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Takeda Pinpoints Four Infectious Diseases Under Vaccines Strategy

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Takeda Pharmaceutical Co. Ltd. has been developing and producing vaccines for over 70 years but more recently the company has formed a specialized, global vaccine business unit with the mission of developing novel vaccines to address global infectious disease threats.

A growing entity, Takeda's vaccine business is keen to use its "agility" and "flexibility" to discovery new vaccines fast, according to senior vice president of the group's global medical office, Gary Dubin.

Dubin, who spent 20 years at **GlaxoSmithKline PLC** before making a move to Takeda in 2015, is preparing Takeda's vaccine business to be able to react rapidly to emerging global health threats like the Zika virus. "We're not trying to tackle every disease or a very broad range of diseases," he told *Scrip*, adding that the R&D unit is currently focused on four key vaccine programs.

Takeda's vaccine unit is targeting Zika, norovirus, dengue fever and polio. There are currently no approved vaccines for Zika or norovirus and Dubin hopes to see Takeda lead the charge in these research areas. Based in Zurich, Dubin already has experience of bringing a first-of-its-kind vaccine to market, having led development of GSK's globally used human papilloma virus inoculation, *Cervarix*.

"Takeda's focus, coupled with the small size of the vaccines unit, makes us pretty agile," Dubin said. "There are now diseases that develop rapidly and being able to respond quickly to these threats is one of the challenges we developers currently face," he said.

Dubin is also the global program team lead for Takeda's Zika vaccine program – which is yet to enter the clinic. He believes progress for this candidate will be rapid. "Even though we are still in preclinical development with our Zika vaccine, because of the program that we've designed, we expect this vaccine to move very quickly once we initiate clinical development," he said. Clinical studies for Takeda's Zika vaccine will start before the end of 2017, Dubin noted.

Meanwhile, Takeda is also exploring a vaccine program for norovirus, the most common cause of acute gastroenteritis across all ages. "It's actually a very interesting virus in that it is one of the few bugs that essentially affects every individual on earth," Dubin said.

Takeda has a vaccine candidate in Phase IIb development for norovirus. It was the first company to launch a human trial for a norovirus preventive treatment and it is currently running the first field efficacy trial for a norovirus product with an FDA investigational new drug designation.

Dubin highlighted the biggest challenge of designing a clinical study for such an unpredictable virus: "There are frequent outbreaks of norovirus that occur all over the world. There is a bit of seasonality to it but it's difficult to predict where norovirus will strike next."

To address this issue, Takeda is running its Phase IIb proof-of-concept efficacy study in a naval base in the US. Dubin added that the military has a long-standing interest in norovirus because it is something that can sweep through military bases, disabling large proportions of its troops.

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Market Intelligence
Lupus pipeline showing signs of renewal following disappointments (p6)

Titans Of Pharma
A snapshot of the industry's top leaders and their businesses (p12)

from the editor

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Scrip took a look at the leadership of the industry's biggest companies, and found out that the CEOs of the top 15 firms received more than a quarter of a billion dollars' worth of overall compensation in 2016. It sounds a lot, but a fair bit is in stock options, and it should be noted that those same firms reported nearly $100bn in net income and had a combined market capitalization of around $2.2 trillion.

In the broader context, no pharma executive came close to US cable company Charter Communications' CEO Thomas Rutledge, who got $98.5m (although this was boosted by a five-year stock option award that won't be repeated before 2020). Nor did any of the top 15 firms award their leaders as much as Regeneron Pharmaceuticals' Leonard Schleifer received ($28.3m, down from $47.5bn in 2015 reflecting a dip in the number of options awarded as well as a larger decline in their value as the company's share price sagged).

It is refreshing to see a woman join the ranks of the titans for the first time, although it is too soon to know if Emma Walmsley's compensation for leading GlaxoSmithKline will measure up to that of her male counterparts. Her predecessor, Sir Andrew Witty, was actually quite modest in his takings with just £6.8m last year.

To see more details on 10 of the leading companies' leaders, along with information on R&D heads, turn to p12-13, or visit our website to view the full 15 "Titans of Pharma".

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ALCYONE Paves Way For J&J/Genmab's Darzalex In Frontline Myeloma
http://bit.ly/2vomjrJ

Data supporting a role for J&J/Genmab's anti-CD38 monoclonal antibody in newly diagnosed multiple myeloma are "as good as could be expected," but the backbone regimen in the trial is rarely used in the US.

