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Alarm As Novartis Exits The Antibiotics Space

KEVIN GROGAN kevin.grogan@informa.com

Novartis AG is the latest big pharma to exit the antibiotics arena, deciding to ditch its antibacterial and antiviral research programs and spend its resources in other areas.

The Swiss major confirmed the decision in an email to *Scrip* saying that workers at its Emeryville, California facilities have been told of the plans. It is also confirmed that some 140 jobs could be cut with other departments being affected including pharmacology, protein sciences and informatics.

It has taken some observers by surprise, given the considerable pipeline of drugs to treat bacterial and microbial infections that had been built up at the Novartis Institutes for BioMedical Research (NIBR). These include a novel monobactam codenamed LYS228 to treat infections caused by multi-drug resistant Enterobacteriaceae which has been granted fast track and Qualified Infectious Disease Product designations by the FDA.

Novartis noted that "while the science for these programs is compelling, we have decided to prioritize our resources in other areas where we believe we are better positioned to develop innovative medicines." The company added that "the need for these types of medicines is clear and to maximize the chances that these programs will one day help patients we are actively engaged in out-licensing discussions with companies focused on developing medicines in these areas."

The reaction to Novartis' withdrawal was one of concern, especially as antimicrobial resistance (AMR) has shot to the top of the global health agenda in recent years amid concerns that not enough is being done to prevent a worldwide catastrophe. Jeremy Farrar, director of the Wellcome Trust, the charitable foundation that is investing heavily in a number of AMR schemes, described the Basel-headquartered group's decision in a tweet as "incredibly bad news and more to come."

He added that "modern medicine depends on controlling infection," writing that "R&D anti-cancer therapies meaningless if cannot prevent/treat infection, same with routine surgery, safe child birth." Novartis has been narrowing its R&D focus since Vas Narasimhan took over as CEO in February, with its priorities lying in cutting-edge medicines for oncology and rare diseases and exploring cell and gene therapy approaches.

The AMR arm of the Wellcome Trust also expressed its fears on Twitter, saying that it was "deeply concerning news" to see that Novartis is the latest big pharma to quit antibiotics R&D, and highlighted the "uncertain future for its promising pipeline."

Novartis joins a number of companies that, put simply, have decided the difficulty and cost involved in developing an antibiotic and then being unlikely to get a reasonable price at the end of it all, is probably not the best use of their resources. Others include **AstraZeneca PLC**, which sold its small-molecule antibiotics portfolio for up to $1.5bn to **Pfizer Inc.** in August 2016. *(Also see "Gottlieb Floats New Antibiotic Payment Model In LPAD Announcement" - Pink Sheet, 12 Jun, 2018.)*

However not all is doom and gloom on the pharma front in the fight to tackle AMR. In March, **Evotec AG** unveiled a part-

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Go Low
Esperion to undercut PCSK9s to gain traction for bempedoic acid (p19)

Blockbuster Pressure
Popular movie stokes drug pricing resentment in China (p20)

Approvals To Watch Out For
13 products set to get FDA decisions this quarter (p14-16)

from the editor

eleanor.malone@informa.com

The exit of another big pharma from antibiotic drug R&D has set the usual alarm bells ringing (see cover story). If the big guns can't see the rationale for developing new drugs, what chance do we have of beating the galloping threat of antimicrobial resistance? All the commitments and calls for action, the working groups and initiatives – what is their value if big players continue to desert the field to focus on "core priorities" that hold more promise for their bottom lines? Novartis admits that the science behind its pipeline projects is "compelling": once again it seems to come down to the economic argument: developing new antibiotics just doesn't pay.

And yet, big pharma companies aren't only pulling out of anti-infectives; most firms have narrowed their focus, doubling down on a few key areas and getting out of others. Yes, unwanted assets are, in many cases, abandoned. But they are also sold, spun out and repurposed, and sometimes they get a new lease of life, freed from the dingier backwaters of a big pharma R&D system.

The ecosystem for smaller companies engaged in antimicrobial R&D is getting healthier, helped by initiatives like CARB-X. Indeed, we report the advance of a novel approach to treating lung infections in cystic fibrosis in Phase IIb from minnow NovaBiotics on p21. Meanwhile, the current quarter could see the US approval for at least two new antibacterials from smaller players (see p14). And the steady expansion of Evotec in the space is another reason to be cheerful. Could antibiotic R&D actually be better off outside big pharma?

Scrip

LEADERSHIP
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
Japan: +81 3 6273 4260
Email: clientservices@pharma.informa.com

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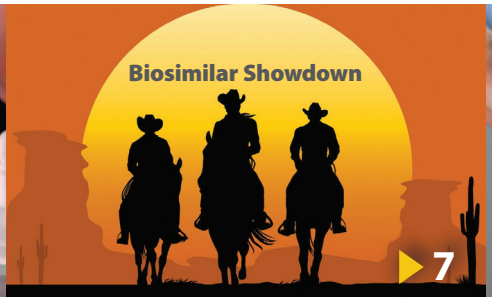

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Roivant Splashes Cash Again To License GSK Skin Disorder Drug
https://bit.ly/2urhMT4
The UK drug maker is tightening its R&D focus by selling on the psoriasis and atopic dermatitis investigational drug tapinarof to Dermavant, banking a hefty £150m up front and possibly another £100m after that.

AbbVie, J&J's Imbruvica Has Rare, But Not Surprising Failure In DLBCL
https://bit.ly/2ut41D5
Analysts generally were not surprised that Imbruvica plus R-CHOP did not provide a significant benefit versus R-CHOP alone in a hard-to-treat type of non-Hodgkin lymphoma.

Authorities Find Accounting Violation By Samsung BioLogics, Prosecutors To Probe
https://bit.ly/2zM9PNg
South Korean financial authorities conclude Samsung BioLogics violated accounting standards by omitting certain information on its joint venture agreement with Biogen from public disclosures, and have ordered further investigation of a corporate governance decision on the handling in accounts of the JV, Samsung Bioepis.

Forbion Sees First Close Of New Biotech Fund
https://bit.ly/2L5t8Gs
With its 2015 third fund Forbion Capital III yielding an internal rate of about 65% and already returning 60% of the money it drew down back to investors, it is probably no surprise that Forbion exceeded its €250M target for its predominantly Europe-focused Forbion IV fund within two months of marketing.

Finance Watch: 2018 Biopharma VC Investment Could Beat 2017 One Quarter Ahead Of Schedule
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With biopharma venture capital investment of $9.67bn during the first half, 2018's total is on track to beat 2017 in the third quarter.

Deal Watch: BioCryst Shareholder Dissent Scuttles Planned Merger With Idera
https://bit.ly/2uqPOqq
AZ's MedImmune to use 4D's AAV vector technology to deliver therapies for chronic lung disease, while Roivant spinout Dermavant licenses Phase III-ready autoimmune candidate tapinarof from GSK.

inside:

Gilenya Patent Upheld, But Who's The Biggest Winner – Novartis or Celgene?

MANDY JACKSON mandy.jackson@informausa.com

Novartis AG may have just won eight more years of market exclusivity for its oral multiple sclerosis drug *Gilenya* (fingolimod), but the victory also was important for **Celgene Corp.**, which will seek approval for its competing S1P receptor modulator ozanimod next year.

The US Patent and Trademark Office (USPO) Patent Trial and Appeal Board (PTAB) in an *inter partes* review (IPR) upheld a Gilenya patent related to dosing regimens that expires in 2027. The IPR decision published on July 11 breathes more patent life into the Novartis drug that was expected to go generic when a composition of matter patent expires in 2019.

Ozanimod may be a safer and more effective S1P-targeting drug for relapsing MS, but availability of generic Gilenya was seen as a key commercial challenge for Celgene, which plans to resubmit a new drug application (NDA) for its candidate to the US FDA early next year. *(Also see "Celgene's Positive Ozanimod Data Puts Focus On MS Commercialization" - Scrip, 22 May, 2017.)* The agency issued a refuse-to-file (RTF) letter in response to the original NDA in February, but Celgene said in May that it will re-file the application in the first quarter of 2019 based on feedback from the FDA.

The company's stock surged on July 12, closing 2.7% higher at $85.60 per share based on the Gilenya IPR decision. Novartis investors also breathed a sigh of relief that the drug's revenue stream might continue for several more years, sending the Swiss pharma's stock 3.4% higher to close at $78.94, even though the dosing regimen patent upheld in the IPR proceeding still could be challenged in court.

The PTAB did not agree with the petitioners' argument that the patent was obvious and apparent to people "skilled in the art" of multiple sclerosis drug development. The IPR petitioners included multiple generic drug manufacturers – **Apotex Inc.**, **Argentum Pharmaceuticals**, **Teva Pharmaceutical Industries Ltd.** and **Sun Pharmaceutical Industries Ltd.**

The drug's composition of matter patent is expected to ensure Novartis maintains exclusive rights to the compound until its expiration in August 2019

Novartis said in a statement to *Scrip* that it is "pleased" with the PTAB decision and the company "continues to believe strongly in the intellectual property (IP) covering our medicines and will continue to vigorously defend our IP rights, including those provided by Orange Book-listed patents covering Gilenya."

The big pharma noted that the drug's composition of matter patent "is expected to ensure Novartis maintains exclusive rights to the compound until its expiration in August 2019. The PTAB decision and the outcome of the IPR for the dosage regimen patent should have no impact on the compound patent."

"Whilst this decision can still be appealed, Novartis states it will now initiate litigation against generic filers," Jefferies analyst Ian Hilliker said in a July 12 note. "This means any generic attempting to launch after expiry of the [composition of matter] patent in [August] 2019 will be launching 'at risk.' Despite increasing competition in the space, this could mean Gilenya sales remain well supported beyond the consensus 2018 peak of circa $3.3bn for up to another nine years on a best-case scenario, rather than decline to circa $900m by 2022 as currently modeled by consensus."

Also, Evercore ISI analyst Umer Raffat pointed out an under-the-radar means by which Novartis could extend its Gilenya franchise. Raffat said in a July 12 note that Novartis is expected to report results in the fourth quarter of 2018 for a 0.25 mg daily dose of the drug, which could be safer and nearly as effective as the current 0.5 mg dose for adults (pediatric patients take 0.25 mg daily).

The analyst noted that the FDA required Novartis to study the 0.25 mg dose when it approved Gilenya 0.5 mg to explore the lower dose's potential to provide meaningful efficacy and reduced toxicity. Citing FDA's analysis, he said that "not only does this trial have a very realistic chance of showing good efficacy, more importantly, it may likely be materially safer than the currently approved Gilenya."

Gilenya's label contains several warnings and precautions, including bradycardia that can occur within hours of administra-

tion of the first dose, and an increased risk for infections due to the drug's mechanism of action that reduces white blood cells. The label also has warnings to monitor for progressive multifocal leukoencephalopathy (PML), elevated liver enzymes, respiratory effects, increased blood pressure and other adverse events. The drug shouldn't be prescribed to patients soon after a heart attack or stroke.

But if Novartis seeks approval for the lower Gilenya dose based on improved safety and similar efficacy to the higher dose, Raffat said the company also could seek new patents based on the data and new dosing. He wrote that "this upcoming Phase III trial has the potential to produce a best-in-class S1P1. Whether that happens is [to be determined], but no one is talking about this optionality."

Even so, Gilenya is not the only important asset in Novartis' MS franchise. The company has two late-stage MS drugs, including the follow-on S1P receptor modulator siponimod (BAF312), which is under FDA review for secondary progressive MS (SPMS).

Novartis also is expected to report Phase III results in relapsing MS (RMS) for the CD20 inhibitor *Arzerra* (ofatumumab) later this year. *(Also see "Novartis's Chief Medical Officer On All Things MS And The Science Of Operations" - Scrip, 8 Mar, 2018.)* It acquired rights to autoimmune indications for the lymphoma drug from **GlaxoSmithKline PLC** in 2015. *(Also see "Novartis Sees Real Value Of Ofatumumab In MS, Pays GSK Up To $1Bn " - Scrip, 21 Aug, 2015.)*

BRAND-NAME MARKET EXTENSION GOOD FOR ALL

Jefferies analyst Michael Yee said in a June 12 report that the longer the MS drug market retains brand-name status the better for **Biogen**, whose revenue is highly dependent on treatments for the disease, and for Celgene, which has been reeling from setbacks toward diversifying its commercial portfolio. Biogen also traded higher on July 12, closing up 1% at $347.66.

But Celgene in particular has been dogged by multiple setbacks since last October, including the RTF letter for ozanimod, which is a crucial asset in the big biotech's plan to diversify its portfolio and offset future revenue declines when the multiple myeloma blockbuster *Revlimid* (lenalidomide) loses patent exclusivity in the next four or five years. *(Also see "More Bad News: Celgene Reveals Refuse-To-File Letter For Ozanimod In MS" - Scrip, 27 Feb, 2018.)*

Yee noted that the potential for Gilenya generics starting in 2019 "made Celgene look bad given ozanimod – which is a better Gilenya – was delayed, so generics could swamp the market before Celgene could get out to patients."

