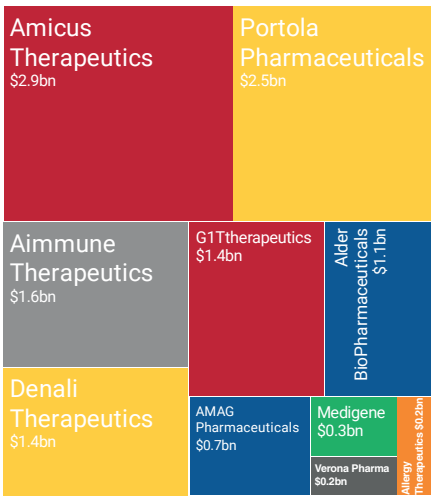
Under The Radar: Potential Small Cap Takeover Targets

JOSEPH HAAS joseph.haas@informa.com

Potential Targets



Likely Acquirers

1. AMAG PHARMACEUTICALS (MARKET CAP $0.7BN)

US specialty firm **AMAG Pharmaceuticals Inc.** is viewed as an acquisition target for companies established in women's health – specifically **Novartis AG** – due to the potential of bremelanotide in hypoactive sexual desire disorder (HSDD). Licensed from **Palatin Technologies Inc.**, the first-in-class melanocortin-4 receptor agonist is thought to offer a better safety and efficacy profile than **Sprout Pharmaceuticals Inc.**'s *Addyi* (flibanserin), which was returned to Sprout by **Bausch Health Companies Inc.** last November. *(Also see "Valeant Returns $1bn Female Libido Drug For Free" - Scrip, 7 Nov, 2017.)* The US FDA is currently reviewing bremelanotide with a March 2019 user fee date; an FDA advisory committee is expected in Q4 2018.

2. MEDIGENE ($0.3BN)

Germany's **MediGene AG** is partnered with **bluebird bio Inc.** on TCR-modified T-cell programs for multiple indications. Its platform targets intracellular tumor antigens that aren't addressable with CAR-T therapeutics. The deal was expanded in May, adding another $500m in earn-outs on top of the $1bn possible under the original agreement. The expanded deal and complementary tech make Medigene a logical acquisition target for bluebird.

3. ALLERGY THERAPEUTICS ($0.2BN)

UK specialty firm **Allergy Therapeutics PLC** has a short-course vaccine candidate for allergic rhinitis – *Pollinex Quattro Grass*– that should begin Phase III in 2019. PharmaVitae says the product has $400m peak earnings potential. Allergy Therapeutics might make a good takeout candidate for a company established in the grass allergy space, such as **Merck & Co. Inc.**

4. VERONA PHARMA ($0.2BN)

UK-based **Verona Pharma PLC**'s first-in-class, inhaled PDE3/4 inhibitor RPL554 could be the first new bronchodilator in 40 years. It is expected to enter Phase III in 2019 as maintenance therapy for COPD and could eliminate the need for adjunctive therapy with inhaled corticosteroids. Verona, which netted $81.1m in its 2017 US IPO, could be targeted by **AstraZeneca PLC** or **GlaxoSmithKline PLC** to enhance their respiratory portfolios.

5. AIMMUNE THERAPEUTICS ($1.6BN)

The US biotech's severe peanut allergy oral immunotherapy AR101 has FDA breakthrough therapy status and has shown strong efficacy versus placebo in Phase III, though there are still safety concerns; additional safety study is due in Q3. BLA filing is expected before end of 2018 and approval second half 2019. PharmaVitae predicts $1.2bn in peak sales potential. AR101 is in a Phase II combination study for peanut allergy with **Sanofi/Regeneron Pharmaceuticals Inc.**'s *Dupixent*. Sanofi might see **Aimmune Therapeutics Inc.** as an attractive takeout target. Aimmune is well underway with launch planning and intends to target 5,000 allergy specialists.

6. G1 THERAPEUTICS ($1.4BN)

G1 Therapeutics Inc. is a US oncology-focused biotech specializing in CDK 4/6 inhibitors. It has two Phase Ib/IIa candidates: trilaciclib for small-cell lung cancer, which may reduce myelosuppression, and G1T38, which in combination with AstraZeneca's *Faslodex* showed best-in-class tolerability in breast cancer at ASCO 2018. Although these candidates are behind approved CDK inhibitors, PharmaVitae perceives market opportunity based on differentiation. Merck & Co. could see G1 as an acquisition target to strengthen its cancer portfolio, after suspending development of its CDK inhibitor dinaciclib.

7. DENALI THERAPEUTICS ($1.4BN)

Still early stage, the neurodegenerative disease-focused US biotech **Denali Therapeutics Inc.** raised the largest Series A round of 2015 at $217m, followed by a $265m IPO in 2017. Denali has two Phase I Parkinson's candidates that target LRRK2, DNL151 and DNL201. Its platform technology offers potential to create first-in-class candidates focused on lysosomal function, glial biology and cellular homeostasis. Denali's *Antibody Transport Vehicle* platform also can generate antibodies that can permeate the blood-brain barrier. Denali could be attractive buyout target for **Takeda Pharmaceutical Co. Ltd.**, its partner in a 2018 neurodegenerative disease collaboration. Also, companies in the neurology space, such as **Biogen Inc.** and **Celgene Corp.**, that might have appetite for risk in areas of high unmet medical need could be interested.

8. ALDER BIOPHARMACEUTICALS ($1.1BN)

The US biotech's CGRP candidate eptinezumab, given as a quarterly I.V., has shown numerically stronger reduction in migraine days than monthly CGRP drugs. **Alder Biopharmaceuticals Inc.** expects to file a BLA first quarter 2019. PharmaVitae thinks the market potential of CGRP class in migraine is underestimated due to too small patient population estimates and the belief that payers will be reluctant to reimburse these products long-term. With **Amgen Inc.**/Novartis' *Aimovig* priced lower than expected in hope of increased access, Alder could be an attractive target for neurology-focused Biogen if payer response to the class is more positive than expected, even though Alder's late entry to market and I.V. formulation will prevent it from being top seller in the class.

9. AMICUS THERAPEUTICS ($2.9BN)

The US rare disease specialist **Amicus Therapeutics Inc.**'s *Galafold* was cleared by the FDA Aug. 10 for Fabry disease, an oral therapy compared to Sanofi's injectable *Fabrazyme*. Galafold is already approved in the EU and Japan. Amicus also has a Phase I/II Pompe disease candidate. The company might be a logical acquisition target for Sanofi, which has the only current marketed therapies for both diseases. PharmaVitae expects big market impact in the US for Galafold, and quick sales growth globally.