Trial And Trial: Bracing For Commercialization Of Cell & Gene Therapies
http://bit.ly/2xGnPCd

As novel cell and gene therapies edge closer to the US market, reimbursement for expensive, long-lasting treatments remains uncertain. AmerisourceBergen Senior VP-Strategy & Commercialization Amy Grogg predicts the first launches will involve many different reimbursement models.

Eisai Fortifies Play With India-Specific Priced Fycompa
http://bit.ly/2vAMbg0

Eisai expects products like *Fycompa* and *Lenvima*, backed by innovative price planks pivoted around improving patient access, to intensify growth in India. Fycompa now debuts at a sub-$1 per day pricing in India.

China Investment Roundup: A Summer Of Cross-Border Transactions
http://bit.ly/2xJh0zQ

It was a busy summer for Chinese pharmaceutical companies and investors who went global shopping, eying mega acquisition deals since China announced plans to accept overseas clinical trial data and global multicenter studies as part of its policies.

Pharma Calls On UK Govt To Fund Centers of Excellence
http://bit.ly/2vo82eJ

The Medicines Manufacturing Industry Partnership says £140m invested in four centers would provide high-skilled jobs and make the UK the first place in the world where drugs can be discovered, made and packaged.

Duzallo Approval Opens Gout Opportunity For Ironwood
http://bit.ly/2vA78rt

Pricing for *Duzallo*, a fixed-dose combination of *Zurampic* (lesinurad) with generic allopurinol, will likely be on par with Zurampic's solo price tag of $371 per month to smooth the way with payers.

inside:

AZ Makes Fresh mRNA Move With Ethris Respiratory Pact

KEVIN GROGAN kevin.grogan@informa.com

AstraZeneca PLC is expanding its presence in the messenger RNA space through a collaboration with German biotech **Ethris GMBH** that will focus on its core respiratory area.

The five-year deal will see the companies develop new stabilized non-immunogenic modified (SNIM) RNA therapies for respiratory diseases using Ethris' proprietary technology. The plan is to find multiple new targets for investigation in asthma, chronic obstructive pulmonary disease and idiopathic pulmonary fibrosis.

Cashwise, Munich-based Ethris will receive €25m upfront plus research funding and is eligible for R&D milestones and royalties. AstraZeneca, through its R&D biologics unit MedImmune, will have the option to take exclusive worldwide licenses for each target covered within the collaboration.

AstraZeneca is no stranger to mRNA, which involves delivering genetic instructions to cells which drive the target cells to produce selected proteins to help prevent or fight diseases, having been in partnership with **Moderna Therapeutics LLC** since March 2013. Its original deal with the privately held US biotech, which focused on cardiovascular, metabolic and renal diseases as well as cancer and involved an upfront payment of $240m, plus a potential extra $180m for the achievement of three technical milestones.

That pact was expanded in January 2016 to include two specific immuno-oncology programmes and in August last year, AstraZeneca increased its stake in Moderna with a $140m investment. That brought its holding in the latter to around 9%. *(Also see "Biopharma Unicorn Moderna Highlights Secretive Pipeline As Investors Await IPO" Scrip, 16 Jan, 2017.)*

However, it seems that AstraZeneca believes that Ethris is the best mRNA partner when it comes to respiratory. The latter's technology can be targeted to the lungs where it helps to replace, inhibit or augment proteins that are involved in causing or exacerbating respiratory disease, and it is hoped that mRNA-based therapeutics may also modify the course of the disease or its symptoms.

Bahija Jallal, executive vice president at MedImmune, noted in a statement that "rapid advances over the last decade have made mRNA a very promising tool for clinical application, and we are excited to collaborate with Ethris, whose advanced platform is leading in RNA delivery to the lung". She added that the pact "complements our respiratory science focused on early intervention and disease modification by adding novel ways to target disease mechanisms that cannot be addressed by other approaches currently in our pipeline."

Most mRNA research has focused on vaccines and Ethris claims that historically it has not been usable as a therapeutic agent because when delivered into the body it activates the immune system and is highly unstable. In addition, in order to be functional, mRNA must enter the target cells of interest by crossing the cell membrane, which requires a carrier system to transport it into them.

The German group, founded in 2009, says its technology can deliver candidates which "overcome the innate instability and immunity of mRNA [as] they evade the innate immune system due to chemical modifications in their building blocks". Ethris also notes that its SNIM RNAs can be administered repeatedly, leading to sustained production of therapeutically active proteins within the body.