Even with litigation possible that could shorten the life of Novartis' dosing regimen patent for Gilenya, Celgene still may be able to gain FDA approval for ozanimod late next year or in early 2020 before generics hit the market. Given the multi-year patent litigation process, ozanimod could even hit the market before generic Gilenya in ulcerative colitis (UC) and Crohn's disease – indications for which Celgene has its drug in Phase III development now. *(Also see "Celgene's Terrie Curran On Building, Broadening The I&I Franchise" - Scrip, 4 Apr, 2018.)*

Evercore ISI's Raffat predicted that Celgene has at least a three-year window to launch ozanimod in the US before generic manufacturers can bring cheaper versions of 0.5 mg Gilenya to market. By then, its improved safety and efficacy may have won enough prescribers and payers over to generate significant MS sales with the potential to bring in more revenue from approvals for US and Crohn's.

Celgene also has an opportunity to price its drug in a way that makes payers especially loyal to the ozanimod brand, since the price of Gilenya and many other MS drugs have been criticized for providing too little value relative their high costs.

For now, the PTAB decision in favor of Novartis' Gilenya dosing patent is more good news that Celgene needs at what could be the end of a tumultuous period, adding to boosted investor confidence based on two recently reported sets of Phase III results for luspatercept. *(Also see "Celgene Notches A Needed Win As Acceleron-Partnered Luspatercept Succeeds In MDS" - Scrip, 29 Jun, 2018.)* The drug, which is being developed in partnerships with **Acceleron Pharma Inc.**, generated positive top-line data in myelodysplastic syndromes (MDS) at the end of June and in beta-thalassemia on July 9. *(Also see "Attention Turns To Celgene's Other Pipeline Prospects Following Second Positive Luspatercept Read-Out" - Scrip, 10 Jul, 2018.)*

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CONTINUED FROM COVER

nership with **Sanofi** to develop an infectious disease pipeline using its technology platform, seeded with more than 10 undisclosed early-stage, preclinical assets from the French drug giant's infectious disease portfolio. Also in February, the $165m REPAIR (Replenishing and Enabling the Pipeline for Anti-Infective Resistance) Impact Fund was set up by Novo Holdings to address the early-stage funding gap, which will invest $20-40m per year over three–five years in about 20 projects.

At the beginning of 2018, the Dutch nonprofit Access to Medicine Foundation issued a report saying that **GlaxoSmithKline PLC** and **Johnson & Johnson** were leading the way in responding to the AMR threat among the large research-based pharmaceutical companies. It added that Pfizer performs particularly well in stewardship measures.

As for biotechs, among the 12 firms that AMF's benchmark covered, **Entasis Therapeutics Holdings Inc.** was top, "particularly when it comes to planning ahead to help ensure successful candidates will be made accessible but also used wisely". It was followed by **Polyphor Ltd.**, **Summit Therapeutics PLC** and **TetraPhase Pharmaceuticals Inc.** in joint second place.

Indeed, it is often argued that solutions to AMR are more likely to come from biotech rather than big pharma and in Europe there is the BEAM (Biotech companies in Europe combating AntiMicrobial Resistance) Alliance, which has 52 members which are collectively developing projects focused upon the cure and prevention of bacterial infections. Biotechs are also tapping into CARB-X (Combating Antibiotic Resistant Bacteria Pharmaceutical Accelerator), the $450m global initiative backed by the US government and the Wellcome Trust.

As for Novartis, it told *Scrip* that the San Francisco Bay area would continue to be home to the Novartis Institute for Tropical Diseases (NITD) and global drug discovery teams focused on 'undruggable' targets in collaboration with the Novartis-Berkeley Center for Proteomics and Chemistry Technologies. NITD's research programs are focused on developing new medicines for malaria, cryptosporidiosis, human African trypanosomiasis, Chagas disease, and leishmaniasis.

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Pfizer Biosimilars And Anti-Infectives Get Higher Profile Under New Structure

JESSICA MERRILL jessica.merrill@informa.com

Pfizer Inc. unveiled a new global business structure July 11 that will organize the company into three businesses versus the existing two, breaking out a separate consumer healthcare business. Most notably for pharma, the organization will include a new hospital medicines business within Innovative Health, and fold biosimilars into the innovative business as well.

The new hospital business unit will include anti-infectives and sterile injectables – which along with biosimilars had previously been managed under Pfizer's Established Health business for off-patent branded and generic medicines. The change will better align the business areas with what Pfizer views as its higher growth opportunities in innovative health.

It will also strengthen the scale of the innovative business versus established products, so that Innovative Medicines (including consumer) will represent 75% of Pfizer's sales, according to the company. With $8.21bn in worldwide revenues in 2017, Innovative Health (including consumer) represented about 66% of Pfizer's consolidated revenues. Pfizer Essential Health generated $5.48bn in 2017.

A NEW HOME FOR BIOSIMILARS

The biosimilar products will be moved to Pfizer's Oncology and Inflammation & Immunology businesses, depending on the products. Pfizer markets the biosimilar *Inflectra* (infliximab-dyyb) a copy of **Johnson & Johnson**'s *Remicade* (infliximab) in the US, but biosimilars is an area the company has targeted for expansion, with several in the pipeline. The company's biosimilar business remains niche for now, but it is a high-growth area. Biosimilars generated $531m in sales globally for Pfizer in 2017, growth of 67%.

Moving biosimilars under the innovative portfolio seems to make sense, because of the commercial and reimbursement challenges associated with marketing the products, particularly in the US. The decision might reflect some of the lessons Pfizer has learned with Inflectra, a launch that has been challenged by J&J's rebating strategy to defend Remicade.

"These units possess significant therapeutic area expertise in the medical, commercial and patient experience domains, and will provide a strong commercialization platform for these medicines," Pfizer said.

Pfizer maintains a significant anti-infectives portfolio within its Established Products unit. The company used to be a big player in antibiotics R&D, although, like most big pharmas, it has de-emphasized the space because of the challenging R&D and commercial dynamics. Pfizer developed the blockbuster *Zyvox* (linezolid), which went generic in 2015 and moved into Pfizer's established portfolio.

In August 2016, Pfizer acquired **AstraZeneca PLC**'s small molecule antibiotics portfolio for up to $1.5bn, and incorporated those products – including the carbapenem *Merrem*, the cephalosporin antibiotic *Zinforo* and the combination antibiotic *Zavicefta* for Gram-negative infections – into the portfolio.

Pfizer acquired its substantial sterile injectables portfolio with the $16bn acquisition of **Hospira Inc.**. in 2015. Sterile Injectable Products (SIP) generated $5.67bn for Pfizer in 2017. "With the increasingly significant role of hospitals in the healthcare system, anti-infectives and sterile injectables will become part of the Innovative Medicines business' Hospital Unit to capitalize on industry trends," Pfizer said.

Analysts applauded the changes, despite what has felt like an endless series of transitions at Pfizer. "The new structure better aligns Pfizer with its growth opportunities, while preserving value-unlocking options," BMO Capital Markets analyst Alex Arfaei said in a same-day research note. "Moving biosimilars to the innovative segment reflects its growth potential."

Deutsche Bank analyst Gregg Gilbert noted, "While not major, we view moving biosimilars and injectables into the innovative business and allowing EM to operate with more autonomy as logical changes."

The latest reorganization is the culmination of organization changes at Pfizer over the last eight years, following the loss of exclusivity for *Lipitor* (atorvastatin) in December 2011. In January 2014, when the company was still considering splitting up the business, Pfizer broke out its mature brand and generic products from the higher-growth portfolio of branded drugs, with an innovative products segment and value products segment.

That organization evolved over the next two years into a Vaccines, Oncology and Consumer (VOC), Global Innovative Pharma and Global Established Pharma. Eventually, VOC was combined with the innovative pharma arm. In September 2016, Pfizer ruled out splitting up the business and moved forward with two business units: Innovative Health and Essential Health.

YOUNG AND HWANG RETAIN ROLES

Most recently, in November 2017, the company announced new leadership to oversee the business units, while promoting the long-time innovative health leader Albert Bourla to chief operating officer. John Young took over leadership of Innovative Health and Angela Hwang stepped in to lead Pfizer Essential Health.

Now the leadership will change again, though Young and Hwang will continue to have prominent roles with the title of group president. Young will oversee internal medicine, oncology (including biosimilars) and rare diseases, while also managing innovative medicines across emerging markets. Hwang will be responsible for inflammation and immunology (including biosimilars), vaccines and hospital medicines, while also managing Pfizer's Consumer Healthcare business.

Established Medicines will be led by Michael Goettler, who joined Pfizer in 2009 with the acquisition of Wyeth and has held various leadership roles, including most recently as global president of Pfizer Inflammation & Immunology.

The consumer group, including all of Pfizer's over-the-counter medicines, will operate relatively autonomously with dedicated manufacturing and regulatory capabilities, Pfizer said. The business generated $3.47bn in 2017. Pfizer is continuing to evaluate strategic alternatives for the consumer unit and expects to make a decision in 2018, the company said.

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Mylan's Fulphila Sets Up The US Market For The Next Biosimilar Showdown

JESSICA MERRILL jessica.merrill@informa.com

Mylan NV has priced its first US biosimilar, *Fulphila* (pegfilgrastim-jmbd), at a 33% discount to the reference drug, **Amgen Inc.**'s *Neulasta* (pegfilgrastim), a steeper discount than the 15% discount **Pfizer Inc.** initially used with the launch of *Inflectra* (infliximab-dyyb) versus **Johnson & Johnson**'s reference drug *Remicade* (infliximab).

The difference could be important when it comes to whether Fulphila will gain traction in a market that has so far not been very receptive to biosimilars. Success could build momentum for future biosimilars in the US, while another lackluster biosimilar launch would most likely temper enthusiasm for investing in biosimilars until policy changes are adopted to foster the commercial market.

Mylan said it priced Fulphila at a wholesale acquisition cost of $4,175 per syringe. That compares to a WAC of $6,231 for Neulasta, according to analysts. Those prices do not take into account rebating and other discounts that bring down the net price of the products. It is expected that Amgen will counter the new biosimilar competition with steep rebating, a tactic that has helped J&J successfully retain market share of Remicade even though it has given up revenues due to the lower price.

Jefferies analyst Michael Yee said in a July 11 research note that Mylan's discount was higher than the 10%-20% discount he had forecasted, but pointed out that the key question remains the level of rebates.

"In reality, the discount of Fulphila is likely closer to 10%-20% and in line with expectations given some of the gross to net rebating for Neulasta," Yee said. "In addition, Amgen is likely locking in contracts for 2019 and hospitals take a comprehensive look at drug efficacy and safety for new products, so it will take some time for Fulphila to be added to hospital formularies."

Fulphila was approved by the FDA in June as the first biosimilar version of Amgen's blockbuster neutropenia drug. *(Also see "Mylan Is First To Clear US Neulasta Biosimilar Hurdle; At-Risk Launch May Not Be Risky" - Pink Sheet, 5 Jun, 2018.)* Mylan's application was initially met with a complete response letter but was approved on the second review, while several other rival biosimilars are also in various stages of review at the FDA, having also received complete response letters.

Neulasta generated $3.93bn in the US in 2017, so being first to market with a biosimilar is an important opportunity for Mylan.

A BELLWETHER FOR BIOSIMILAR SUCCESS

The launch of Fulphila will be closely watched by the industry as a marker for the commercial success of biosimilars in the US. Pfizer's disappointing launch of Inflectra – the first monoclonal antibody biosimilar, which launched in the US in late 2016 – has raised some red flags. FDA Commissioner Scott Gottlieb has even started ringing the warning bells that the market might never materialize if commercial incentives aren't in place for biosimilar manufacturers.

The big commercial problem for biosimilars is that the branded manufacturer has more leverage with payers and insurers when it comes to negotiating coverage, simply because of the high volume of product they distribute versus a new biosimilar – particularly when biosimilars are not currently interchangeable with reference products.

Pfizer filed a lawsuit against J&J in September 2017 alleging that the company's rebating practices for Remicade are anticompetitive because the company tied rebates to exclusive contracts that allow only Remicade to be reimbursed. *(Also see "Pfizer Sets The Stage For A Biosimilar Showdown Over Exclusive Contracts" - Scrip, 20 Sep, 2017.)* In some cases, J&J has also tied rebates to other portfolio products, a tactic known as bundling.

"Mylan's approach is distinctly different from Remicade biosimilars," Bernstein Research analyst Ronny Gal said in a July 12 note. "With the WAC set lower, Mylan likely has learnt the lesson from Pfizer and will be in a better position to play the ASP game."

ASP refers to average sales price – the payment methodology used by CMS to reimburse drugs like Neulasta under Medicare Part B. ASP is the sales of a drug to all purchasers in the US by a manufacturer divided by the total number of units sold, a figure that is net of price concessions and rebates. Gal said Neulasta's ASP was only $4,453 in the July CMS report, putting Fuphila's WAC price at a 6.3% discount to Neulasta's net price, based on that pricing scale.