10. PORTOLA PHARMACEUTICALS ($2.5BN)

US-based **Portola Pharmaceuticals Inc.** has the oral anticoagulant *Bevyxxa* and Factor Xa inhibitor antidote *AndexXa* on the market, with a third pipeline candidate (cerdulatinib for hematologic malignancies) slated to enter pivotal trials in 2019. Bevyxxa sales have been non-material to date, and the EMA issued a negative review this past March. Andexxa obtained US approval in May but Portola still needs FDA approval for a manufacturing process that will facilitate production sufficient to grow sales. With Portola's CEO retiring in August, these issues indicate a big pharma buyout might be beneficial. **Bristol-Myers Squibb Co.**, **Pfizer Inc.**, **Bayer AG** and **Johnson & Johnson** are likely suitors due to their stakes in the factor Xa anticoagulant market; acquiring Portola could increase uptake of their growing brands by using their manufacturing expertise to ensure the Andexxa launch goes smoothly, PharmaVitae notes.

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Bayer Targets COPD In Haplogen Antiviral Pact

KEVIN GROGAN kevin.grogan@informa.com

Bayer AG is entering the field of chronic obstructive pulmonary disease by linking up with the Austrian biotech **Haplogen GMBH** to develop new antiviral compounds aimed at tackling the respiratory disease.

The collaboration will build on discoveries developed at Haplogen in the field of broadly acting rhinovirus therapeutics since its founding in 2010. That work has been supported by a collaboration with **Evotec AG** since 2012, in a deal which added the German group's expertise in medicinal chemistry and early drug development, and indeed funding, to the program.

The basis for that program, which was licensed in by Haplogen from the Whitehead Institute of MIT in Boston, and has received financial support from the Austrian Research Promotion Agency, has been that respiratory viral infections, especially rhinoviruses, are a frequent cause of COPD exacerbations. Therefore the approach adopted by Haplogen and Evotec has been to look at ways to disrupt the multiplication of the responsible virus by inhibiting its replication.

Privately owned Haplogen, a spin-out of CeMM, the Research Center for Molecular Medicine of the Austrian Academy of Sciences, said in a statement that "the collaboration with Bayer now brings the competences and the funds of an international pharmaceutical company" to the respiratory program "and opens opportunities to develop medications for patients based on the assets" created by Haplogen. Joerg Moeller, head of R&D at Bayer's pharmaceuticals division, noted that COPD is "the third leading cause of mortality worldwide. New treatments are urgently needed and we are pleased to collaborate with Haplogen to develop meaningful innovations."


Joerg Moeller

Bayer is getting an exclusive license to worldwide rights to programs developed within the collaboration and both Haplogen and Evotec will get cash from the undisclosed upfront fee, plus potential milestone and royalty-based payments.

A spokesperson for the Leverkusen-headquartered drug maker told *Scrip* that the Haplogen pact is currently the only one in the area of COPD. However it has other pipeline candidates in the area of lung diseases, notably BAY1237592, a soluble guanylate cyclase (sGC) activator for pulmonary hypertension, which is Phase I trials – a key drug in Bayer's marketed portfolio is the sGC stimulator *Adempas* (riociguat) for pulmonary hypertension. BAY1211163, another sGC activator, is also in Phase I studies for acute respiratory distress syndrome, while BAY1097761, an inhaled pegylated adrenomedullin, is in Phase I for the same indication.

The Haplogen deal was announced a day after Bayer's shares lost as much as 10% of their value (Aug. 13) after its newly acquired agricultural business Monsanto was ordered to pay $289m by a US court to a man who said an ingredient used in the weedkiller *Roundup* – glyphosate – had caused his cancer.

The case is the first of possibly thousands of lawsuits in the US over alleged links. Bayer said in a statement it was confident, "based on the strength of the science, the conclusions of regulators around the world and decades of experience," that glyphosate does not cause cancer when used according to the label." Monsanto intends to appeal.

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It's No Cosentyx/Taltz But Ilumya Pleases Customers, Says Sun

ANJU GHANGURDE anju.ghangurde@informa.com

It's a tough market that **Sun Pharmaceutical Industries Ltd.**'s IL-23p19 inhibitor *Ilumya* (tildrakizumab) is readying to plunge into in the US, but the Indian firm believes that its product comes with significant positives and is quite "liked" by customers.

Sun's CEO (North America) Abhay Gandhi acknowledged that Ilumya, which is a late entrant in the segment, was entering a "competitive crowded" psoriasis market, with competitors that are "bigger" and have been in that business "a longer time," but maintained that it's a challenge that the firm has to overcome.

"It's the status that we are in and we have to fight it," Gandhi said on the Sun's Q1FY19 earnings call, post market hours Aug. 14.

Gandhi said the overall profile of Ilumya in terms of its efficacy, "the lasting effect" that the product shows for patients and the "very low incidence" of side effects were clearly "huge positives" which were "creating an impact", with physicians to whom the firm was "talking to" and KOLs "who understand the product intimately," as well as with payers.

Ilumya is expected to directly take on **Johnson & Johnson**'s first-in-class IL-23 blocker, *Tremfya* (guselkumab), in a rather crowded psoriasis market. And the prominent IL-17 inhibitors that Ilumya goes up against include **Novartis AG**'s *Cosentyx* (secukinumab) and **Eli Lilly & Co.**'s *Taltz* (ixekizumab), while anti-TNFs like **AbbVie Inc.**'s *Humira* (adalimumab), J&J's *Remicade* (infliximab) and **Amgen Inc.**'s *Enbrel* (entanercept) have long been around.

TIME TO GAIN EXPERIENCE

The Sun management also acknowledged the familiarity of physicians with IL-17 inhibitors, given that the class has been used for a longer period of time.

"It will take them [physicians] some time to gain experience and get the same level of comfort with the IL-23 class. It's for all the marketeers to try and address that and make sure that this segment grows. We're clearly seeing that growth happening, we'd obviously like that to be faster," Gandhi noted.

In response to an analyst's query around Ilumya's attributes such as its PASI [Psoriasis Area Sensitivity Index] score versus competition, Sun's management maintained that customers tend to look at things "holistically" and not just based on one parameter.

"My sense is that they like the product," said Gandhi.

The company said that PASI was essentially only a scale used for measuring outcome in clinical trials, and physician outlook for Ilumya had been encouraging.

"By and large, the doctors who've been part of the study and with whom we've discussed ... are very happy with the overall performance of the product both in terms of overall efficacy and duration of response and continued response," Sun's founder and managing director Dilip Shanghvi said on the call.

Ilumya was approved by the FDA based on the results of two pivotal Phase III trials, Resurface 1 and Resurface 2, that enrolled 926 patients. Both studies met the primary efficacy endpoints, demonstrating significant clinical improvement with Ilumya 100mg compared to placebo when measured by at least 75% of skin clearance (PASI 75) and Physician's Global Assessment (PGA) score of "clear" or "minimal" at week 12 after two doses. Treatment efficacy is typically measured by reduction of PASI from baseline: a 75% reduction is known as PASI 75; a 90% reduction is PASI 90; and PASI 100 is total clearance of skin disease.

NOT AS BIG AS COSENTYX, TALTZ

But Shanghvi also sought to emphasize that Ilumya isn't expected to get the traction of the big brands already on the market, at least for now. "Clearly, it's not going to be as big as Cosentyx or Taltz – clearly not in a short period of time; otherwise we would be looking at very different numbers than what we are looking at right now," the Sun boss added.