RESPIRATORY KEY PLATFORM

Given AstraZeneca's travails in oncology, highlighted by the failure of its PD-L1 inhibitor *Imfinzi* (durvalumab) in the high-profile Phase III MYSTIC trial to hit the PFS endpoint in non-small cell lung cancer, the Ethris deal is a timely reminder that respiratory is a key platform in AstraZeneca's long-term growth plans. Its blockbusters *Symbicort* (budesonide/formoterol) and *Pulmicort* (budesonide) are still selling well despite being battered by generic competition but there is pressure on the targeted late-stage asthma products benralizumab and tralokinumab to offset the patent losses.

The pressure increased in May when tralokinumab failed the Phase III STRATOS 1 study in severe asthma patients inadequately controlled despite receiving inhaled corticosteroids plus a long-acting beta2-agonist. However, AstraZeneca still has high hopes for the drug in a sub-population of patients with an elevated biomarker associated with increased IL-13 activity.

Analysts believe benralizumab has a better chance of success. Datamonitor Healthcare's PharmaVitae team forecasts that the interleukin-5 inhibitor will see greater uptake than other late-phase biologics for the treatment of asthma and it will generate revenues of $2.4bn by 2025. They think benralizumab has a faster onset of action compared to **GlaxoSmithKline PLC**'s *Nucala* (mepolizumab) and **Teva Pharmaceutical Industries Ltd.**'s *Cinqair* (reslizumab), the two IL-5 biologics that reached the asthma market in late 2015 and early 2016.

Further down the respiratory pipeline, AstraZeneca recently entered into a deal with **Pieris Pharmaceuticals Inc.** to develop inhaled products based on the latter's *Anticalin* technology. *(Also see "AstraZeneca Taps Pieris For Inhaled Asthma Anticalins" Scrip, 3 May, 2017.)*

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Inside The Lupus Pipeline: Reasons For Optimism

JESSICA MERRILL jessica.merrill@informa.com

The lupus drug development landscape is showing signs of renewal after a string of disappointments, with several new drugs for systemic lupus erythematosus (SLE) and lupus nephritis (LN) moving through mid-to-late stage development. Big pharmas like **AstraZeneca PLC**, **Johnson & Johnson** and **Roche**'s **Genentech Inc.**, as well as smaller companies like **Aurinia Pharmaceuticals Inc.** and **Corbus Pharmaceuticals Holdings Inc.** are pushing ahead in lupus, despite considerable challenges.

"From my perspective, this is the best time ever for development of new therapies for lupus," Lupus Foundation of America CEO Sandra Raymond said in an interview. "I would say that right now there is probably over $1bn and closer to $2bn being spent in this field. My glass is half-full. I feel really optimistic about the landscape for lupus development."

Other experts working in the field of lupus agree. "I'm amazed by how much interest there is. There's got to be probably 20 to 30 drugs in development for lupus," said lupus specialist Richard Furie, chief of the division of rheumatology at Northwell Health and an investigator in several lupus trials.

Biomedtracker lists more than two dozen drugs in Phase II or Phase III development for systemic lupus erythematosus (SLE) and lupus nephritis (LN).

"I'm quite encouraged about the state of the field," added Jeffrey Siegel, who as an FDAer helped develop the agency's lupus guidance document and now works at Genentech as global head of rheumatology and rare diseases and immunology product development.

Lupus has been almost an anomaly in autoimmune disease, where the drug industry has invested heavily over the last two decades and where diseases like rheumatoid arthritis, psoriasis and ulcerative colitis have seen dramatic improvements. Lupus, however, has seen little in the way of new therapeutics in the last 50 years. **GlaxoSmithKline PLC**'s *Benlysta* (belimumab) is the one exception. It was approved by the FDA in 2011 with a lot of fanfare, given the high unmet medical need, but the FDA approval in a narrow indication in just a subset of patients with SLE and moderate efficacy in clinical trials didn't result in the blockbuster GSK had been hoping for.

Benlysta even today remains a niche product, though growing double digits and GSK continues to invest behind it, including new trials in lupus nephritis, in pediatric patients and in combinations, as well as a recently launched new subcutaneous formula. But given the prevalence of the disease and the substantial unmet need in lupus, many drug makers are enthusiastic about the opportunity. Experts insist it is a blockbuster market opportunity.