"For the first six months on the market, hospitals are reimbursed on WAC+6%," Gal reminded investors. "So, to the extent Mylan provides 30% discount, early adopters are in position to pocket material discounts." On the other hand, he noted that he expects Amgen to defend its Neulasta brand with bundled contracts, as J&J has done in some cases for Remicade. *(Also see "Exclusive Remicade Contracts Are Slowing Biosimilar Uptake" - Scrip, 1 Aug, 2017.)*

One big advantage Fulphila could have versus the Inflectra experience is that pegfilgrastim is a short-term acute medication, not one used chronically – which means there is a steady stream of patients new to treatment. Mylan CEO Heather Bresch has said she is encouraged by the profile of the drug and how the launch could unfold differently from some other chronic disease drugs that have been more challenging.

(Also see "Mylan Poised To Launch Its First US Biosimilar, With A Stacked Pipeline Behind It" - Scrip, 12 Apr, 2018.) Mylan has even noticed some similar hurdles with the launch of generic *Copaxone* (glatiramer), a complex small molecule generic that **Teva Pharmaceutical Industries Ltd.** has been able to defend with price discounts.

Bernstein's Gal agreed there is a lot riding on the launch of Fulphila. "This is an indicator for the biosimilar enterprise," he said. "If Mylan's biosimilar ends up as a market failure, it suggests that the US market does not allow adoption of lower-priced drugs unless the US health care system adapts."

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Job Cuts Seen At Dr Reddy's Amid Cost Recalibration

ANJU GHANGURDE anju.ghangurde@informa.com

Dr. Reddy's Laboratories Ltd. has initiated efforts to set right its skewed cost structure as it seeks to restore growth momentum in the backdrop of a challenging year gone by and the tough overall business environment.

Significant headcount reduction plans are believed to be in the cards as part of these efforts, with an estimated 100 personnel in R&D and related sections expected to move on soon, industry sources told *Scrip*. The sources claimed that overall cuts could run into several hundred (speculated by some to be more than 500) across various operational and business segments.

The personnel cuts come as the Hyderabad-based company undertakes a major re-calibration as it seeks to transition to a "leaner and flexible" cost structure, focusing on areas such as network and portfolio rationalization, improving plant operating efficiencies, R&D site optimization and productivity. The efforts are expected to bring about cost savings of "multiple hundreds of crores" [INR100cr =$14.6m], the firm's top brass had indicated earlier. *(Also see "Dr Reddy's Charts Sharp Cost Overhaul Amid Weak Q1" - Scrip, 28 Jul, 2017.)*

Dr Reddy's currently has more than 23,500 employees, according to the firm's latest annual report.

SYSTEMATIC EXERCISE

Dr Reddy's didn't comment on specifics around headcount reductions but told *Scrip* that it continues to focus on "optimizing costs" as an organizational priority.

"We have embarked on a systematic exercise to transition to a leaner and flexible cost structure in multiple areas of our operations. We would not like to comment further on the specifics of these initiatives at this point in time," the company maintained.

However, Dr Reddy's top management, in the latest annual report, noted that the "revenue crunch" in FY2017 and FY2018 had drawn the company's attention to costs; from the start of FY18, there has been a "totally focused" drive on eliminating "needless layers and unnecessary costs."

"This will continue throughout FY2019 and thereafter, with the aim to create a leaner, internationally cost-competitive and more nimble organization," Chair Satish Reddy and Co-Chair and CEO GV Prasad said in their letter to shareholders as part of the annual report.

All eyes are also expected to be on new COO and ex-Teva executive Erez Israeli, as he steers the firm through this turbulent phase. Israeli took over from Dr Reddy's old-timer Abhijit Mukherjee earlier this year. Some analysts believe more "impactful" measures may be in store, referring to previous management commentary.

CEO Prasad, at the time of the firm's Q4 earnings call in May, referred to cost saving opportunity in many areas, "from rationalizing the manufacturing network, optimizing our portfolios, removing wastefulness in many areas – including manning levels and multiple places."

"And we so far have not touched the core, it's only looking at areas where we can save without any impact on operations. Moving forward, we will actually see divestments of some sites and also other non-contributing expenditures that we have," Prasad said.

Interestingly, in its presentation at the Jefferies Healthcare Conference in June, Dr Reddy's specified that while more than 70% of its North America revenues are reliant currently on internal manufacturing sites, by 2021 it hopes to have a "diversified manufacturing network" with almost 50% of revenues coming from "partner manufacturing sites."

ONGOING CHALLENGES

But tough cost-control measures are neither unusual in the pharmaceutical industry nor specific to Indian firms like Dr Reddy's, given the generally challenging environment.

Teva Pharmaceutical Industries Ltd. is among the firms that also have initiated a major overhaul in the recent past. The Israeli multinational is slicing its workforce as part of restructuring plans – these are expected to achieve $1.5bn of savings in 2018 and $3bn by the end of 2019. *(Also see "Schultz Swings The Cleaver At Teva, Cutting 25% Of The Workforce" - Scrip, 14 Dec, 2017.)*

Headwinds in key markets like the US have dented earnings of several leading Indian firms, which depend on it for a large chunk of their revenues. Dr Reddy's, with more than 40% of its sales from the US, reported a 6% decline in US revenues to INR59.82bn in FY18. This was largely on account of higher price erosion due to channel consolidation and increased competition in certain key molecules such as valganciclovir, azacitidine, decitabine, the firm indicated at the time of its Q4 FY18 results.

Exacerbating the situation for Dr Reddy's has been GMP deviations at its manufacturing plants that supply the US, though some of the sites have since made the compliance cut or are in the process of doing so. In late June, Dr Reddy's said its active pharmaceutical ingredient (API) plant 3 at Bollaram and API plant 1 in Jinnaram, both in Medak district, Telangana, had received an Establishment Inspection Report (EIR) from the US FDA.

EIRs generally are provided when no enforcement action is contemplated, or after enforcement action is concluded. An EIR typically includes, among others, the investigator's narrative report and any refusals, voluntary corrections, or promises made by the firm's management.

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Flurry Of Marketing Collaborations Set India Deal Street Abuzz

ANJU GHANGURDE anju.ghangurde@informa.com

India's pharma deal street is abuzz with action around in-licensing and co-marketing/co-promotion. Front-line Indian firms are leveraging their commercial strength to firm up alliances with foreign companies seeking to push deeper and make a larger impact for their new products in the country's competitive market.

Typically, such alliances also allow Indian firms to expand their portfolios or plug gaps therein, with the foreign companies keen to use their partner's marketing footprint for greater reach and a concerted product push. Besides, ongoing pressures in the US, a key revenue contributor for several leading Indian firms, has meant these companies are keener than ever to expand growth on their home turf.

Dr. Reddy's Laboratories Ltd. kicked off the action earlier this week by sealing a pact with **UCB Group** to distribute and co-promote the Belgian firm's epilepsy therapy *Briviact* (brivaracetam); under the deal Dr Reddy's has the exclusive right to distribute Briviact in India, a company statement said July 9.

With a third of patients with epilepsy currently uncontrolled on their existing medicines, UCB sees the partnership as an important step towards providing "value together" to patients by making Briviact available as an additional treatment choice. India accounts for nearly one-sixth of the global burden of epilepsy with over 12 million people suffering from the disease.

Dr Reddy's and UCB have been transactional in the past as well. In 2015, Dr Reddy's snapped up a select portfolio of UCB's established products business in India, Nepal, Sri Lanka and the Maldives for INR8bn ($128m at the time), augmenting its presence in the dermatology, respiratory and pediatric segments.

DEAL MOMENTUM

The Briviact deal was followed by **Glenmark Pharmaceuticals Ltd.** rolling out **Helsinn Group**'s combination anti-emetic, *Akynzeo* (netupitant/palonosetron), recently in-licensed from the Swiss firm. Glenmark has exclusive marketing rights for the product in India and Nepal under the arrangement, the first such deal for the Swiss cancer care products group in India.

Helsinn referred to Glenmark's "excellent footprint" in this region and commitment to providing the best treatment options for people with cancer. Akynzeo is already marketed in the EU, the US, and several other markets. *(Also see "Deal Watch Asia Focus: Pfenex Licenses Asian Rights To Forteo Copy To NT Pharma Group" - Scrip, 24 Apr, 2018.)*

Glenmark, like some other Indian competitors, appears to have intensified its in-licensing efforts. In February, it launched *Nourkrin Woman*, a proteoglycan replacement formula for normalizing hair growth cycle (licensed from Denmark-headquartered **Pharma Medico**) while in January this year it introduced a biosimilar of adalimumab (licensed from **Zydus Cadila**).

In-licensing deals are also expected to be a key prong in the growth strategy of top Indian firms like **Cipla Ltd.**. The company, which hopes to achieve India sales of $1bn in FY19, launched seven in-licensed products last fiscal year. The Mumbai-based company lists plans to ramp up in-licensing efforts in rest-of-world and other markets among its business priorities for FY19.

DIABETES ACTION

Significantly, the competitive diabetes segment continues to witness active partnering activity in India. Multiple deals have dotted this high-growth segment over the past few years.

Boehringer Ingelheim GMBH and **Lupin Ltd.** are now expanding their partnership to co-market the oral antidiabetic therapies *Gibtulio Met* (empagliflozin + metformin) and *Ajaduo* (empagliflozin + linagliptin). The partners will co-market these across India under different brand names, a joint statement from the firms said July 11.

The empagliflozin/linagliptin product is the world's first approved combination of an SGLT-2 inhibitor and DPP-4 inhibitor.

In 2015, BI and Lupin had struck a deal for co-marketing linagliptin. BI had, at the time, termed the tie-up an "ideal partnership" where it brought the research and scientific excellence for linagliptin, with Lupin contributing its "marketing excellence and brand equity" among key clinician categories to drive and facilitate product access.

Lupin, which straddles multiple alliances in the diabetes space, is the fastest-growing company among leading firms in the Indian anti-diabetes market. It already has an alliance with **Eli Lilly & Co.** and is also responsible for marketing and sales of **LG Life Sciences Ltd.**' insulin glargine in India.

Sales of Lupin's diabetes portfolio have grown by more than twice the market growth rate, it said.

COMPETITIVE SPACE

Other alliances – both long-standing and new – have marked the diabetes sector in India, given the competition and size of the market. **Novartis AG**, which has been selling the DPP-4 inhibitor vildagliptin and this drug in combination with metformin hydrochloride in India since 2008, has partnerships with a number of firms including **USV Ltd.** for the product.

India's top-ranked pharma firm **Sun Pharmaceutical Industries Ltd.** also co-markets **Merck & Co. Inc.**'s sitagliptin as *Istavel* and the sitagliptin plus metformin combination under the brand name *Istamet* under its alliance with the US firm. More recently, Cipla firmed up a partnership with Lilly's Indian subsidiary for the marketing and distribution of Lilly's *Basaglar* (insulin glargine injection) in India.

With more than 72 million cases of diabetes in 2017, India lags only China in terms of patient numbers for the disease. The Indian diabetes market is valued at INR113.36bn ($1.65bn) and is growing at around 12% as per IMS MAT (moving annual total) data for April 2018.

Four out of five of the top-selling brands on the Indian pharmaceutical market are anti-diabetes therapies, with *Mixtard* (human premix insulin) leading the pack, show data from the market research agency AIOCD Pharmasofttech AWACS.

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Indivior Withdraws 2018 Guidance Due To Competitive Pressures On Suboxone, Sublocade

JOSEPH HAAS joseph.haas@informa.com

Addiction-drug focused **Indivior PLC** yielded somewhat to competitive pressure on two fronts on July 11, withdrawing its earlier 2018 net revenue guidance of $1.13bn-$1.17bn, citing both generic competition for its opioid dependence product *Suboxone* (buprenorphine/naloxone sublingual film) and slow uptake of the recently launched *Sublocade* (injectable buprenorphine).

The UK-headquartered company said it can't reliably provide revised net revenue guidance, but hopes to be able to do so during its third quarter earnings call, scheduled for Nov. 1. A crucial variable could be resolved well before then, however, as the US District Court for the District of New Jersey is slated to rule July 12 on Indivior's request for a temporary restraining order (TRO) on **Dr. Reddy's Laboratories Ltd.** at-risk launch of generic Suboxone. There is already a preliminary two-week temporary stay on the launch.

The Indian firm obtained US FDA approval for its generic on June 15 – along with **Mylan NV** – and said it would launch at-risk, despite ongoing patent challenges by Indivior. Mylan has not launched its generic version of Suboxone but settled patent litigation with Indivior at undisclosed terms in September 2017. Jefferies Equity Research analysts have speculated that Mylan's settlement staves off launch of that company's generic until 2023, also the year in which **Par Pharmaceutical** can launch its own generic under a settlement with Indivior.

Indivior announced July 11 that while it does not know the exact amount of generic Suboxone sold by Dr. Reddy's before the New Jersey court issued the temporary stay, it is seeing a market impact from the generic's entry into the US market. Market share loss has accelerated recently for branded Suboxone down two-and-a-half basis points to a 52% share, Indivior said.