Cosentyx delivered a strong show in Novartis's recent Q2 results, beating consensus and raking in $701m for the Swiss multinational.

Expectations are, however, generally riding high with the current fiscal year seen as a relatively big launch year for Sun Pharma. India's top-ranked drug firm is expected to introduce Ilumya in the second quarter of FY2019, while *Cequa* (cyclosporine A, ophthalmic solution 0.09%; previously OTX-101), which has just received FDA approval, is expected to be launched in the US "during the course of this year." A third product, *Yonsa* (abiraterone acetate), has just been commercialized in the US.

Sun has cautioned investors that the commercialization plans will entail significant initial costs, though.

"Although we have built the front-end infrastructure for the specialty business in the US, there will be specific marketing and other costs at the time of the launch of these products. They will entail high upfront investments," Gandhi reiterated.

HALOL BACK ON TRACK

The US ramp-up comes in the backdrop of a generally challenging generic pricing environment there, though Sun reported an 8% increase in US finished dosage sales to $380m for the first quarter ended June 30.

Sun is also awaiting approvals from the US FDA for two other specialty products, *Xelpros* (latanoprost BAK-free eyedrops) and *Elepsia XR* (levetiracetam extended-release tablets), filed from its Halol site, which recently made the compliance cut, ending long-running FDA scrutiny. Both products have been in-licensed from Sun Pharma Advanced Research Company (SPARC), Sun's listed R&D spin-off.

"With this development we now expect a gradual improvement in our business and new approvals from Halol for the US market, including two specialty products in-licensed from SPARC," Shanghvi said.

For the quarter ended June 30, Sun reported a 16% increase in overall sales to INR71.39bn ($1.01bn), while net profits for the period stood at INR9.83bn. Net profit for the corresponding quarter last year was adversely impacted by a INR9.51bn settlement with certain plaintiffs related to the modafinil antitrust litigation in the US. Excluding the impact of this settlement, adjusted net profit was up by 87% over the first quarter last year.

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First In 10 Years, But Lenvima's First-Line Liver Label Could Be Challenged Soon

MANDY JACKSON Mandy.Jackson@informausa.com

The agreement earlier this year between **Eisai Co. Ltd.** and **Merck & Co. Inc.** to partner on the continued development and commercialization of *Lenvima* (lenvatinib mesylate) appears to be a particularly important defensive move for both companies as the kinase inhibitor has won an important new approval in liver cancer.

Eisai and Merck said on Aug. 16 that the FDA cleared Lenvima for first-line treatment of unresectable hepatocellular carcinoma (HCC), marking the first US approval in the front-line HCC setting in a decade, although it probably won't take another decade for additional competitors to emerge in this indication. Until then, Lenvima may be a formidable rival for **Bayer AG**'s and **Amgen Inc.**'s *Nexavar* (sorafenib), which has enjoyed a decade without a major competitor in the first-line liver cancer setting, since the Eisai/Merck drug bested the older kinase inhibitor in the Phase III REFLECT study.

"Aside from the positive efficacy data for Lenvima, factors such as once-daily dosing and comparable cost to Nexavar will help Lenvima compete in the so-far monopolized market that is first-line HCC," Biomedtracker analysts noted in May 2017 when Eisai reported the REFLECT results. "Even further, although dosing-related safety concerns were brought up considering Lenvima's Phase I/II trial, no such concerns have been highlighted in this Phase III trial versus Nexavar, as Lenvima even sustained a higher treatment duration than Nexavar (5.7 months versus 3.7 months)."

The Lenvima approval in first-line HCC came slightly earlier than expected, according to Morgan Stanley analyst Shinichiro Muraoka in an Aug. 17 note. An FDA decision originally was expected on May 24, but was moved back three months due to apparent procedural issues at the agency, he noted.

"We expected US approval on Aug. 24, so the good news comes a week earlier than we expected. We see limited [Eisai] share price impact given that the US approval for the treatment of hepatocellular carcinoma (HCC) was in line with market expectations," Muraoka wrote.

Eisai's stock closed down 1.7% on the Tokyo Stock Exchange on Aug. 17. Muraoka estimated that Eisai may receive a milestone payment from Merck in its fiscal second quarter (July-September) totaling ¥10bn ($90.5bn).

IO COMBO COMPETITION NOT TOO FAR OFF

Both Lenvima and Nexavar may have additional competitors in HCC in the not-too-distant future, at least in later lines of therapy, from the likes of **Exelixis Inc.**'s *Cabometyx* (cabozantinib) as well as immuno-oncology blockbusters and IO combination regimens with PD-1/PD-L1 inhibitors.

Fortunately for Eisai, which discovered and developed Lenvima internally, it partnered with Merck in time to defend the drug's place in the liver cancer market as a monotherapy and in combination with PD-1 inhibitors, including Merck's *Keytruda* (pembrolizumab). Eisai received $300m up front, but the deal is worth up to $5.67bn in option fees, R&D expenses and milestone payments.

The companies noted when they announced the collaboration in March that Lenvima and Keytruda together have shown positive efficacy in solid tumors in an ongoing Phase Ib/II basket trial. The combination has received breakthrough therapy designations from the FDA in both renal cell carcinoma (RCC) and endometrial cancer based on interim findings from the study.

The partnership also boosts Keytruda's potential in HCC and RCC where **Bristol-Myers Squibb Co.**'s PD-1 inhibitor *Opdivo* (nivolumab) is in the lead in the pursuit of liver and kidney cancer indications.

There is one Lenvima/Opdivo study under way – a 26-patient Phase Ib trial in HCC in Japan – but it has the same design as an ongoing 30-patient Phase Ib study testing Lenvima/Keytruda in the US. Both trials are enrolling patients with HCC who've tried other available therapies and both IO combination studies have expansion phases to test the combos in first-line unresectable HCC.

A Phase Ib study also recently was initiated to test Bayer's kinase inhibitor *Stivarga* (regorafenib) in combination with Keytruda in previously untreated advanced HCC.

DEFENSE AGAINST NEW SECOND-LINE DRUGS

Both Opdivo and Stivarga are approved as monotherapies to treat HCC patients who progressed after treatment with Nexavar. But while Keytruda is not approved for liver cancer in any setting in the US, Merck does have a supplemental biologic license application (sBLA) for the PD-1 inhibitor in previously treated HCC that the FDA accepted for priority review in July with a Nov. 9 action date.

Going forward, the IO combination data in first-line HCC will be important, since several competing therapies are coming in the second-line monotherapy setting.

Exelixis' kinase inhibitor Cabometyx had positive Phase III results in second-line HCC in January of this year and the drug is under FDA review for this indication with a PDUFA date in January of next year.

Eli Lilly & Co.'s sBLA for the VEGFR-2 inhibitor *Cyramza* (ramucirumab) in second-line HCC also is pending at the FDA with approval expected by the end of September.