There are many subsets of lupus, but at the core of the disease is a hyperactive immune system that attacks the body's healthy cells. SLE is a chronic disease that waxes and wanes and can result in chronic fatigue, joint pain, skin flushes or organ damage. LN is a more acute subset of lupus, when the disease targets the kidneys and can lead to kidney failure. There is also cutaneous lupus erythematosus, a form of lupus that impacts the skin. Many researchers working in the field suspect lupus might be sub-segmented even further as drug makers learn more about the disease.

LEARNING FROM EXPERIENCE

The heterogeneity of lupus has been one of the biggest challenges to drug development. As Genentech's Siegel explained it, "We know in lupus there are a number of different processes that drive disease activity. We know that B cells are important. We know that different cytokines are important and we know that certain cells are important, antibodies and cytokines. We don't know for sure which ones are on a critical path to driving disease activity."

The challenge is figuring out the critical processes that are driving disease activity and developing therapeutics to target them.

Some learnings from the development and experience with Benlysta have helped advance the field, and the same is true for some drugs that failed in clinical development. Benlysta is a first-in-class BLyS-specific inhibitor that blocks the binding of soluble BLyS, a B-cell survival factor, to its receptors on B-cells. By binding to BLyS, Benlysta inhibits the survival of B cells including autoreactive B cells. Some drug makers are also evaluating B-cell depleting strategies.

"For many years, these insights have been building," said GSK clinical development leader Raj Punwaney. "It's understanding all these areas, B-cells, T-cells, innate immunity that has started to come to fruition over the last decade or so, and I think that is certainly why we have seen many different assets coming forward and being tested in the clinic now."

DEPLETING B-CELLS

Genentech is studying *Gazyva* (obinutuzumab), approved for chronic lymphocytic leukemia and follicular lymphoma, for the treatment of lupus nephritis in the Phase II NOBILITY trial. Gazyva is a monoclonal antibody that targets the CD20 antigen expressed on the surface of B-lymphocytes.

Genentech already tested its first-generation CD20 B-cell depleting therapy *Rituxan* (rituximab) in lupus, but announced disappointing results in 2009.

"We didn't get the results we were hoping for, but we did get a lot of learnings from that, and we've used that in developing our new program with lupus nephritis and NOBILITY," Siegel said.

Obinutuzumab depletes B-cells in a different way that could be more effective at addressing the driver of disease activity, he said. "Obinutuzumab has been shown to deplete B-cells in tissues and not just in peripheral blood. We understand from experimental models that obinutuzumab depletes B-cells in lymph nodes, which is important in an immune response in lupus and is one of the reasons we think obinutuzumab is particularly promising for lupus nephritis."

ANIFROLUMAB IMPRESSES

Other drug companies are exploring different mechanisms of action. AstraZeneca is one of the current leaders in the field, with a drug called anifrolumab currently in Phase III testing. Anifrolumab is a monoclonal antibody against the type I interferon (IFN) receptor that inhibits the activity of all type I IFNs, which play a role in lupus. The positive results of a Phase II trial testing anifro-

lumab in SLE were published in *Arthritis and Rheumatology* in November 2016, showing the study met its primary and secondary endpoints with treatment with anifrolumab resulting in significantly greater rates of improvement across a broad range of composite and organ-specific disease activity measures (SLE Responder Index 4), as well as reduction in oral corticosteroid use, compared with placebo.

"I'm truly very excited about their Phase II results. I think the entire lupus key opinion leader community was very excited," Lupus Foundation of America's Raymond said.

Furie, who was the principal investigator in the Phase II trial, noted that "the Phase II data were the best clinical trial data we've ever seen in lupus, especially for patients with rash."

Datamonitor Healthcare forecasts that anifrolumab will see the highest uptake of new targeted therapies in the US and EU by 2022.

AstraZeneca has initiated two Phase III trials, with enrollment already completed in the first trial and the second one expected to be fully enrolled later this year. AstraZeneca is targeting a regulatory filing for anifrolumab in 2019.

"We modeled our Phase III trial very similarly to the Phase II trial," Raj Tummala, the global clinical lead for anifrolumab told *Scrip*. "One of the key learnings that we learned in Phase II was that site selection was really critical. You have to include sites that really understand lupus, so we built that into our Phase III program." One of the biggest differences in the Phase III trials is that the primary endpoint is at one year, versus six months with the Phase II study.

In Phase II, AstraZeneca also narrowed down a subgroup of patients who were more likely to benefit from treatment, those patients with an elevated IFN gene signature at baseline. The company incorporated the same subgroup into the Phase III trials and anifrolumab is being developed with an IFN gene signature test.