Noting that the eventual impact of Dr. Reddy's at-risk launch could be even greater – even if the New Jersey court rules in favor of the TRO request on July 12 – Indivior anticipates a $25m net revenue impact from loss of market share to Dr. Reddy's.

Further, Indivior said that discounting of generic tablet competitors to Suboxone has resulted in the branded product being discounted by 75%-80% below list price. This has further reduced Suboxone's profitability in its most price-sensitive channel (managed Medicaid), with the company estimating a negative $50m net-revenue impact due to this factor in 2018.

Suboxone sublingual film, introduced in 2010, and its oral tablet predecessor Subutex, which lost patent protection in 2009, are a blockbuster franchise for Indivior. Together, the two products yielded sales of $1.216bn in 2013, declining to $1.115bn in 2014, $1.014bn in 2015, then rising slightly to $1.058bn in 2016, before resuming a gradual decline. In a June 18 note on the impact of generic competition to the franchise, Morgan Stanley estimated that full-year 2017 sales would total $1.093bn and fall further in 2018 to $922m.

For fiscal year 2017, Indivior reported US net revenue increased 2% to $877m year-over-year, and grew 1% in Q4 2017 to $207m. The buprenorphine/naltrexone franchise comprises the vast majority of Indivior's sales – estimated as high as 90%.

But the business has not been without controversy. Although the company defended the formulation change from the oral tablet to the buccal film formulation as improving compliance, it faced congressional scrutiny and a multi-state suit about price increases and coercing switches from the tablet to the film version.

Indivior has reported small price increases in the past couple years, but noted that those were offset by rebating.

SUBLOCADE UPTAKE SLOWER THAN EXPECTED

Meanwhile, Sublocade – approved by the FDA last December as an opioid-addiction treatment – is seeing lower-than-expected patient number throughput this year, Indivior said. The company said it is encouraged by positive patient and physician feedback on the product, which has market access for approximately 55% of covered US lives.

Despite its slow uptake, Indivior got a reprieve from new competition when **Braeburn Pharmaceuticals Inc.**'s buprenorphine injection candidate CAM2038, which was on a similar timeline, received a complete response letter from the FDA.

However, "friction in the new distribution and reimbursement model" has negatively affected physicians' willingness to prescribe Sublocade, Indivior claimed, leading it to project that 2018 net revenue for the drug will be $25m-$50m below its prior guidance of $100m. Indivior still predicts eventual peak sales of $1bn for the product, however.

Indivior is investigating cost-saving opportunities to offset this anticipated loss of revenue, with a goal of realizing at least $25m in such savings this year, the company added.

In a same-day note, Jefferies analyst James Vane-Tempest estimated that Indivior's 2018 aggregate sales could come in 11% lower than previous guidance, with earnings-per-share down as much as 24%. He maintained a "buy" rating on Indivior shares, but Jefferies separately put out a second note on July 11 removing Indivior from the companies on its list of franchise picks. "The stock has materially underperformed its benchmark, necessitating removal from the list given stop loss parameters," the note states.

The TRO request is not Indivior's first showdown with Dr. Reddy's over Suboxone. In August 2017, the US District Court for the District of Delaware ruled that Dr. Reddy's generic does not infringe any of three Indivior patents protecting Suboxone, which accounted for roughly 80% of Indivior's US revenue the year before. Indivior appealed the Delaware court's ruling, and a decision is expected in 2018 or 2019.

Indivior's request for a TRO cites another patent not among those subject to the 2017 Delaware court ruling. At a preliminary injunction hearing on June 28, the New Jersey court agreed to a two-week TRO halting the Dr. Reddy's launch, saying that a final ruling would be given July 12.

TOUGH MARKET SEGMENT

While use of addiction treatments has grown in light of the opioid crisis, it has been hard for innovative formulations to get to market and make much impact against generics of buprenorphine and naloxone. Abuse-deterrent opioid products have faced similar challenges.

In July 2017, a Tufts Center for the Study of Drug Development report estimated that 96% of all opioid products prescribed in the US during 2015 were not abuse-deterrent, despite widespread concern about opioid dependence. Since 2010, the FDA has approved 10 opioid products with abuse-deterrent claims, but across the board they have struggled to gain market traction.

Due to these issues, **KemPharm Inc.** recently announced that it plans to market its recently approved opioid *Apadaz* (benzohydrocodone/acetaminophen) – which does not have an abuse-deterrence claim but does have language describing its abuse-deterrent properties in labeling – at generic-level pricing in partnership with a generic drug maker or pharmacy benefit manager.

However, Indivior has confidence in the addiction-therapy segment. "Market growth continues to benefit from legislative changes that have expanded [opioid-use disorder] treatment capacity as well as increased overall public awareness of the opioid epidemic. As a result, growth in both the number of physicians waivered to administer medication-assisted treatment and those able to treat to the new permitted level of 275 patients (from 100 patients) continued in Q1 2018," the firm stated in its Q1 earnings release. **Alkermes PLC**'s competing *Vivitrol* (naltrexone), approved to treat both opioid abuse and alcohol abuse, totaled $146.8m in US sales in 2016, increasing 84% to $269.4m in 2017. For the current year, the product's $62.7m in first quarter sales represent a 7% uptick year-over-year.

Indivior noted Suboxone film "had an average market share of 57% in 2017, compared to 61% in 2016, and 2017 exit share was 56%, compared to 61% exiting 2016." It attributed the decline in share to "continued competition in the most price sensitive payors that have prioritized lower priced generic tablet options."

The company also stated that growth was "partially offset by share loss to generic competition in price sensitive US payors, unfavorable mix from increased US Medicaid business and continued tactical rebating in the US."

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Genmab Moves On From Darzalex/Tecentriq Failure With Bispecifics Deal

JO SHORTHOUSE joanne.shorthouse@informa.com

Genmab AS and **immatics biotechnologies GMBH** have inked a deal to develop multiple bispecific immunotherapies in oncology.

Looking to follow on from success with *Darzalex* (daratumumab), the Danish biotech is to gain exclusive access to multiple novel proprietary tumor targets identified by Immatics Biotechnologies' technology, in a collaboration between the two companies to develop T-cell engaging bispecific immunotherapies targeting multiple cancer indications.

Genmab will pay Immatics $54m, with the company eligible to receive up to $550m further in development, regulatory and commercial milestone payments for each product, as well as tiered royalties on net sales.

Speaking to *Scrip* about its choice of partner, Immatics' chief medical officer Carsten Reinhardt said that Genmab had "demonstrated commitment to, and capabilities in, advancing new approaches in immuno-oncology. Genmab's proprietary antibody technologies together with our XPRESIDENT and Bispecific TCR technology platforms, results in complementary know-how and experience that plays to the strengths of both parties."

The research will combine Immatics' XPRESIDENT and Bispecific TCR technology platforms with Genmab's proprietary antibody technologies. The companies will exclusively discover and develop immunotherapies directed against three proprietary targets, Genmab has the option to exclusively license up to two additional targets to expand the partnership at predetermined economics.

Genmab will be responsible for development, manufacturing and worldwide commercialization. Immatics will have an option to contribute certain promotion efforts at predetermined levels in selected countries in the EU.

Reinhardt also said that the company had seen a "a significant increase" in interest from big pharma and biotech for both intracellular targets and TCR-based approaches over the past few years. "This in our opinion reflects the significant unmet medical need for immune-oncology therapies beyond the few currently pursued targets such as CD19 and to expand specific immunotherapy beyond hemato-oncology into the solid tumour space."

GENMAB'S MATURATION

While Genmab has had success with *Arzerra* (ofatumumab) and more so Darzalex, analysts have wondered what will come next as the company matures.

In a recent note, Morningstar analyst, Kelsey Tsai, said that the company "has transitioned out of the cash-burning stage and is now on its way toward becoming a more mature biotech firm, with a plan to retain more product ownership in its pipeline in exchange for more developmental risk and cost."

With Darzalex expected to have strong penetration in the first and second-line multiple myeloma markets, with peak product sales forecast at over $8.5bn, Genmab is eligible to receive tiered double-digit royalties (12-20%) from its development partner **Johnson & Johnson**. With money to burn, Genmab is making moves to feed its pipeline which looks healthy but still very early.

One such piece of the pipeline is tisotumab vedotin, an investigational antibody-drug conjugate (ADC) developed in collaboration with **Seattle Genetics**. It is designed to target the tissue factor antigen on the surface of cancer cells.

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Otsuka Bags Novel Antibody Tech, Pipeline In $430m Visterra Buy

IAN HAYDOCK ian.haydock@informa.com

Otsuka Pharmaceutical Co. Ltd. has entered into a definitive agreement to pay around $430m in cash for the private US antibody technology venture **Visterra Inc.**, in a step the major Japanese pharma firm says will boost its presence in renal and infectious diseases with unmet needs.

The deal, already approved by both companies' boards, is expected to close in the third quarter subject to usual antitrust clearances.

The move will give Otsuka a novel antibody technology platform and a mostly preclinical pipeline led by a Phase II, pan-strain hemagglutinin candidate for hospitalized influenza A patients, VIS410, and other antibody candidates for renal disorders, pain and cancer, including a potential first-in-class treatment for immunoglobulin A nephropathy (IgAN).

ASSET STRENGTH

Kabir Nath, the president and CEO of Otsuka America Pharmaceutical, Inc., Otsuka's commercial arm in the US, told *Scrip* that: "We had been looking at Visterra's assets for possible licensing, and were impressed by the strength of their platform.

"While Otsuka has traditionally been a small molecule company, we have made targeted acquisitions in the past and we saw unique and focused technology in Visterra. In kidney diseases in particular, there is still not much innovation but a lot of unmet need, with no approved therapies for IgAN, for instance."

Otsuka has some precedent for area-focused acquisitions, paying $886m for US oncology specialist **Astex Pharmaceuticals Inc.** in 2013.

This was followed by a $3.5bn deal for neurology company **Avanir Pharmaceuticals Inc.** completed in 2015.

Waltham, Massachusetts-based Visterra was founded in 2007 around research into epitope characterization by Dr. Sam Sasisekharan at the Massachusetts Institute of Technology, and a founder of **Momenta Pharmaceuticals Inc.** and **Cerulean Pharma Inc.**.

The company's proprietary *Hierotope* platform enables design and engineering of antibody drugs that bind to a specific epitope related to the function of an antigen. Such "hierotopes" are seen as critical to the structural and functional integrity of the target antigen/pathogen.

Analysis of atomic interactions allows the identification of target hierotopes against which selective antibodies can be developed, one advantage of the approach being that specific antibody sites can be altered to optimize effect, Visterra says.

"We believe this broad array of tools provides a novel and unique approach to designing and engineering MAbs, and confers benefits such as longer half-life through Fc engineering," Visterra president and CEO Dr. Brian Pereira told *Scrip* in an interview.

"Otsuka saw a unique platform, and we both felt there would be a good fit in terms of differentiated approaches [to antibodies] and also culturally.

"We were looking for an ex-US partner in the kidney disease area, where we have a very robust pipeline…the relationship with Otsuka checked many boxes, including in terms of their open-minded approach to creativity and innovation, and global financial resources and development and commercial expertise," Pereira said.

Visterra also has capabilities in bispecific antibodies and antibody-drug conjugates, he noted, with several in the early pipeline.

For its part, Otsuka has been looking for novel platforms, including in antibodies, to enhance its drug discovery efforts and pipeline of biologics.

"Our first priority [after the acquisition] will be to move Visterra's pipeline forward," Nath told *Scrip*.

KIDNEY DISEASE PIPELINE

Otsuka already has a strategic presence in renal disorders through tolvaptan (marketed mainly as *Samsca*), an aquaretic vasopressin receptor 2 antagonist for hyponatremia.

But compared with oncology and CNS/neurology, and besides tolvaptan, its current pipeline in the field is relatively sparse, comprising the HIF-prolyl hydroxylase inhibitor vadadustat in Phase III in the US and EU for anemia from chronic kidney disease, and the V2 receptor antagonist OPC-61815 for cardiac edema (Phase II in Japan).

By contrast, Visterra has a well-stocked cupboard across various areas. Leading the pack is VIS410, moving into Phase IIb program in around 400 hospitalized flu patients requiring oxygen support, helped by a $38.8m committed grant (rising up to a possible $214m) from the US DHHS's Biomedical Advanced Research and Development Authority.

The mAb is designed to halt viral replication and has already shown statistically significant reductions in nasal secretion viral levels (up to 91%) in an early Phase II in H1N1 flu.

NEEDS IN NEPHROPATHY

Otsuka was initially drawn to Visterra's program in nephropathy, where the US venture's candidate VIS649 targets a unique APRIL hierotope. The antibody also does not bind to and activate complement, an advantage because renal complement deposition can exacerbate kidney disease.

The hope is to gain orphan designation for IgAN (also known as Berger's disease) in both the US and EU, Visterra said, and both Pereira and Nath pointed to the pressing need in the disease.

It is the most common cause of primary kidney disease globally, and 20-40% of patients eventually require dialysis or transplants over 20 years after diagnosis, but there are as yet no approved therapies worldwide.