Eisai and Merck note that liver cancer is the second leading cause of cancer-related death with 750,000 deaths globally each year; 780,000 people are diagnosed annually – and about 85%-90% of liver cancer cases are HCC.

Lenvima's first US approval was in February 2015 for the treatment of locally recurrent or metastatic, progressive, radioactive iodine-refractory differentiated thyroid cancer (DTC) with approval in May 2016 in combination with everolimus for advanced RCC after one prior anti-angiogenic therapy.

In addition to HCC, RCC and endometrial cancer, Merck and Eisai also are studying or plan to test Lenvima in combination with Keytruda in lung, head and neck, and bladder cancers and melanoma.

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BMS's Opdivo Enjoys IO First-Mover Advantage In SCLC

EMILY HAYES emily.hayes@informa.com

US FDA approval of **Bristol-Myers Squibb Co.**'s PD-1 inhibitor *Opdivo* in relapsed small cell lung cancer based on response rate data marks a breakthrough and gives the drug a lead in a new indication, though it's unclear for how long given that **Roche**'s competing *Tecentriq* has demonstrated an overall survival benefit in an earlier line of therapy.

The FDA granted accelerated approval for Opdivo (nivolumab) in metastatic small cell lung cancer (SCLC) after progression on platinum-based chemotherapy and at least one other line of therapy on Aug. 17.

This marks the first approval of an immuno-oncology drug for SCLC.

"With this landmark approval based on the open-label Phase I/II CheckMate 032 trial, Opdivo becomes the first therapy to be approved for SCLC in nearly 20 years, introducing an entirely new treatment modality to SCLC," Biomedtracker analysts commented on the news.

The approval in SCLC adds to Opdivo's existing indications for relapsed non-small cell lung cancer, recurrent metastatic squamous cell carcinoma of the head and neck, renal cell carcinoma, melanoma, classical Hodgkin lymphoma, urothelial carcinoma and microsatellite-high or mismatch repair deficient colorectal cancer.

Opdivo has been the leading drug in the PD-1/L1 family, but **Merck & Co. Inc.**'s competing PD-1 inhibitor Keytruda (pembrolizumab) has assumed a dominant role in non-small cell lung cancer (NSCLC), and sales began to overtake Bristol's drug in the second quarter.

About 10%-15% of lung cancers are the SCLC type and there will be an estimated 27,000 new cases diagnosed yearly in the US. Treatment options are limited and the five-year survival rate is only 2%.

Currently, topotecan chemotherapy (Novartis's *Hycamtin* and generics) represents the standard of care for SCLC.

Morningstar Research has forecast that in 2022, the NSCLC market for PD-1/L1 inhibitors will be worth $17bn versus $2bn for SCLC. With a first-mover advantage in this indication, Bristol's Opdivo is expected to take a 45% share of the market, followed by Merck with 25%, Roche with 20% and AstraZeneca with 10%, according to Morningstar projections.

MODEST EFFICACY

Bristol's filing was supported by data from an SCLC cohort in the Phase I/II CheckMate 032 study of cancer patients with disease progression after platinum-based chemotherapy.

The Phase III CheckMate 331 study is comparing overall survival for Opdivo versus chemotherapy and the Phase III CheckMate 451 study tests Opdivo with the company's CTLA4 inhibitor *Yervoy* (ipilimumab) as maintenance therapy in extensive-stage SCLC after completion of platinum-based chemotherapy. Results from both studies are expected by the end of the year.

In CheckMate 032, out of 109 SCLC patients enrolled, 13 (12%) responded to treatment, including 12 partial responses and one complete response. This effect was not dependent on the level of expression of the PD-L1 biomarker, the company reported.

Seventeen percent of patients received Opdivo for greater than six months, and 9% of patients received Opdivo for more than one year. The median duration of response was 17.9 months.

Side effects most commonly reported included fatigue (45%), decreased appetite (27%) and musculoskeletal pain (25%).

Biomedtracker analysts noted that the efficacy results in CheckMate 032 are at best only comparable to chemotherapy in second- and later lines of therapy.

"The accelerated approval despite the open-label design, the small number of patients and modest results underscores the immense unmet need for new therapies in this area," they explained.

Most patients with SCLC relapse and median survival is typically only four or five months. In the CheckMate 032 study, the median survival was 4.4 months, which is similar to older therapies, but prescribers may want to use Opdivo due to the comparably better safety profile, Biomedtracker said.

In addition to Opdivo, three other PD-1/L1 inhibitors are in Phase III for SCLC – Roche's Tecentriq (atezolizumab), **AstraZeneca PLC**'s *Imfinzi* (durvalumab) and Merck's Keytruda. All three are being tested in newly diagnosed SCLC whereas Opdivo is not being positioned for treatment-naïve patients.

Roche reported in July that Tecentriq and chemotherapy improved overall survival compared with chemotherapy alone in an interim analysis of the Phase III IMpower133 trial of first-line use in extensive-stage small cell lung cancer patients. Data are slated for release at the International World Conference on Lung Cancer annual meeting in Toronto next month.

Roche subsidiary **Genentech** tells *Scrip* that it will file the data with the FDA and other global regulatory authorities "as soon as possible."

Keytruda is being tested with chemotherapy in the KEYNOTE 604 study and Imfinzi is being tested with AstraZeneca's CTLA4 inhibitor tremelimumab along with chemotherapy in the CASPIAN study. Both are first-line trials.

LEAD MAY BE SHORT-LIVED

Commenting on the news of the Opdivo approval by email to *Scrip*, oncology H. Jack West noted that this is a setting where there is "no enthusiasm" for the most-evidence based treatment of relapsed SCLC – topotecan, an agent that has very modest efficacy, requires a lot of time in the clinic for patients receiving treatments and has challenging toxicity.

"Prior to the introduction of immunotherapies here, many if not most thoracic oncology specialists and community-based general oncologists alike often favored less evidence-based options despite the lack of proven benefit, based on a conclusion that the clinical value and therapeutic index of topotecan is so low that just about any marginally active alternative is sufficient," said West, who is medical director of thoracic oncology at the Swedish Cancer Institute in Seattle.

Nivolumab and the combination of nivolumab with ipilimumab both have shown very limited response rates, yet have been included in National Comprehensive Care Network guidelines, as there is a recognition that the minority of patients who do respond have a durable response, often with little or no toxicity, West noted.

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Regeneron And Teva's Fasinumab Crosses One Threshold; More Remain

JESSICA MERRILL jessica.merrill@informa.com

Partners **Regeneron Pharmaceuticals Inc.** and **Teva Pharmaceutical Industries Ltd.** slightly trail rivals **Pfizer Inc.** and **Eli Lilly & Co.** in reporting the first positive Phase III data on a potential new class of drugs for pain – nerve growth factor (NGF) inhibitors – revealing on Aug. 16 that their anti-NGF candidate fasinumab significantly reduced pain compared to placebo. But as with Pfizer/Lilly's tanezumab, fasinumab's safety will remain a big focus as additional trials read out.

Fasinumab's efficacy data, while significant, appears modest versus placebo, which could present more challenges when it comes to commercializing a new drug with safety issues that could require onerous monitoring.