"From what we understand, 75% to 80% of lupus patients have type 1 IFN gene signature that is high," Tummala said.

Johnson & Johnson is taking yet another approach, studying its currently marketed *Stelara* (ustekinumab), approved for plaque psoriasis, psoriatic arthritis and Crohn's disease, in a Phase II trial for SLE. The company is also exploring an interferon in an early Phase I trial in lupus, and gained a potential new lupus drug with the acquisition of **Actelion Pharmaceuticals Ltd.** earlier this year, cenerimod, an S1P1 modulator.

"We have a number of early/mid/late compounds in development in immunology that may have relevance to the lupus population," J&J's global therapeutic head-immunology Susan Dillon said.

Celgene Corp. believes SLE is an excellent targeted market for its immunology and inflammation unit to invest in. The company is testing two different approaches early in the clinic.

"In our case, we believe that we have now identified a mechanism that may address multiple disease pathways," I&I president Terrie Curran said. Celgene is testing CC-220 in a Phase II dose-ranging study. It's a novel oral immunomodulatory drug that binds to cereblon, which reduces levels of ikaros and aiolos, two proteins implicated in the development and survival of the immune cells that help cause inflammation in lupus.

Lupus patients have higher than normal levels of ikaros and aiolos and Curran believes that targeting the proteins associated with lupus, instead of the varying physical symptoms, offers the potential to transform the treatment paradigm.

In January, Celgene announced the acquisition of a company called **Delinia, Inc.** for $300m upfront; the company specialized in the development of targeted regulatory T-cell (Treg) therapies to treat immune disorders without suppressing the immune system – and Celgene believes the lead drug candidate, DEL106, could work in lupus and other autoimmune diseases. DEL106 is a novel interleukin-2 (IL-2) mutein Fc fusion protein designed to preferentially upregulate Tregs.

CHALLENGING ENDPOINTS

Another issue for drug developers working in lupus is determining the best clinical trial endpoints to study to show efficacy.

"If you look at several different patients with lupus, they present in completely different ways," Genentech's Siegel said. "One patient may present with skin problems and joint problems, another with kidney problems and joint abnormalities."

"Figuring out ways to study drugs to see if they have benefits for all manifestations of lupus has been quite complicated," he said. Trials typically rely on a composite scale like the Safety of Estrogens in Lupus Erythematosus National Assessment Systemic Lupus Erythematosus Disease Activity Index (SELENA-SLEDAI). The approval of Benlysta was based on two Phase III studies that relied on a novel composite endpoint that was not validated at the time, known as the SLE Responder Index-4 (SRI-4), which GSK and partner **Human Genome Sciences Inc.** developed with the support of the FDA, as a three-component endpoint to capture clinically meaningful changes in disease activity through assessment of clinical manifestations, laboratory values, organ system effects and general health status.

"There are limited regulatory precedents, and the published guidance are very broad," J&J's Dillon said. "Furthermore, the lupus community only recently began to embrace some endpoints, like the SRI, that appear to perform reasonably in trials."

Plus, many patients who participate in clinical trials are on strong background therapy, including antimalarial drugs, corticosteroids and immunosupressants, including Roche's *CellCept* (mycophenolate), which can influence clinical data.

As the clinical trial failures in lupus have mounted, some in the community have begun to believe that the trend is the result of flawed clinical trial design rather than efficacy.

Some drug makers are now focusing on lupus nephritis rather than SLE, partly because of the critical unmet need, but also because the clinical trial design and endpoints in the targeted, organ-specific subset seems more clear cut.

COMBINATIONS A POSSIBILITY

Some experts in the field are starting to think about combining novel targeted agents to deliver a bigger efficacy punch to patients. GSK is already studying Benlysta in combination with Rituxan in Phase III.

"We are very motivated at GSK to try to advance the field of therapy for lupus and that's really the motivation behind the combination therapies," Punwaney said. "We don't want to just make patients feel improved, but help them feel well again."

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View Select Drugs In Mid-Stage Clinical Development For SLE And LN here: http://bit.ly/2wZVY20

Lupus Nephritis May Be As Straightforward As Lupus R&D Gets

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Targeting lupus nephritis could be a more straightforward path to market for new lupus drugs – or at least that is what some drug makers are hoping. Lupus nephritis affects a smaller subset of patients than the more common systemic lupus erythematosus (SLE) and it could have some advantages when it comes to drug development: diagnosis is done by a test, the clinical endpoints are well defined, the condition can be life-threatening, and there are no approved treatments.