Visterra notes the annual worldwide incidence is estimated at 25 per million, but is higher in eastern Asian populations and lower in the US (at 10 per million).

Other companies with late-stage candidates in the area include **Omeros Corp.** with OMS721 (Phase III), while there are six Phase II products including **Apellis Pharmaceuticals Inc.**'s APL-2 and **Astellas Pharma Inc.**' Astagraf XL, Informa's BioMedTracker shows.

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From the editors of PharmAsia News.

Siga Ready For Next Phase, New Cash With Smallpox Drug Approval

SUE SUTTER sue.sutter@informa.com

With the US FDA approval of the smallpox drug *Tpoxx* (tecovirimat) now behind it, **Siga Technologies Inc.** is looking forward to an influx of as much as $91m, plus the proceeds from a priority review voucher sale, to help expand the drug's indications and add new pipeline assets consistent with the company's health security focus.

The FDA approved tecovirimat, an oral inhibitor of the orthopoxvirus VP37 envelope wrapping protein, on July 13 for the treatment of human smallpox in adults and children weighing at least 13 kg.

It is the first drug approved for treatment of smallpox, a contagious and sometimes fatal infectious disease that was eradicated worldwide in 1980 but is viewed as a potential bioweapon threat.

The product was developed under the infrequently used "Animal Rule," which provides a regulatory route to approval when human efficacy studies are not ethical or feasible. While efficacy was demonstrated in animals, safety was established in healthy human volunteers.

The approval, which came more than three weeks before the drug's user fee goal date, is in line with an FDA advisory committee's unanimous support at a May 1 meeting.

The drug will be available initially only through the US government's Strategic National Stockpile (SNS), Siga said.

"Tpoxx is proof that public-private partnerships work when the partners are committed to a focused mission," Siga CEO Phil Gomez said in a press release announcing the approval. "FDA approval of Tpoxx achieves an important objective for both Siga and our lead partner in the US government, the Biomedical Advanced Research and Development Authority (BARDA). The approval validates this novel smallpox therapy as an important medical countermeasure in response to a potential smallpox outbreak."

Tpoxx's development has been funded by BARDA under a base contract of $472m, almost $410m of which is for the manufacture and delivery of 1.7m courses of Tpoxx treatment to the SNS, with another $62.5m for certain development and support activities.

As of March 31, the company had received $368.9m under the base contract related to the manufacture and physical delivery of 1.7m Tpoxx courses to the SNS. The company also contributed 300,000 courses at no additional cost to BARDA, bringing the total number of stockpiled courses of treatment to 2m.

Regulatory approval means Siga is now entitled to a $41m "hold back" payment under the existing contract, provided that BARDA confirms there is no difference between the approved product and the doses that already have been delivered to the SNS, Siga said.

In addition, since the FDA approved a seven-year expiry for Tpoxx, Siga will request that BARDA exercise an option under the contract for a $50m payment to the company based on the extended shelf-life determination. "The exercise of this option is at the sole discretion of BARDA," the company said.

Tpoxx's approval also brings Siga a priority review voucher, the first awarded under the material threat countermeasures incentive program created by the 21st Century Cures Act.

As with the tropical disease and rare pediatric disease voucher programs, the holder of a medical countermeasures voucher may secure a priority review for one of its own products or sell the voucher to another company. Publicly announced voucher sales in 2017 have ranged from $110m-$150m, well below the peak of $350m in 2015.

In an interview in June, Siga's Gomez told *Scrip* the company would look to sell the voucher and possibly use the proceeds to acquire new assets in the health security space.

"Siga will look to maximize the value of the PRV for its shareholders, which may include exploring a sale or other transaction," the company told *Scrip* July 16. "Siga will evaluate relevant opportunities as they arise."

INDICATION AND GEOGRAPHIC EXPANSION

Currently, tecovirimat is Siga's only publicly disclosed pipeline asset, although the company is already exploring formulation and indication expansions.

Siga is developing an intravenous formulation of tecovirimat pursuant to a BARDA contract that ends in December 2020.

"BARDA is working toward the approval of an intravenous formulation of Tpoxx next year for patients who are too young or too sick to take oral medications," BARDA Director Rick Bright said in a statement.

Siga is also evaluating tecovirimat for prophylactic use and as an adjunct to the smallpox vaccination to prevent disease and reduce vaccine-related complications.

Smallpox is caused by the variola virus, which is in the orthopox genus of viruses. Siga's development program used two orthopoxvirus animal models – non-human primates/monkeypox, and rabbits/rabbitpox – as surrogates for variola virus models due to the lack of reliable variola virus animal models.

The successful use of a monkeypox animal model to demonstrate efficacy led some FDA advisory committee members to urge that the company study the drug's potential utility for treating monkeypox outbreaks in humans. Panelists pushed back on the notion that such studies would not be feasible due to geographic challenges of studying outbreaks in certain countries in Africa.

Siga said it would examine the feasibility of expanding Tpoxx's label to include other orthopoxviruses.

"What we're focused on post-FDA approval is finding partners that might allow us to start to evaluate the drug for monekypox," Gomez said in the June interview. "As was highlighted in the AdComm, those are difficult places to do controlled clinical trials, and clearly access to health care is a challenge. But given Ebola outbreaks, given public health infrastructure increasing, we're hopeful we'll eventually be able to get to a point where we might be able to provide the drug in controlled clinical studies to evaluate it for that."

The company is also eyeing regulatory approvals abroad now that tecovirimat has passed FDA muster.

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13 Approvals To Look Out For In Q3

ALEX SHIMMINGS alex.shimmings@informa.com

AGIOS PHARMACEUTICALS TIBSOVO (IVOSIDENIB) FOR ACUTE MYELOGENOUS LEUKEMIA

PDUFA date: Aug. 21

Agios Pharmaceuticals Inc. is hoping its small-molecule inhibitor of isocitrate dehydrogenase 1 (IDH1) will become the first targeted treatment to relapsed or refractory acute myeloid leukemia (AML) patients who have an IDH1 mutation. Although IDH1 mutations are estimated to occur in only 6-10% of AML patients, they are associated with poor disease prognosis.

Agios has already introduced a new treatment paradigm with the IDH2 inhibitor *Idhifa* (enasidenib), for the 8-19% of AML patients who carry IDH2 mutations, which was approved by the FDA last year.

The new application is supported by data showing an overall response rate of 41.6%, with durable remission rates, as well as favorable transfusion independence rates that were achieved across multiple response categories.

These results validate the benefit of targeting IDH1, establishing ivosidenib as part of a wave of new, targeted therapies for the treatment of AML, said analysts at Biomedtracker. Datamonitor Healthcare is forecasting sales of ivosidenib for AML across the US, Japan and five major EU markets to reach $86m by 2025.

KYOWA HAKKO KIRIN'S MOGAMULIZUMAB FOR CUTANEOUS T-CELL LYMPHOMA

PDUFA date: Sept. 4

Kyowa Hakko Kirin Co. Ltd.'s plans for its humanized monoclonal antibody targeting CCR4 mogamulizumab in the US have hit setbacks in the form of a three-month delay while the FDA reviewed additional documentation related to the manufacturing section of the biologics license application (BLA), and the arrival late last year of a rival, **Seattle Genetics Inc.**' *Adcetris* (brentuximab vedotin).

The FDA accepted Kyowa Hakko Kirin's BLA for mogamulizumab to treat cutaneous T-cell lymphoma (CTCL) in patients who have received at least one prior systemic therapy, and granted it priority review status, but a decision is not now expected until Sept. 4.

CTCL is a rare form of non-Hodgkin's lymphoma in which malignant T lymphocytes localize to the skin, and its main subtypes are mycosis fungoides (the most common) and Sézary syndrome. This BLA is supported by data from the MAVORIC study, which enrolled mycosis fungoides patients as well as Sézary syndrome patients.

Seattle Genetics' Adcetris was approved in November 2017 for CD30-expressing CTCL patients with mycosis fungoides who have received prior systemic therapy, and in its Phase III pivotal trial, had a PFS of 15.8 months versus 3.6 months for patients receiving physician's choice therapy. This, Biomedtracker analysts point out, is substantially better than the 7.7 months PFS seen with mogamulizumab and will likely give Adcetris a competitive advantage. On the other hand, mogamulizumab may be approved for a wider group of patients as the MAVORIC trial enrolled mycosis fungoides patients as well as Sézary syndrome patients. If approved, mogamulizumab will be a first-in-class option for CTCL, an orphan disease with an unmet medical need.

ABBVIE AND NEUROCRINE BIOSCIENCES' ELAGOLIX FOR ENDOMETRIOSIS

PDUFA date: Aug. 6

A decision on **AbbVie Inc.** and **Neurocrine Biosciences Inc.**'s NDA for their investigational, orally administered gonadotropin-releasing hormone (GnRH) antagonist elagolix for endometriosis is finally expected in August after it was pushed back by three months by the FDA.

Though the application was granted a priority review, the companies announced in April that the FDA had extended the timeline to review additional information regarding liver function tests provided by AbbVie. Despite the slight delay, elagolix has the potential to be the first approved drug for the treatment of endometriosis in more than 10 years.

The application was supported by data from nearly 1,700 women with moderate-to-severe endometriosis-associated pain in two identical Phase III studies. In these, both elagolix doses produced a significantly higher response rates for reduced menstrual pain (dysmenorrhea) and non-menstrual pelvic pain associated with endometriosis at months three and six.

The injectable GnRH agonist *Lupron* (leuprolide), which is also available generically, has been a standard treatment for endometriosis but has some troublesome side effects, including amenorrhea (lack of menstruation) and loss of bone mineral density.

Elagolix by contrast has a more favorable safety profile that is consistent with the partial hormone suppression associated with its mechanism of action. Safety findings across Phase III trials and showed reduced rates of amenorrhea (lack of menstruation) and reduced bone density loss (at the lower dose) compared with GnRH agonists.

AMICUS THERAPEUTICS' GALAFOLD (MIGALASTAT) FOR FABRY DISEASE

PDUFA date: Aug. 13

A positive approval decision on August 13 for **Amicus Therapeutics Inc.**'s migalastat by the FDA is looking likely, analysts at Biomedtracker say, in what would be a relief for the company which experienced a hiccup with its application.

Migalastat is intended to treat Fabry disease in patients 16 years or older who have amenable genetic mutations. This rare disease is caused by deficiency of the α-galactosidase A enzyme, which degrades specific lipids in lysosomes that would otherwise accumulate and cause irreversible organ damage. Migalastat is designed as a chaperone therapy to stabilize certain mutant enzymes to facilitate normal trafficking to lysosomes, thereby reducing lysosomal substrate accumulation.

Migalastat is already approved in the EU, Japan and other markets, including Australia and Canada, but the FDA said in late 2016 that it wanted a new 12-month gastrointestinal safety study. The following July, the agency in a surprising U-turn agreed that the company could submit the NDA for accelerated review based on existing data after the company submitted new analyses, as well as data on cardiac and renal effects, longer term extension data, and the experience

of patients taking the commercial drug in Europe, especially those switched from enzyme replacement therapies.

In addition to its unique mechanism, migalastat is available orally, which is an advantage over the established enzyme replacement therapy, Sanofi's *Fabrazyme* (agalsidase alfa), the only Fabry disease treatment to be approved by the FDA since 2003.

If approved, migalastat is expected to have a strong market impact in the US, and Amicus expects its migalastat global revenue from 2017 to double this year.

SHIRE'S LANADELUMAB FOR HEREDITARY ANGIOEDEMA

PDUFA date: Aug. 26

Shire PLC's lanadelumab is a monoclonal antibody inhibitor of plasma kallikrein being developed for the prevention of angioedema attacks in patients 12 years and older with hereditary angioedema (HAE). If approved, lanadelumab has the potential to change the HAE treatment landscape by being the first monoclonal antibody to prevent HAE attacks.

The BLA is supported by data from four clinical trials, including the pivotal Phase III HELP study reported last May, when Shire CEO Flemming Ørnskov said the data vindicated its purchase of originator company Dyax Corp in late 2015. HELP evaluated subcutaneous lanadelumab versus placebo over 26 weeks in HAE patients 12 years of age or older and showed that a 300 mg dose every two weeks resulted in an 87% reduction in the mean frequency of HAE attacks.

With Dyax, Shire also acquired the older HAE therapy *Kalbitor*, a 60-amino acid polypeptide inhibitor of kallikrein, which is approved in the US for treatment of acute HAE. Lanadelumab works differently to prevent HAE attacks by directly targeting plasma kallikrein to inhibit excessive bradykinin formation.

TETRAPHASE PHARMACEUTICALS' ERAVACYCLINE FOR INTRA-ABDOMINAL INFECTIONS

PDUFA date: Aug. 28

A welcome novel antibiotic is expected to reach the market soon: **TetraPhase Pharmaceuticals Inc.**'s eravacycline, a broad-spectrum, fluorocycline antibiotic, as a twice-daily intravenous treatment for complicated intra-abdominal infections (cIAI). Eravacycline is a more potent version of tigecycline with a similar spectrum of activity and pharmacokinetics and is effective against Gram-negative multidrug-resistant (MDR) pathogens, including carbapenem-resistant enterobacteriaceae, *Acinetobacter baumannii*, and colistin-resistant bacteria carrying the mcr-1 gene.