Drug makers are hopeful NGF inhibitors could offer a new way to treat pain beyond non-steroidal anti-inflammatory drugs (NSAIDs) and highly addictive opioid medications. But while late-stage anti-NGF drugs have demonstrated efficacy, the bigger question has addressed safety.

The entire class has a history with clinical holds due to safety concerns, including severe joint damage and neuro-musculoskeletal events. The full class was put on clinical hold back in 2010. A Phase IIb study testing fasinumab specifically in patients with chronic lower back pain was put on a clinical hold in 2016 based on cases of arthropathy (joint damage) in patients with osteoarthritis. The setback came just one month after Regeneron signed Teva as a risk-sharing partner on fasinumab.

More recently, Regeneron and Teva announced earlier this year they were halting the high dose of fasinumab in ongoing Phase III trials following a risk-benefit assessment by the independent data monitoring committee. As a result, the companies are testing a low 1 mg dose of the drug at two different intervals, four weeks and eight weeks.

The first Phase III study for fasinumab met both co-primary endpoints in patients with chronic pain from osteoarthritis of the knee or hip, the companies announced. The co-primary endpoints were change in pain at week 16 versus baseline and change in function at week 16 versus baseline, as measured by the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain subscale and physical function sub-scale.

But Jefferies analyst Biren Amin questioned the modest efficacy result after the companies reported decreases in pain score of -2.78 at four-week dosing and -2.25 at eight-week dosing. That would correspond to a 12% and 7% improvement, respectively, versus placebo, Amin said, when calculated as absolute changes on the WOMAC pain scale. Regeneron disagreed with that assessment, however, and said the pain improvement is much higher, 78% and 45%, respectively.

ARTHROPATHIES NOTED

The study was designed to specifically monitor for arthropathies and fasinumab generally was well tolerated at the interim analysis, the companies said. The study monitored for arthropathies with regularly scheduled radiographic monitoring beginning at week 24, as well as clinical evaluation.

Among the approximately 65% of patients who completed their first radiographic assessments, the placebo-adjusted rate of adjudicated arthropathies was approximately 2%. No cases of osteonecrosis were identified to date, the companies reported.

But any kind of requirement to monitor for safety in an approved NGF inhibitor's label could be a difficult hurdle in achieving significant sales given the market dynamics.

"While the company views it as comparable to NSAIDS, we would highlight that NSAIDs are oral, available at generic prices and do not require regular radiographic monitoring," Amin said.

LONGER-TERM RESULTS

After the initial efficacy assessment at week 16, patients continue on therapy for an additional 36 weeks, followed by a subsequent 20-week off study drug follow-up period. The full data will be presented at a future medical congress.

Regeneron and Teva said the data support further study; the companies are enrolling patients with chronic pain caused by osteoarthritis of the knee or hip in three Phase III trials, including one long-term safety study and two studies comparing fasinumab to standard pain therapies. The studies will enroll more than 7,000 patients.

"We are encouraged by these data and look forward to advancing our pivotal Phase III fasinumab program in patients with osteoarthritis of the knee or hip who currently have very limited therapeutic choices to treat their chronic pain, other than with non-steroidal anti-inflammatory drugs or opioids," Regeneron Chief Scientific Officer George Yancopoulos said in a statement.

Investors remain cautious on fasinumab given the safety hurdle. As Evercore ISI analyst Umer Raffat said in a same-day note: "Investors in Teva are assuming a near-zero on this drug after the higher doses were previously discontinued in Phase III. The results today are still quite preliminary, and we need much more follow-up and longer-term data to really understand if this drug could be real."

If fasinumab does progress through clinical development, the drug also likely will be competing against tanezumab. One disadvantage for fasinumab could be the lower dose that is being studied, although that is still unclear given the limited data that have been released. The Regeneron/Teva trial enrolled 646 patients to two treatment arms or placebo. The two treatment regimens were 1 mg every four weeks or 1 mg every eight weeks.

Pfizer and Lilly may have an advantage since they completed a Phase III study in patients with osteoarthritis of the knee or hip with two higher doses of their NGF inhibitor tanezumab, a 2.5 mg dose and a 2.5 mg starting dose with a 5 mg follow-up dose.

But Regeneron cautioned that it is difficult to make cross-trial comparisons.

Pfizer and Lilly announced positive topline data from an initial Phase III trial in July, showing improvements in the same co-primary endpoints of pain and physical function, but the companies did not release any detailed data, so the amount of improvement is unclear.

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Biohaven Readies Glutamate Modulator For PhIII In Anxiety

EMILY HAYES emily.hayes@informa.com

Biohaven Pharmaceuticals Holding Co. Ltd. is moving its glutamate modulator BHV-0223 into Phase III following positive results in a small Phase II study of social anxiety disorder.

BHV-0223 is a unique, sublingual formulation of the glutamate transporter modulating agent riluzole – a reformulation of a now-generic, oral drug for amyotrophic lateral sclerosis (ALS) – that dissolves quickly in the mouth. The candidate was developed using dissolving tablet technology licensed from **Catalent Inc.**

Development of riluzole in a range of central nervous system conditions, including general anxiety disorders, social anxiety and panic disorder, was pioneered and patented at **Yale University** by Vladimir Coric, now CEO at Biohaven, and colleagues. Biohaven has a patent for exclusive rights for development in these conditions and intellectual property applications have been filed.

Biohaven reported positive results on Aug. 16 from an investigator-initiated study, which tested the drug against placebo in 21 subjects with social anxiety disorder and clinically significant fear of public speaking.

Participants were treated with 35 mg of BHV-0223 or placebo one hour prior to two anxiety-provoking performance tests. Investigators were looking for an improvement that reached a p-value significance threshold of at least 0.10, rather than the usual 0.05, due to the small size of the study, on the Visual Analogue Scale (VAS), a psychometric response measure, compared with baseline.

Biohaven reported top-line results showing a 14.4-point advantage for those treated with BHV-0223 relative to placebo on the VAS. The p-value was 0.56, which was a better outcome than expected. The drug also was safe and well-tolerated.

Some 6.8m people in the US have generalized anxiety disorders and treatment options include benzodiazepines, which are associated with risks of sedation and addiction, generic gabapentin and serotonin reuptake inhibitors.

CEO Coric explained to *Scrip* that glutamate modulators like BHV-0223 have a number of advantages in the treatment of anxiety in that they are not addictive and don't present risks for impairment of cognition, sedation and addiction.

For a small study, the exec said the finding was pretty robust and noted that "you couldn't ask for more in a proof-of-concept study."

Based on these results, the company is moving BHV-0223 into a registrational study before the end of the year in generalized anxiety disorder (GAD), Coric said. The randomized trial will enroll 300 people and use a more traditional anxiety endpoint – the Hamilton Anxiety Rating Scale – to measure efficacy.

If the first study is positive, the company will run a second registrational study sometime next year and if all goes well the drug could be approved within two years in GAD.

Additionally, an NDA is slated for submission by the fourth quarter for BHV-0223 in amyotrophic lateral sclerosis (ALS), via the 505(b)2 regulatory pathway. The company had $217m in cash at the end of the last quarter, enough to fund its BHV-0223 and other drug development activities through the end of 2019. Its most advanced pipeline asset is the Phase III oral CGRP inhibitor rimegepant, for which Biohaven intends to seek FDA approval in 2019 for the acute treatment of migraine headaches.

EARLY BHV-0223 DATA GET POSITIVE RECEPTION

Biohaven's BHV-0223 dataset generally was well received. The company's stock price rose from $33.67 to close at $35.10 on Aug. 16.

Biomedtracker analysts described the Phase II data as encouraging, though the p-value was not as stringent as 0.05. More information is needed on baseline values to understand the magnitude of the effect, the analysts added.

"It is notable that the medication was given one hour prior to performing each of two impromptu speech tasks as this highlights the acute anxiolytic potential of BHV-0223. While, the company is yet to provide further details pertaining to safety and tolerability data, it is positive that top-line results appear to suggest that BHV-0223 is safe and well-tolerated," Biomedtracker noted.

Biomedtracker analysts also observed that positive results in a larger study would put the drug in a strong pipeline position as the mechanism of action is differentiated from antidepressants, including **Allergan PLC**'s selective serotonin reuptake inhibitor *Viibryd* (vilazodone), which is approved for depression and in Phase III for GAD.

Morgan Stanley analyst Matthew Harrison said in an Aug. 16 note that Biohaven's data are interesting but early; data from more robust studies are needed before the firm will change its modeling.

Investors are not placing significant value on Biohaven's glutamate research currently as attention is more focused on rimegepant for migraine. The company reported positive Phase III results for rimegepant in March, but the CGRP space is very competitive – rivals include Allergan's ubrogepant.

Biohaven intends to submit an investigational new drug application for a second CGRP receptor antagonist called BHV-3500 and start a Phase I study in the second half of this year.

Morgan Stanley projects a 2020 launch and peak sales for rimegepant of $1.4bn. Harrison said his firm is modeling a revenue contribution for Biohaven's glutamate platform starting in 2019, with peak sales of $250m.

Glutamate abnormalities play a role across central nervous system disorders, including ALS, Alzheimer's and ataxia, and Coric noted that "we are just starting to see the tip of that." Biohaven will follow the science as it develops this candidate, he said.

Biohaven notes that it has worldwide rights to "a broad library" of riluzole prodrugs, including troriluzole (BHV-4157), which is in Phase II/III development for spinocerebellar ataxia (SCA), obsessive compulsive disorder (OCD) and Alzheimer's disease.

In addition to glutamate transporter modulators, the company's glutamate platform includes candidates that work on a different mechanism – glutamate N-methyl-D-aspartate, or NMDA, receptor antagonism.

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Christopher Keeling
Tel: +44 (0) 20 3377 3183 | Email: christopher.keeling@informa.com

Private Longeveron Bets On Stem Cells For Inflammation, Aging Diseases

EMILY HAYES emily.hayes@informa.com

Miami-based private regenerative medicine start-up **Longeveron** is aiming its stem cell therapies at a target with high unmet need that it feels gets unfairly overlooked by biopharma – aging frailty – as well as the more familiar geriatric field of Alzheimer's disease.

Longeveron points out that more than 10% of people aged 60 and above have aging frailty and figures suggest that will equate to 50 million by 2050.

Aging frailty is a separate from Alzheimer's, but there is overlap in that some with aging frailty have cognitive decline and Alzheimer's patients may also be frail, co-founder and Chief Scientific Officer Joshua Hare explained in an interview with *Scrip*.

A number of indexes are used to assess frailty. For example, according to criteria developed by Linda Fried and colleagues at the Johns Hopkins University Center on Aging and Health, frailty is marked by the following five factors: unintentional weight loss, exhaustion, muscle weakness, slowness while walking and low levels of activity.

Being frail leaves people vulnerable to loss of muscle mass, or sarcopenia, and to debilitating falls.

Frailty is the lead indication targeted by Longeveron, a private start-up founded in 2014 that is developing allogeneic human mesenchymal stem cells for aging and aging-associated diseases exclusively licensed from the University of Miami (for undisclosed terms).

HOME-GROWN STEM CELLS

Longeveron was founded in 2014 by Hare, who also is founding director of the University of Miami's Interdisciplinary Stem Cell Institute, and Donald Soffer, a prominent real estate developer in Florida and the lead investor behind the licensing deal with the University of Miami and the launch of Longeveron. Execs won't disclose the exact initial financing terms, but say it was enough to get the company through its first four years.

Since then, the company also has secured a total of $3.75m in grants from a range of sources – the Maryland Technology Development Corporation (TEDCO), the National Institutes of Health's National Institute on Aging (NIA), the Alzheimer's Association and the US Small Business Information Research's Small Business Technology Transfer (STTR) program.

Longeveron now harvests and grows stem cells, which it calls Longeveron Mesenchymal Stem Cells (LMSCs), at its facility in Miami, using bone marrow from adult donors to make allogeneic treatments. The company's website notes that manufacturing is under US FDA oversight and complies with regulatory requirements – so "patients and physicians can be confident that an exceptionally safe and high-quality product is delivered."

Hare, who is the company's chief scientific officer, says that Longeveron has filed a portfolio of use and composition of matter patents and has a strong intellectual protection strategy. However, the firm is keeping quite a lot as trade secrets; for example, the nuances of production and manufacturing will not be in the public domain.

Longeveron currently is looking to fill its chief executive officer and chief commercial officer positions.

INFLAMMATION IN AGE-RELATED DISEASES

Hare said frailty is a core area of geriatric medicine, but has been somewhat overlooked by biopharma companies, who tend to be more focused on Alzheimer's.

However, Phase III failures in Alzheimer's disease after promising mid-stage data unfortunately are the norm. **Eli Lilly & Co.** announced in June it was dropping the beta secretase cleaving enzyme (BACE) inhibitor lanabecestat after poor Phase III data. Lanabecestat was Lilly's second major late-stage disappointment in Alzheimer's disease in as many years after its amyloid-targeting antibody solanezumab failed in a third Phase III study in November 2016.

Other notable Alzheimer's drug failures include **Merck & Co. Inc.**'s BACE inhibitor verubecestat, **Pfizer Inc./Johnson & Johnson**'s anti-amyloid antibody bapineuzumab and **Takeda Pharmaceutical Co. Ltd.**'s *Actos* (pioglitazone).

Biogen Inc./Eisai Co. Ltd.'s anti-amyloid antibody BAN2401 has looked promising, but recently released mid-stage data raised questions about trial design, spurring doubts about prospects in Phase III.

Hare said it's disappointing that all of the tremendous research over an 18-year-period has not yielded a new drug for Alzheimer's, but feels there is a need for more investigation into inflammation as a target for aging frailty and Alzheimer's disease.