If approved, TetraPhase Pharmaceuticals' eravacycline will likely be used in three main ways: first-line empiric treatment where antibiotic-resistance is suspected (such as hospitalized patients and patients from skilled nursing facilities); second-line empiric treatment where the first line antibiotic failed and no culture can be obtained; and in confirmed cases of antibiotic resistance. Biomedtracker analysts said this treatment landscape represented a significant market opportunity for eravacycline.

Two pivotal Phase III studies, IGNITE 1 and IGNITE 4, formed the basis of the antibiotic's filings and under the guidance set by the FDA and the European Medicines Agency (EMA), their primary endpoint was clinical response at the test-of-cure visit.

ELI LILLY'S EMGALITY FOR MIGRAINE

PDUFA date: September

The second of the novel CGRP inhibitors for migraine, **Eli Lilly & Co.**'s *Emgality* (galcanezumab), is expected to get the go-ahead at the end of September, when, if all goes well, it will join **Novartis AG**/**Amgen Inc.**'s *Aimovig* (erenumab) on the market.

Galcanezumab has been jostling with **Teva Pharmaceutical Industries Ltd.**'s fremanezumab to be next in this new drug class and has been helped by manufacturing concerns at Teva's contractor, **Celltrion Inc.**, which are expected to push back its launch until the end of the year. The BLA for galcanezumab, submitted in September 2017, was based on data from three Phase III studies: EVOLVE-1, EVOLVE-2 and REGAIN.

While the data supporting efficacy and safety of these three products as preventives for episodic and chronic migraine are comparable, the drugs may be differentiated through investigations into secondary indications.

Here galcanezumab can hope to distinguish itself in several ways, Biomedtracker analysts say. In a subgroup analysis of galcanezumab's three pivotal trials, it appeared more effective in refractory episodic migraine patients who had failed at least two previous preventives than Aimovig did in its LIBERTY trial. Additionally, galcanezumab showed efficacy in preventive-refractory patients with chronic migraine, a population for which Aimovig did not produce data for.

Furthermore, patients with episodic cluster headache experienced statistically significant differences in the reduction of weekly cluster headache attacks with galcanezumab compared with placebo.

Additionally, a recent post-hoc subgroup analysis of galcanezumab's pivotal trials highlighted the drug's efficacy in patients who had previously failed preventive treatment with Botox.

"While these differentiators will aid galcanezumab in competing with other anti-calcitonin gene-related peptide preventives, galcanezumab remains unlikely to outperform Aimovig overall. Aimovig will possess a first-to-market advantage and benefit from the extensive commercial resources of Novartis and Amgen," said Biomedtracker.

Datamonitor Healthcare's PharmaVitae projects galcanezumab's sales to attain a peak of $2.3bn in 2026, which will be exceeded by Aimovig as it grows to $2.8bn.

AZEDRA FOR NEUROENDOCRINE TUMORS

PDUFA date: July 30

Azedra is a targeted radiotherapeutic under development by **Progenics Pharmaceuticals Inc.** for the treatment of malignant, recurrent and/or unresectable pheochromocytoma and paraganglioma, types of neuroendocrine tumors.

Progenics completed the rolling submission of the NDA in November 2017, and the agency subsequently granted Progenics' request for priority review and set an action date of April 30, but the review was extended by three months to July 30 following the submission of additional chemistry, manufacturing, and controls (CMC) information by Progenics.

Data from a pivotal Phase IIb open-label, multicenter conducted under a special protocol assessment (SPA) showed Azedra met the primary endpoint which evaluated the proportion of pheochromocytoma and paraganglioma patients who achieved a 50% or greater reduction of all antihypertensive medication for at least six months.

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The study also showed favorable results from a key secondary endpoint evaluating the proportion of patients with overall tumor response as measured by RECIST criteria.

PFIZER'S DACOMITINIB FOR NON-SMALL CELL LUNG CANCER

PDUFA date: September

Pfizer Inc.'s pan-human epidermal growth factor receptor (EGFR) family tyrosine kinase inhibitor (TKI) dacomitinib is likely to struggle against its rivals if it finally reaches the market despite recent positive new Phase III OS data from is pivotal ARCHER 1050 study.

The drug is being developed for the first-line treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with EGFR-activating mutations. The FDA accepted the company's NDA and granted priority review for dacomitinib in April 2018, and the product is also under review at the EMA for the same indication.

The filings rest on results from the Phase III ARCHER 1050 study comparing dacomitinib to gefitinib (**AstraZeneca PLC**'s *Iressa*), which met its PFS primary endpoint over the older product. Patients who received dacomitinib had a median PFS of 14.7 months compared with 9.2 months for gefitinib. The study also met the secondary endpoint showing that the median OS was 34.1 months with dacomitinib compared with 26.8 months with gefitinib.

While dacomitinib experienced a challenging path towards regulatory approval when the previous Phase III ARCHER 1009 and BR.26 trials failed to meet their primary endpoints, regulatory approval in first-line EGFR mutation-positive patients could soon be attainable with the updated positive PFS and OS results from ARCHER 1050, Biomedtracker said.

PFIZER'S LORLATINIB FOR NSCLC

PDUFA date: August

Another potential new Pfizer product hoping for approval shortly is lorlatinib, an investigational, anaplastic lymphoma kinase (ALK) tyrosine kinase inhibitor (TKI) for the treatment of patients with ALK-positive metastatic NSCLC, previously treated with one or more ALK TKIs. Lorlatinib was specifically designed to inhibit ALK variants with secondary mutations associated with resistance to first- and second-generation ALK TKIs, and to penetrate the blood brain barrier.

The submission is based on data from the Phase II portion of a Phase I/II clinical trial evaluating lorlatinib in patients treated in distinct cohorts based on prior therapy. Full results from the Phase II portion of the trial were presented at the World Conference on Lung Cancer in October 2017. In these results, overall response rate benefit was observed in patients who failed crizotinib, suggesting lorlatinib could gain easy adoption initially as a second-line therapy.

"With the promising results presented recently, lorlatinib has potential to become an effective second-line treatment option for patients with ALK-positive advanced NSCLC," said analysts at Biomedtracker.

INSMED'S ARIKAYCE FOR RESPIRATORY TRACT INFECTIONS

PDUFA date: Sept. 28

Insmed Inc.'s once-daily amikacin liposome inhalation suspension (ALIS) a could potentially be the first approved inhaled therapy for adults with nontuberculous mycobacteria (NTM) lung disease caused by *Mycobacterium avium* complex (MAC).

Through Insmed's proprietary liposomal technology, ALIS delivers amikacin directly to infected cells to eradicate the bacteria. ALIS added to guideline-based therapy (GBT) against GBT alone met its primary endpoint of patients achieving culture conversion at six months (29% versus 9%, $p<0.0001$) in a registrational study. Additionally, GBT took approximately 30% longer to convert, demonstrating that ALIS is not only more effective but faster. An FDA Advisory Panel Meeting is scheduled for August 7. The product has received orphan, breakthrough therapy, fast-track and qualified infectious disease product designations.

SHIONOGI'S LUSUTROMBOPAG FOR THROMBOCYTOPENIA

PDUFA date: Aug. 26

Shionogi & Co. Ltd. is playing catch up with **Dova Pharmaceuticals Inc.** in the thrombocytopenia space with its lusutrombopag, which is expected to get FDA approval in late August for the treatment of thrombocytopenia in patients with chronic liver disease (CLD) who are at increased risk of bleeding associated with invasive procedures.

Its Durham, N.C.-based rival obtained US FDA approval of *Doptelet* (avatrombopag) on May 21, when it became the first oral drug alternative to platelet transfusions for this patient population.

Lusutrombopag's NDA submission is based on two Phase III clinical trials, L-PLUS1 (Japan) and L-PLUS2, in which lusutrombopag met the pre-specified primary efficacy endpoints of both pivotal trials. Of note, the L-PLUS 1 study highlighted that the proportion of patients who required no preoperative platelet transfusion was significantly greater with lusutrombopag (79.2%) than with placebo (12.5%). In the L-PLUS2 trial, top-line results revealed that 64.8% of lusutrombopag patients versus 29% of placebo patients met the primary endpoint, which was defined as the proportion of patients who required no platelet transfusion prior to the primary invasive procedure and no rescue therapy for bleeding from randomization through seven days following the procedure.

ALLERGAN'S ULIPRISTAL ACETATE FOR UTERINE FIBROIDS

PDUFA date: August

Another product whose PDUFA date has been pushed back is **Allergan PLC**'s ulipristal acetate, a selective progesterone receptor modulator for the treatment of abnormal uterine bleeding in women with uterine fibroids. The original PUDFA date was set within the first half of 2018; but in February, the FDA notified Allergan that the PDUFA target action date had been extended to August 2018.

The NDA for ulipristal acetate appeared very promising until two EMA public health advisories raised safety concerns. In February 2018, the EMA's Pharmacovigilance Risk Assessment Committee (PRAC) responded to reports of serious liver injury with ulipristal acetate. In May 2018, the PRAC concluded its review of ulipristal acetate and said that the medicine must not be used in women with liver problems and that all women taking ulipristal acetate should have a liver function test once a month during treatment.

The negative opinion on ulipristal acetate's safety will likely influence the FDA's approval decision and, at the very least, warrant clear warnings on its label advising regular liver function tests which will restrict its use, says Biomedtracker.

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

Amgen Puts Evenity Filing Back On Track With TIMI Cardiovascular Risk Review

JOSEPH HAAS joseph.haas@informa.com

Amgen Inc. and **UCB Group** have refiled the biologics license application (BLA) for their osteoporosis candidate *Evenity* (romosozumab) with a highly regarded study group's review of the drug's cardiovascular risk, hoping that will allay concerns that led to a complete response letter last July and which could limit the drug's competitive profile.

An evaluation of adverse event data by the Thrombosis in Myocardial Infarction (TIMI) study group at Brigham & Women's Hospital is part of the refiled application, the partners announced July 12.

Romosozumab, an anabolic therapy intended to address high risk of bone fracture in menopausal women with osteoporosis, is Amgen's lone bone health candidate in clinical development, save for label-expansion efforts for its osteoporosis blockbuster *Prolia* (denosumab). Prolia, a 60 mg dose of denosumab, along with *Xgeva*, a 120 mg dose of the monoclonal antibody, both are blockbusters with growing sales, comprising an important commercial franchise for Amgen.

But denosumab faces patent expirations in June 2022 in Europe and February 2025 in the US, meaning romosozumab could be the big biotech's primary bone health product in a few years, if it obtains regulatory approval. A first-in-class sclerostin-inhibiting antibody, romosozumab also is awaiting approval in Japan and Canada, with decisions expected by Sept. 30, according to Biomedtracker, and in the EU, where a final opinion by the Committee on Products for Medicinal Health (CHMP) is expected between October and the end of April.

While originally filed at the FDA in 2016 backed by the 7,180-patient Phase III FRAME study along with Phase I and Phase II data, the new filing also incorporates the TIMI findings and data from the 4,093-patient Phase III ARCH study, as well as the 245-patient Phase III BRIDGE study in men with osteoporosis. After the 2016 filing, the FDA and the sponsors agreed that data from ARCH should be included in the approval decision, but an imbalance in cardiovascular risks between study drug and placebo in ARCH led to the complete response letter (CRL). Morgan Stanley analyst Matthew Harrison called the revised BLA "clearly robust" and said in a July 13 note that the TIMI review could prove key to romosozumab's chances for approval on second review. At the time it received the CRL, Amgen noted that no cardiovascular safety signal had been seen in the larger FRAME study.

"While detailed results were not provided, [Amgen] management noted that the conclusions of the TIMI analysis were consistent with prior data and will be shared at a medical conference," Harrison wrote, adding that he is taking a "wait-and-see" approach on romosozumab's chances "given the significant issues management needs to overcome."

Biomedtracker did not adjust romosozumab's likelihood of approval upon announcement of the refiling, leaving its estimate at 82%, seven percentage points below average for a Phase III osteoporosis candidate. Amgen and UCB intend to present the TIMI results at an upcoming medical meeting.

Prolia and Xgeva combined brought in nearly $1bn during the first quarter of 2018 for Amgen, with the former posting sales of $494m, up 16% year-over-year, and the latter bringing in $445m, up 11%. For full-year 2017, Prolia yielded global sales of $1.97bn, up 20% over 2016, while Xgeva earned $1.58bn, up 3%. The products generally derive about two-thirds of their revenue from US sales, with the rest from the EU.

The romosozumab CRL was seen as diminishing the earnings potential of an expected blockbuster, and also giving a boost to **Radius Health Inc.**'s competing anabolic therapy *Tymlos* (abaloparatide), which was also seen as a potential blockbuster when it launched in May 2017 with a wholesale acquisition cost of $19,500 per year.

To date, the Tymlos US launch has performed adequately, but unspectacularly, according to Leerink Partners analyst Geoffrey Porges. He pointed out in a May 10 note about Radius that first quarter sales of $14.5m topped consensus estimates by 7% and appeared to place the drug on an $80m-$85m run rate for its first full year on market.

Both romosozumab and Tymlos are expected to compete head-to-head with **Eli Lilly & Co.**'s *Forteo* (teriparatide), which brought in $1.75bn in 2017 for 17% growth over the previous year. However, Forteo yielded $312.2m during the first quarter of 2018, down 10% year-over-year, which the pharma attributed to reduced sales volume as well as discounting.

Amgen and UCB have been partnered since 2004, when UCB bought out **Celltech Pharmaceuticals Inc.** for about $2.7bn, to collaborate on the value of targeting sclerostin with antibody therapies.

HISTORY OF R&D FAILURE

According to Biomedtracker, romosozumab and **Mereo BioPharma Group PLC**'s BPS804, in Phase IIb for osteogenesis imperfecta, are the only sclerostin-targeting agents in clinical development. Amgen and UCB suspended development of romosozumab for bone fractures and mechanical defects in 2013, and stopped work on another sclerostin inhibitor, AMG 167, in 2014.

Between efforts by Amgen, Mereo, Lilly and **OsteoGeneX Inc.**, Biomedtracker lists nine efforts to develop sclerostin-targeting drugs that were suspended between 2013 and 2016. Along with *Aimovig* (erenumab), a novel migraine therapy approved by FDA in May, romosozumab and biosimilars (such as *Mvasi*, a biosimilar of **Roche**'s *Avastin* (bevacizumab) approved in September) are viewed as Amgen's best catalysts for offsetting the impact of competitors' biosimilar versions of its products, such as *Enbrel* (etanercept) and *Aranesp* (darbepoetin alfa).

The company's other late-stage assets with recently accomplished or near-term milestones include approvals of additional indications for Prolia, the multiple myeloma drug *Kyprolis* (carfilzomib) and leukemia drug *Blincyto* (blinatumomab) as well as regulatory submissions for *Kanjinti* (ABP 980), a biosimilar for Roche's *Herceptin* (trastuzumab), and Phase III results for ABP 710, a biosimilar for **Johnson & Johnson**'s *Remicade* (infliximab).

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Esperion Aims Low On Price For Bempedoic Acid

EMILY HAYES emily.hayes@informa.com

Esperion Therapeutics Inc. has a tough hill to climb if it gets to market with its cholesterol therapy bempedoic acid, a feat that has proven challenging for the highly effective PCSK9 inhibitors. The company is betting that if the drug costs payers and patients less than the injectable PCSK9 inhibitors that will help it gain traction.

Esperion is aiming for an annual list price of $3,500 and now is guiding for a net price of about $2,200 – a level that analysts have been projecting, the company's executives explained in an interview after its Investor Day presentation on July 10.

Bempedoic acid is a first-in-class inhibitor of ATP citrate lyase (ACL) that upregulates the LDL-C receptor in order to reduce cholesterol synthesis. Esperion is developing the drug as an oral LDL cholesterol-lowering option for statin-intolerant patients that is complementary to **Merck & Co. Inc.**'s oral *Zetia* (ezetimibe), which blocks cholesterol absorption and is now generic.

But there are many options aside from Zetia, including high dose generic statins and injectable PCSK9 inhibitors – **Amgen Inc.**'s *Repatha* (alirocumab) and **Sanofi**/**Regeneron Pharmaceuticals Inc.**'s *Praluent* (evolocumab) are approved and have demonstrated a benefit for cardiovascular risk reduction in outcomes studies.

Bempedoic acid is being positioned for use on top of maximally tolerated statins, so arguably it is not directly in competition, but in practice maximally tolerated may be no statin at all, that is for patients with statin intolerance. Statin intolerance, however, is a subjective term. The FDA has questioned whether the PCSK9 sponsors used adequate criteria for statin intolerance in their trials and has highlighted evidence showing that patients may actually tolerate statins if the therapy is tried a second time, a move that could save payers the expense of an expensive branded therapy.

Esperion estimates that the PCSK9 inhibitors now have a net price of $5,000 to $6,000 after rebates.

The wholesale acquisition cost (WAC) for both PCSK9 inhibitors is $14,500 per year, but the sponsors have offered substantial discounts due to pressure and demand from prescribers and payers. ISI Evercore analyst Umer Raffat concluded in a March 12 note that the sales figures for the second half of 2017 suggested an annual net price of about $8,000 for PCSK9 inhibitors.

PCSK9 inhibitors have faced enormous challenges in the market including high pricing relative to generic statins, injectable delivery in a traditionally oral market, and what some describe as a modest benefit for reducing cardiovascular events in major outcomes studies. *(Also see "Outcomes Claim May Help Amgen Make Case For PCSK9 Inhibitor Repatha" - Scrip, 1 Dec, 2017.)*

Sanofi announced in March that it would lower the price of Praluent and align it with the conclusions of the Institute of Clinical and Economic Review (ICER), the independent drug pricing review body, which got data from the ODYSSEY outcomes trial for Praluent in advance and performed a new value benchmarking analysis. *(Also see "Praluent Pricing: Collaboration With ICER Sets A New Standard" - , 12 Mar, 2018.)*

Esperion is aiming for the vast population of patients who can't tolerate statins. However, statin intolerance is not a precisely defined term. Esperion and other companies are aiming to treat patients who are on maximally-tolerated statin therapies, which for intolerant patients may mean no statins.

FAVORABLE LIST PRICE

The $3,500 list price compares well with the $14,000 to $15,000 per year list price for the PCSK9 inhibitors, especially considering Chief Commercial Officer Mark Glickman's disclosure during Esperion's July 10 call that initially payers thought bempedoic acid would be priced similar to the PCSK9 drugs. Now, Glickman said, it actually will be "nowhere near the cost of a PCSK9 – not to the payer, and especially not to the patient."

The company notes that many patients on lipid-lowering therapies are covered by Medicare and may have steep co-pays that are based on the WAC price, so it sees its lower list price as an advantage and it is making access a priority.

The risk versus benefit of the drug is yet to be proven. Esperion has released three Phase III studies so far and while the trials have been positive, there was an imbalance in death rates that was a cause for alarm among investors.

Esperion addressed these concerns during its July 10 investor day call, providing cumulative data for completed Phase II and Phase III studies to date in 4,006 patients. Across trials, the rate of liver enzyme elevations was 0.52% versus 0.15% for placebo. That compares to 0.2% at the lowest and 2.3% at the highest dose of **Pfizer Inc.**'s statin *Lipitor* (atorvastatin), Esperion noted. Across trials the rate of serious adverse events was 9.2% for bempedoic acid versus 8.9% for placebo. There were a total of 14 deaths among patients on bempedoic acid versus two for placebo. (See chart below.)

John Jenkins, former director of the Office of New Drugs (OND) at the FDA's Center for Drug Evaluation and Research – now a principal in drug and biological products at Greenleaf Health in Washington, D.C. – said during Esperion's investor event that the FDA will look at the totality of the safety data, but that clearly data from longer randomized studies are very informative to understanding the safety experience with bempedoic acid.

Steve Nissen, chair of cardiology at the Cleveland Clinic, said during the call that he views the liver changes as completely in line with what has been seen in studies of statins, which have a similar mechanism of action, so this is completely a "non-issue."

As for the deaths reported so far, Nissen said that he is "a little surprised" that people were "making such a big deal about the imbalance in mortality."

While there were 14 deaths for bempedoic acid versus two for placebo, there were also twice as many people on the test drug than placebo, so the ratio for a difference is more like 7:2, he said.

Nissen cautioned against the "tyranny of small numbers" and overreacting to small differences.

The data monitoring committee has not raised any flags, he noted, adding that he is "fine with where we stand."

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Downward, Eastward or Inward? Blockbuster Film Puts Cancer Drug Prices In China Spotlight

BRIAN YANG & ANJU GHANGURDE

Already facing official pressure to cut drug prices, makers of high-priced cancer products in China have another potential crisis to deal with: rising public resent over the lack of access to cancer drugs, stirred up by a widely popular movie.

"Dying to Survive" is based on a true story. A Shanghai-based businessman selling Indian herbs, Lu Yong, found himself in the cross-hairs after a cancer patient pleaded to him for help. The patient was suffering from chronic myeloid leukemia and could not afford highly effective treatments. In despair, the patient proposed a business idea to Yong, to bring in cheaper Indian generic drugs and sell these to local CML patients.

As they were not approved in China, the Indian generics were deemed to be illegal, and selling them would be a punishable act subject to years in prison.

Yong tested the waters anyway and the initial transaction blossomed into a hugely lucrative business. Soon, droves of patients started lining up in front of his shop to buy the drugs.

Yong was later arrested during a police raid and sentenced to five years in jail, but freed two years after his sentence was reduced for "helping the poor patients".

DOWNWARD TREND TO CONTINUE?

The success of Dying to Survive has drawn Chinese national attention again to the prices of cancer drugs, many of them manufactured by multinationals and not covered by the National Drug Reimbursement List (NDRL) or provincial reimbursement lists before 2015, when the events began unfolding.

Since 2015, when Zhejiang province started covering 15 high-priced drugs such as *Gleevec* (imatinib), *Iressa* (gefitinib), *Herceptin* (trastuzumab), *Erbitux* (cetuximab), and *Alimta* (pemetrexed), the prices have gradually decreased. In return for coverage, Zhejiang cut the prices by around 19% on average.

In 2017, 15 cancer drugs were also incorporated into China's NDRL, including *Mabthera* (rituximab), Herceptin, and *Velcade* (bortezomib). Gleevec was put on the list and 80% of its treatment costs were covered, substantially reducing the individual burden of CML patients from roughly CNY21,000 ($3,150) before the coverage to CNY2,200.

Entering 2018, the attention on cancer drugs prices seemingly reached new heights, and the government has taken several high-profile measures including cutting tariffs and taxes to appeal to the public.

One measure included lowering import tariffs for anticancers from 3-6% to zero. Later, the government reduced the value added tax (VAT), which accounts for a large portion of imported drug prices, from 17% to 6%.

Such measures aside, the government also took a more personal approach to the issue. During a trip to Shanghai, Chinese Premier Li Keqiang made a stop to visit **Roche**'s campus, making a point that cancer drug prices need to be affordable.

More price cuts could be on the way, partially fueled by the wide popularity of the movie and the continually rising pressure, observers say.

Furthermore, some say the fact that a domestic film with a Robin Hood-style rebellious message has cleared the screening authorities in what is a tightly-controlled environment for foreign movies shows that the government is willing to tackle the issue and further pressure drug makers, meaning more downward trends for high-priced cancer drugs could be forthcoming.

INWARD PUSH?

Also, the success of the movie could prompt policies that support growth in the approval, manufacturing and supply of domestic anticancer generics. So far, many who have seen Dying To Survive have expressed a profound feeling that made in China generics, although available on the market, have been unable to gain wider traction and compete with originator drugs. Some official steps have already taken place. In April, the government issued *Circular No.20, Comments On Reforms of Policies to Improve Supply and Use of Generic Drugs*, aimed at making drugs more accessible and affordable, including widely prescribed products for cancer. Some potential measures include compulsory licensing, tax incentives, and substitution to support the use of domestic generics.

These latest moves coupled with ongoing requirements for bioequivalence testing and incentives for products that have passed such testing, may well bolster the domestic generics sector as part of an inward push to cut cancer drug prices.

EASTWARD TOO?

In other initiatives, China is also offering tariff relief to India and a potential opening to Indian cancer drugs to enter China legally. However, the potential "Panda Meeting Tiger" route will be a bumpy one, experts and analysts from the Indian pharma industry say.

Could Chinese patients and the overall healthcare system benefit from increased access to cut-price Indian anticancers?

The popularity of Dying to Survive has obviously impacted the Chinese Ambassador to India Luo Zhaohui, who recently tweeted about the movie being a "black comedy". "Reflect how Indian medicine is welcomed by Chinese people," the ambassador tweeted on July 6.

But industry experts believe that it will take much more than just a successful film to steer any increased Indo-China bonhomie in the pharmaceutical space.

In particular, the Indian pharmaceutical industry appears to be keeping close watch on the unfolding US-China trade tit-for-tat; they believe China's approach to genericization may well hinge on how these frosty relations eventually shape up.

Dilip Shah, secretary general of the Indian Pharmaceutical Alliance, which represents leading Indian firms, told *Scrip* that a lot would depend on how China decides to "pull back" from the trade war with the US. If it opts to "appease" the US on intellectual property rights (IPRs), it is

unlikely that there would be any significant change in its attitude towards generics and access, he said.

"On the other hand, China can also leverage IPRs to take on the US and not go beyond the [World Trade Organization's] TRIPS Agreement [on IPRs]. That would open up China's market for affordable quality products from India," Shah, a former commercial director of Pfizer India, predicted.