The Foundation for the National Institutes of Health Biomarkers Consortium recently launched a project to develop biosignatures for Alzheimer's disease and major depression, looking to add to the understanding about inflammatory responses in the brain and their relation to central nervous system disorders.

Longeveron pointed out that frailty research is a major priority for the NIA and the Claude D. Pepper Older Americans Independence Centers, a Los Angeles-based network of centers that receive funding each year to advance research in extending independence of older Americans.

NIA noted that "research on the basic biology of age-related diseases and conditions is a major focus of study across NIA." Some of that research addresses the process of inflammation, "which leads over time to changes in cell, tissue, and organ structure and function. Inflammation may increase the susceptibility to and rate of progression of age-related pathologies and may contribute to frailty, independent of overt disease. This and other risk or protective processes that may occur at various stages, from early life on, may influence health and survival outcomes in old age," the NIA website says.

The NIA supports research into the role of stem cells in tissue maintenance and the possibilities of cell-based therapies and regenerative medicine: "Stem cells are the ultimate precursors to all the cells of the body, and they are important tools for both cell-based therapies and regenerative medicine. It is clear that tissues and organs lose function with advanced age, and such losses may result from declines in stem cell function."

Longeveron At A Glance

Location: Miami
Financing: Initial private financing undisclosed, $3.75m in grants
Disease areas: Aging frailty, Alzheimer's disease and metabolic syndrome
R&D Focus: Biological solutions for aging and aging-associated diseases through allogeneic human mesenchymal stem cells harvested and home grown from adult-donor bone marrow
Founding date: 2014
Founders: Joshua Hare and Donald Soffer
Management team: Joshua Hare, CSO; Suzanne Liv Page COO; Anthony Oliva, Senior Scientist
Scientific Advisors: Jeremy Walston (Johns Hopkins), Laura Dugan (Vanderbilt University), Elena Volpi (University of Texas), Hidenori Arai (National Center for Geriatrics and Gerontology)
Employees: 15

Longeveron notes that people with aging frailty have a chronic low-grade inflammation that can weaken the immune system, and believes its mesenchymal stem cell therapy alleviates inflammation and promotes endogenous tissue repair, which translates into a stronger body and an enhanced immune system. Hare stressed that the goal of treatment is to improve quality of life – not merely to improve the length of life.

Currently, aging frailty is addressed mainly through behavioral approaches, such as diet and exercise.

COMPANY TOUTS UNIQUE SELLING POINT

Longeveron does not see many direct competitors and believes it has a unique selling point.

"We are comfortable that we are in a fairly secure space in terms of developing this technology for this indication," Hare said.

According to the Biomedtracker database, four other stem cell products are in the pipeline for Alzheimer's disease, all of which are in Phase I or I/II.

A number of companies are taking a different approach to aging-related diseases – eliminating accumulated senescent cells. Brisbane, Calif.-based **Unity Biotechnology Inc.**, for example, notes that senescent cells – which secrete harmful proteins that cause inflammation – are a "fundamental mechanism of aging and a driver of many common age-associated diseases."

Unity's lead candidate UBX0101 is a senolytic small molecule inhibitor of the MDM2/p53 protein interaction that entered Phase I for osteoarthritis of the knee in the second quarter.

Oisín Biotechnologies in Seattle has developed a DNA-targeted intervention to clear senescent cells and reduce aging pathologies.

But pharma isn't completely overlooking aging and frailty, Pharmavitae principal analyst Zara Fulton commented. For example, **AbbVie Inc.** and Google's **Calico Life Sciences LLC** are extending and putting more money – $500m each – into a collaboration on aging-related disease first inked in 2014, which AbbVie notes has yielded more than two dozen preclinical programs in oncology and neuroscience to date.

Aging and frailty as a target indication presents an interesting economic case for big pharma, which likely explains its sluggishness in this space, Fulton said. Many conditions are associated with aging, or accumulation of damage – such as cardiovascular diseases, Alzheimer's and type II diabetes. However, it appears that the health care system in the US has a long way to go before payers will start reimbursing drugs with generic life-extending claims – the first targets for such treatments may be wealthy individuals who could pay out of pocket, she suggested.

"I think the economic case for status quo disease-specific R&D is a much easier one for big pharma to sell to its investors," Fulton said.

BUILDING THE EVIDENCE FOR STEM CELLS

Longeveron already has three clinical studies ongoing – a Phase IIb randomized study with LMSCs in 120 participants with aging frailty, a Phase I randomized study with LMSCs in 30 Alzheimer's disease patients, and a Phase I/II randomized study using LMSCs to improve flu vaccine response in 43 people with aging frailty. A Phase IIb randomized safety and efficacy study in metabolic syndrome is listed on clinicaltrials.gov, but has not started recruiting yet.

The company's priority is the Phase IIb study in aging frailty in adults aged 70-85. The study's primary endpoints are change in the six-minute Walk Test (6MWT) distance compared to placebo at 180 days post-infusion and change in tumor necrosis factor (TNF)-alpha, an inflammatory marker, compared to placebo at 180 days post-infusion.

Hare said enrollment is ahead of schedule and results are expected in the first quarter of 2019.

Phase I and II data were published in the *Journals of Gerontology* in March 2017. In a Phase I study of 15 frail patients, a single infusion resulted in improvements in the 6MWT and TNF levels. In a Phase II study of 30 frail patients, there were improvements on a number of parameters, including physical performance, the 6MWT, forced expiratory volume and TNF levels. In both studies, treatment was well-tolerated.

"Both studies are early-phase trials of a small number of participants, designed primarily to assess safety, so conclusions about efficacy need to be treated with caution. Even so, the results are striking and, at minimum, pave the way for large randomized Phase III clinical trials," University of Sydney's David Le Couteur wrote in an editorial about the data. "The possibility that stem cells might be 'vehicles for youthful regeneration of aged tissues' has been well recognized — studies of mice have shown that transplantation of stem cells improves cardiac and reproductive function and, in humans, frailty is associated with reduced circulating MSC," the editorial notes.

Le Couteur also pointed out the value of having just a single, well-tolerated administration for older people.

In terms of challenges, Hare acknowledged that Longeveron will need to get financing to get all the way through approval. Depending on how good the Phase II data are, the company may pursue accelerated approval pathways with the US FDA.

Longeveron has enough cash to last for at least 12-18 months and in addition to grants it is considering a Series C venture capital round with private investors and bankers.