IPR issues have been a long-standing prickly issue between the US and China, with the US Trade Representative keeping China on the Priority Watch List for the 14th consecutive year in its most recent Special 301 report.

In the pharmaceutical space, the US has also been pressing China on a range of issues such as providing effective protection against unfair commercial use, as well as unauthorized disclosure, of test or other data generated to obtain marketing approval for pharmaceutical products.

It is also demanding that China expedite its implementation of an effective mechanism for the early resolution of potential patent disputes.

NON-TARIFF BARRIERS REMAIN

Meanwhile, though China lifted import tariffs on 28 drugs including anticancers effective May this year, the Indian industry claims it is actually more concerned about the remaining non-tariff barriers that impede market access.

IPA's Shah indicated that industry's top ask is that China facilitate the speedy approval of product registrations.

Despite these lingering concerns, the Indian government too has been keen to facilitate the export of generic drugs to China. India's Department of Commerce in coordination with the Embassy of India at Beijing had earlier commissioned a study on "Enhancing Indian Exports of Pharmaceutical products to China" under the Market Access Initiative Scheme to better understand the Chinese market and help the Indian pharma industry shape their China entry strategies for generic drugs.

The study examines a range of issues including the pharmaceutical market, the distribution system, procurement and bidding processes, and the regulatory landscape in China. It also provides recommendations on how to access the Chinese market and is reported to underscore the importance of joint ventures, given the seeming preference given to domestic players under the Chinese procurement and tendering process.

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From the editors of PharmAsia News.

Cystic Fibrosis: NovaBiotics Advances Old Dog With New Tricks

ELEANOR MALONE eleanor.malone@informa.com

NovaBiotics Ltd. is making plans to progress its oral treatment for cystic fibrosis exacerbations into Phase III by early next year, after reporting positive Phase IIb results. The company is hopeful that it will be able to file for approval of *Lynovex* (cysteamine) in 2020 should Phase III studies prove positive. It sees its therapy for acute use as complementary to other approaches to treating and managing CF.

CEO Deborah O'Neil told *Scrip* that the treatment had the potential to provide better control of CF exacerbations than current antibiotic treatment alone. "It's those episodes that chip away irreversibly at lung function. The focus of nearly every other therapy is to prevent those happening in the first place, but even patients on disease modifiers still exacerbate," she said. "The idea here is to preserve lung function, to get patients through those episodes with less collateral damage."

On average, adult patients have 1.5 exacerbations per year, once their lungs have become colonized with pathogenic organisms like *Pseudomonas aeruginosa*. The main intention with oral Lynovex is to treat acute episodes in adults rather than children. This is because exacerbations tend to kick in from around the late-teens.

Lynovex (NM001) is a hard gel capsule formulation of cysteamine, an aminothiol compound that has been used for decades in a different dosage and frequency to treat the rare metabolic disease cystinosis, under the brand name *Cystagon*. Cystagon is sold by **Mylan NV**, with **Recordati Industria Chimica & Farmaceutica SPA** having acquired the rights for certain territories including Europe in April 2018.

Cysteamine is a breakdown product of co-enzyme A, and acts as an immune effector molecule but also has antimicrobial and anti-inflammatory effects. As Lynovex, it has a multimodal mechanism of action: it kills Gram-negative and Gram-positive respiratory bacteria associated with CF infections and colonization, and potentiates the activity of currently used anti-infective drugs for CF. It disrupts and prevents the formation of biofilms by CF-associated pathogens, which leads to long-term, antibiotic-insensitive colonies. And it is also highly mucolytic, breaking down the mucus in the airways.

"In a way it's like aspirin: it's one of those very old molecules that's been around for a while and does more than one thing," said O'Neil. "The idea with our oral form of cysteamine is to use a sledgehammer to crack a nut: get as much in for 14 days as is safe and you see an effect with. And it's something that all patients can take."

The six-arm Phase IIb CARE CF 1 study assessed the use of five different dosages/regimens of Lynovex versus placebo as an adjunct to standard of care therapy (antibiotics) in 89 adult patients with exacerbations of cystic fibrosis-associated lung disease. A reduction in CF respiratory symptom severity as well as a reduction in blood white cell count after two weeks were associated with a specific dosage and regimen of Lynovex; both were clinically and statistically significant, the Aberdeen, UK-based company reported. It noted that improvements were mirrored by changes in health-related questionnaire scores, sputum levels of inflammatory mediators and a 4% increase in lung function, while Lynovex patients' sputum also contained less bacteria than those on placebo.

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

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

Selected clinical trial developments for the week 6–12 July 2018

LEAD COMPANY/PARTNER	COMPOUND	INDICATION	COMMENTS
PHASE III RESULTS PUBLISHED			
Novartis AG	*Gilenya* (fingolimod)	chronic inflammatory demyelinating polyneuropathy	FORCIDP; *The Lancet Neurology*, July 2018.
PHASE III INTERIM/TOP-LINE RESULTS			
AbbVie Inc./Johnson & Johnson	*Imbruvica* (ibrutinib) plus chemo	diffuse large B-cell lymphoma	PHOENIX; missed primary endpoint.
Takeda Pharmaceutical Co. Ltd.	*Ninlaro* (ixazomib), post-transplant	multiple myeloma, maintenance therapy	TOURMALINE-MM3; met PFS primary endpoint.
Cassiopea SPA/Cosmo Pharmaceuticals NV	*Winlevi* (clascoterone)	acne	Met endpoints.
Celgene Corp./Acceleron Pharma Inc.	luspatercept	beta-thalassemia, transfusion dependent	BELIEVE; met primary and secondary endpoints.
CTI BioPharma Corp./Servier SA	*Pixuvri* (pixantrone) plus rituximab	B-cell non-Hodgkin's lymphoma	Missed PFS primary endpoint.
KemPharm Inc.	KP415	ADHD in children	Met primary and secondary endpoints.
Zogenix Inc.	ZX008 (low-dose fenfluramine)	Dravet syndrome	Met primary and secondary endpoints.
PHASE III INITIATED			
Quark Pharmaceuticals Inc.	QPI-1002	acute kidney injury after cardiac surgery	QRK309; siRNA targeting p53.
Seattle Genetics Inc./ Astellas Pharma Inc.	enfortumab vedotin	bladder cancer	EV-301; in advanced disease.
Zynerba Pharmaceuticals Inc.	ZYN-002 (cannabidiol)	fragile X syndrome	CONNECT-FX; in children.
Janssen R&D LLC/MorphoSys AG	*Tremfya* (guselkumab)	Crohn's disease	GALAXI; in moderate to severe disease.
Orion Pharma	levosimendan, oral	amyotrophic lateral sclerosis	REFALS; to enhance lung function.
PHASE III ANNOUNCED			
Catabasis Pharmaceuticals Inc.	edasalonexent	Duchenne muscular dystrophy	POLARIS; in children aged 4-7 years.
PHASE II INTERIM/TOP-LINE RESULTS			
Oyster Point Pharma Inc.	OC-02	dry eye, nasal spray	PEARL; improved symptoms, well tolerated.
GlaxoSmithKline PLC/Dermavant Sciences Ltd.	tapinarof	atopic dermatitis	Symptoms improved.
resTORbio Inc.	RTB101	respiratory tract infections	Reduced infections in the elderly.
PhaseBio Pharmaceuticals Inc.	PB1046	pulmonary arterial hypertension	Signs of efficacy, well tolerated.
Scynexis Inc.	SCY-078	fungal infections	DOVE; effective, well tolerated.
PTC Therapeutics Inc.	*Translarna* (ataluren)	Duchenne muscular dystrophy	Improved symptoms in young children.
BioArtic/Eisai Co. Ltd.i/Biogen Inc.	BAN2401	Alzheimer's disease	Slowed disease progression.
Regulus Therapeutics Inc./Sanofi	RG-012	Alport syndrome	Encouraging clinical results, but animal tox. concerns.

Source: Biomedtracker

EUSA CEO Says Divestment Gives It Funds, Clears Way For Cancer And Rare Disease Focus

STEN STOVALL sten.stovall@informa.com

UK-based **EUSA Pharma** says it can now concentrate solely on developing its two oncology assets while hunting for new ones after agreeing to sell its critical care portfolio to Belgium-based **Laboratories SERB** (SERB) for an undisclosed sum.

Lee Morley, EUSA Pharma's chief executive officer, told *Scrip* the deal "now lets us focus on our oncology assets without distraction."

He said the divestment was also good for SERB as it broadened the privately held group's portfolio of medicines for rare and life-threatening diseases and confirmed the company's ambition to grow its positioning as a key specialty pharma player covering niche indications. The agreement is subject to customary closing conditions and the companies anticipate completion in the third quarter of 2018.

The UK-based biotech, established just three years ago, will now have two pivotal assets: *Fotivda* (tivozanib) which has been approved in Europe for treating advanced renal cell carcinoma, and *Qarziba* (dinutuximab beta) which has EU approval for treating high risk neuroblastoma in children.

The announced divestment by EUSA of its critical care unit to SERB coincided with the approval of Qarziba by the National Institute for Health and Care Excellence (NICE) to treat children with high-risk neuroblastoma.

"We're delighted with the NICE decision as Qarziba will now be fully reimbursed in the UK," CEO Morley said. He added that EUSA was now preparing the Qarziba BLA for filing in the US later this year.

Its other key asset, Fotivda, won approval in Europe in August last year and was backed by NICE in February as a first-line treatment option for advanced renal cell carcinoma. It is also currently reimbursed in Germany and Austria. On July 9 it was also approved by the Scottish Medicines Consortium (SMC).

"We will launch Fotivda in the Netherlands in the coming weeks and expect to be launched across the other major markets in Europe - France, Italy and Spain - by the end of this year," Morely said.

Fotivda is an oral, once-daily, potent selective vascular endothelial growth factor receptor tyrosine kinase inhibitor (VEGFR-TKI) that works by reducing the supply of blood to the tumour to deny it food and oxygen. EUSA licensed certain rights to the drug from US-based **Aveo Pharmaceuticals Inc.** in 2015.

CEO Morley said EUSA would now drive and grow its oncology franchise, both organically and through in-licensing, partnering and acquisition. He said proceeds from the divestment to SERB would help fund that strategy. He did not divulge what SERB paid for EUSA's critical care business.

"We are looking for more products in oncology and rare disease addressing high unmet need and which are differentiated from other products already on the market. Meanwhile we'll drive our pipeline assets - Fotivda and Qarziba - into other indications, both within the broader indication and outside that."

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Ex-Zealand Pharma head ***David Horn Solomon*** is joining ***Silence Therapeutics*** as its new CEO, effective immediately. Solomon was also the CEO of Bionor Pharma and Akari Therapeutics, and was the managing partner of Nordic healthcare fund, Sund Capital. He has earlier served as a faculty member at Columbia University's College of Physicians and Surgeons in New York City. Commenting on Silence's propsects, Solomon said he was "particularly impressed" with the near-term opportunities, including the lead program in iron overload disorders which is progressing toward clinical trials.

Malin Corporation plc has appointed ***Ian Curley*** as chairman, effective immediately. Curley has had a long career in business and was most recently the CEO of Ardagh Group, which is listed on the NYSE. Malin also appointed healthcare executives ***Jean-Michel Cosséry*** and ***Rudy Mareel*** as non-executive directors. Each of ***Owen Hughes***, ***Bob Ingram***, ***Darragh Lyons***, ***Kieran McGowan*** and ***Donal O'Connor***, will step down from the Malin board with immediate effect.

Merck KGAA has hired ***Maria Rivas*** as senior vice president, head of global medical affairs. Rivas brings significant medical affairs experience leading large teams across a breadth of therapeutic areas at major global pharmaceutical companies including Merck, Sharpe and Dohme (MSD), AbbVie, and Bayer and Eli Lilly. To support Merck's pipeline, focused on oncology, immuno-oncology and immunology, Rivas will be responsible for bridging the efforts in R&D and commercialization of products, most importantly for several new product launches on the horizon.

APEIRON Biologics, a company focused on cancer immunotherapy, has promoted CFO ***Peter Llewellyn-Davies*** to the position of CEO, following the retirement of ***Hans Loibner***. Most recently, Llewellyn-Davies worked for cancer immunotherapy companies Medigene and Wilex, now Heidelberg Pharma. ***Manfred Reichl***, chairman of APEIRON's Supervisory Board said of Loibner's career at the biotech: "He hands over a company with a promising and innovative clinical development pipeline in the field of cancer immunotherapies."

Respiratory delivery specialist **Vectura Group plc**, has hired ***Paul Fry*** from T Cell Receptor biotech Immunocore to be its new CFO and executive director with effect from 29 October 2018. Fry succeeds Andrew Derodra who leaves the Group and Board on 31 July 2018. Interim arrangements from within the Vectura group are in place ahead of Paul joining the company. Prior to Immunocore, Fry worked at Vodafone and at GlaxoSmithKline for more than 25 years, where he where he held a number of senior roles including head of global finance services and as CFO for GSK's Italian pharmaceutical business.

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