Published online 20 August 2018 *From the editors of Start-Up*

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 10–16 August 2018

LEAD COMPANY/PARTNER	COMPOUND	INDICATION	COMMENTS
PHASE III RESULTS PUBLISHED			
Pfizer Inc.	talazoparib	breast cancer	EMBRACA; the *NEJM*, Aug. 2018.
Theratechnologies Inc./ TaiMed Biologics Inc.	*Trogarzo* (ibalizumab-uiyk)	HIV/AIDS, multidrug resistant	*NEJM*, Aug. 16, 2018.
PHASE III INTERIM/TOP-LINE RESULTS			
ViiV Healthcare/ Janssen Pharmaceutical Cos	cabotegravir LA plus rilpivirine LA long-acting injections	HIV/AIDS	ATLAS; met primary endpoint with once monthly injections.
Regeneron/Teva Pharmaceutical Industries Ltd.	fasinumab	knee and hip osteoarthritis pain	FACT LTS & OA; met co-primary endpoints.
UPDATED PHASE III RESULTS			
Catalyst Biosciences Inc.	marzeptacog alfa	hemophilia A and B with inhibitors	Positive results, well tolerated.
PHASE III INITIATED			
Orphayzme A/S	arimoclomol	amyotrophic lateral sclerosis (ALS)	ORARIALS-01; increases heat-shock protein levels.
Eli Lilly & Co./Incyte Corp.	*Olumiant* (baricitinib)	systemic lupus erythematosus (SLE)	BRAVE 1,2; an oral JAK inhibitor.
PHASE II INTERIM/TOP-LINE RESULTS			
Biohaven Pharmaceutical Holding Co. Ltd.	BHV-0223 (riluzole sublingual)	generalized anxiety disorder	Reduced fear of public speaking.
Entasis Therapeutics Inc.	ETX2514 combined with sulbactam	complicated urinary tract infections	Positive results, well tolerated.
Realm Therapeutics plc	PRO22	atopic dermatitis	No difference from vehicle in primary endpoint.
Aerie Pharmaceuticals Inc.	*Rhopressa* (netarsudil) eye drops	glaucoma	Improved trabecular outflow.
PHASE II INITIATION			
VistaGen Therapeutics Inc.	AV-101	anti-suicidal effects	In Army veterans.
Taiwan Liposome Co., Ltd.	TLC590 (ropivacine)	post-surgery pain	A liposomal formulation.
Sihuan Pharmaceutical Holdings Group Ltd.	pirotinib	non-small cell lung cancer	In China.
Allergan plc	brazikumab	ulcerative colitis	In moderate to severe active disease.
TikoMed AB	ILB	amyotrophic lateral sclerosis	With an undisclosed mode of action.
Inovio Pharmaceuticals Inc.	*Pennvax-GP* multi-subtype vaccine	HIV/AIDS	Combined with its electroporation device.
Iovance Biotherapeutics Inc.	LN-145 (tumor infiltrating lymphocytes)	ovarian cancer, osteosar-coma, soft-tissue sarcoma	In up to 54 patients.
Izana Bioscience	namilumab	ankylosing spondylitis	In moderate to severe disease.

Source: Biomedtracker | Informa, 2018

ViiV/Janssen's Long-Acting Anti-HIV Injections Impress

JOHN DAVIS john.davis@informa.com

ViiV Healthcare and **Janssen Pharmaceutical Cos.** have reported positive top-line data from the Phase IIII ATLAS study with another of its two-drug regimens for the treatment of HIV/AIDS, this time with a once-monthly injectable combination, giving a boost to their overall development strategy of reducing the pill burden for patients, while maintaining efficacy.

With a plethora of agents available to treat HIV/AIDS, developers like ViiV Healthcare and Janssen have turned some of their attention to improving the patient experience by putting different drug combinations in a once-daily pill, increasing the interval between dosing, or by evaluating combinations of fewer drugs.

However, a shift to treating HIV with only two drugs at a time has to be carefully assessed to make sure that viral resistance doesn't emerge much quicker than with combinations of three drugs or more. Analysts at Datamonitor Healthcare noted the top-line ATLAS data should provide physicians with confidence that treatment can be simplified in patients who have already achieved virologic suppression.

"There is now a growing body of evidence to suggest two-drug regimens containing a potent integrase inhibitor with a high barrier to resistance have comparable efficacy to standard three-drug regimens," the analysts comment. "ViiV Healthcare's other two-drug regimens have also demonstrated non-inferior efficacy to three-drug regimens: *Tivicay* (dolutegravir)/*Epivir* (lamivudine) in the treatment-naïve setting and *Juluca* (dolutegravir/rilpivirine) in the maintenance setting."

Should cabotegravir/rilpivirine gain approval in the maintenance setting, without concerns about resistance, sales of the regimen should grow gradually to more than $1.3bn, Datamonitor Healthcare analysts estimate. Under a co-development collaboration between Janssen and ViiV Healthcare, the HIV/AIDS specialty company jointly owned by **GlaxoSmithKline PLC**, **Pfizer Inc.** and **Shionogi & Co. Ltd.**, the switching of HIV patients from a daily standard-of-care oral three-drug regimen to two intramuscular long-acting injections given once-monthly is being evaluated in the Phase III Antiretroviral Therapy as Long-Acting Suppression (ATLAS) study.

The top-line data from ATLAS showed that administering long-acting intramuscular formulations of ViiV's cabotegravir and Janssen's non-nucleoside reverse transcriptase inhibitor, rilpivirine LA, had similar efficacy at week 48 to various oral three-drug daily regimens of anti-HIV-1 therapies. The injectable regimen met the primary endpoint for non-inferiority (the proportion of patients with plasma HIV-1 RNA equal to or greater than 50 copies per ml), the companies reported on Aug. 15. Further, the safety, virologic response and drug resistance results for the injectable regimen were consistent with the results from the Phase II LATTE and LATTE-2 studies.

ViiV and Janssen said full results from the study would be presented at an upcoming scientific meeting. Top-line results from FLAIR, a second pivotal study evaluating the long-acting injectable regimen in treatment naïve patients living with HIV, are expected later this year. Also in play is the ATLAS-2M study, which is evaluating an every two-months dosing schedule for cabotegravir LA plus rilpivirine LA, compared with a once monthly dosing schedule.

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Executive	To Company	New Role	From Company	Previous Role	Effective Date
Anthony S. Gibney	Achillion Pharmaceuticals Inc	Chief Business Officer and Executive Vice President	Leerink Partners	Managing Director and Co-Head of the Biotechnology Investment Banking Team	15-Aug-18
Susie Jun	Allogene Therapeutics	Chief Development Officer	Abbvie	Vice President, Head of Development	14-Aug-18
James P. Tursi	Antares Pharma	Chief Medical Officer, Executive Vice President, Head of Research and Development	Aralez Pharmaceuticals Inc	Chief Medical Officer	8-Jun-18
Thierry Darcis	Bellicum Pharmaceuticals	General Manager of Europe	Zogenix, Inc	Executive Vice President and General Manager, Europe	8-Jun-18
Yuling Li	CBT Pharmaceuticals Inc	Senior Vice President, Process Development and Manufacturing	MedImmune	Director, Research and Development and Fellow in BioPharmaceutical Development	16-Aug-18
John Weet	EyePoint Pharmaceuticals Inc	Senior Vice President, Regulatory Affairs and Quality	Collegium Pharmaceutical	Vice President of Regulatory Affairs And Quality Assurance	15-Aug-18
Jaren Madden	Gamida Cell Ltd	Vice president, investor relations and corporate communications	Shire plc	Global head of research and development communications	8-Jun-18

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