Given the high hurdle to developing new drugs for lupus and the high rate of clinical trial failures in the field, some drug makers like **Aurinia Pharmaceuticals Inc.** and **Roche**'s **Genentech Inc.** are hoping that by targeting lupus nephritis, they will have better success.

The drug industry is investing substantially in drug development across the lupus spectrum, with several drugs now moving through mid- to late-stage development. Advancements in the understanding of the autoimmune disease, the unmet need and the multi-billion commercial opportunity are all driving investment.

"I list lupus nephritis as the number one unmet need," said lupus specialist Richard Furie, chief of the division of rheumatology at Northwell Health and an investigator in several lupus trials. SLE is an autoimmune condition in which a hyperactive immune system attacks the body's healthy tissues. It manifests in many ways, targeting the skin, joints and organs. Lupus nephritis happens when the immune system targets the kidneys, which can lead to kidney failure, dialysis or transplantation.

There is some discrepancy over the prevalence of lupus in the US, which some experts say is hundreds of thousands of patients while the Lupus Foundation of America puts much higher at 1.5m. Aurinia believes about 500,000 people in the US have SLE, and as many as 60% of them have clinical lupus nephritis requiring treatment.

A SERIOUS CONDITION WITH TANGIBLE EFFECTS

Aurinia chief medical officer Neil Solomons said the serious nature of lupus nephritis is important because it is so tangible.

"Patients understand it. It's also considered a very severe manifestation of lupus," he said. "Often the very thing they are worried about is lupus nephritis. They can tolerate the fatigue, but the kidney inflammation is going to send them to the hospital."

Genentech's global head of rheumatology, rare diseases and immunology product development Jeffrey Siegel said, "We think lupus nephritis is an area of particular unmet medical need. With current treatment, there is a lot of toxicity."

There are no approved treatments for lupus nephritis, but standard of care is typically intense immuno-suppressants, namely Roche's *CellCept* (mycophenolate mofetil) and corticosteroids.

Aurinia's voclosporin in Phase III and Genentech's *Gazyva* (obinutuzumab) in Phase II are two of the most advanced drugs in development for lupus nephritis. Voclosporin is a novel calcineurin inhibitor that blocks interleukin-2 and T-cell mediated immune responses. Voclosporin is getting some attention after the drug performed well in a Phase IIb study, showing the drug improved complete renal response rate for patients with lupus nephritis relative to the comparator at 48 weeks.

In May, Aurinia initiated a confirmatory Phase III trial, AURORA, that will similarly compare voclosporin to placebo when added to current standard of care with CellCept and corticosteroids, at 52 weeks. The company expects results sometime in 2019.

Gazyva, meanwhile, is a monoclonal antibody that targets the CD20 antigen expressed on the surface of B-lymphocytes. Genentech already tested its first-generation CD20 B-cell depleting therapy *Rituxan* (rituximab) in lupus, but announced disappointing results in 2009. Obinutuzumab depletes B-cells in tissue as well as in peripheral blood, which could make it more effective at addressing the driver of disease activity, he said.

"For lupus nephritis, there are not that many variations on a trial design," Northwell's Furie said. "We have metrics for measuring outcomes in lupus nephritis." Furie is leading Genentech's Phase II trial of obinutuzumab, called NOBILITY.

"It's basically lab tests, proteinuria, blood creatinine, which is a measure of kidney function," he added. But that doesn't mean the area isn't without its challenges. "In a way, it's straightforward. The problem is there are confounding background medicines."

Genentech hopes to ease the issue of concomitant medicines in NOBILITY by permitting lower concomitant doses of corticosteroids and mycophenolate mofetil, though levels that are still consistent with current treatment guidelines, Siegel added.

Lupus Foundation of America CEO Sandra Raymond agreed the background medications can confound trial results. "We've got people on strong background medications in trials where it is very difficult to see the difference between the investigational medication and the background medication they are on," she said.

In the Aurinia Phase IIb clinical trial, the primary endpoint was complete response based on a composite endpoint including: confirmed urine protein/creatinine ratio (UPCR) of less than or equal to 0.5 mg/mg; normal, stable renal function, presence of sustained, low dose steroids; and no administration of rescue medications.

Healthy individuals usually excrete very small amounts of protein in the urine, while increased protein excretion is usually a sign of kidney damage.

Confirming the right patients are enrolled in clinical trials for lupus nephritis is also more straightforward than trials for SLE because diagnosis is confirmed with a biopsy.

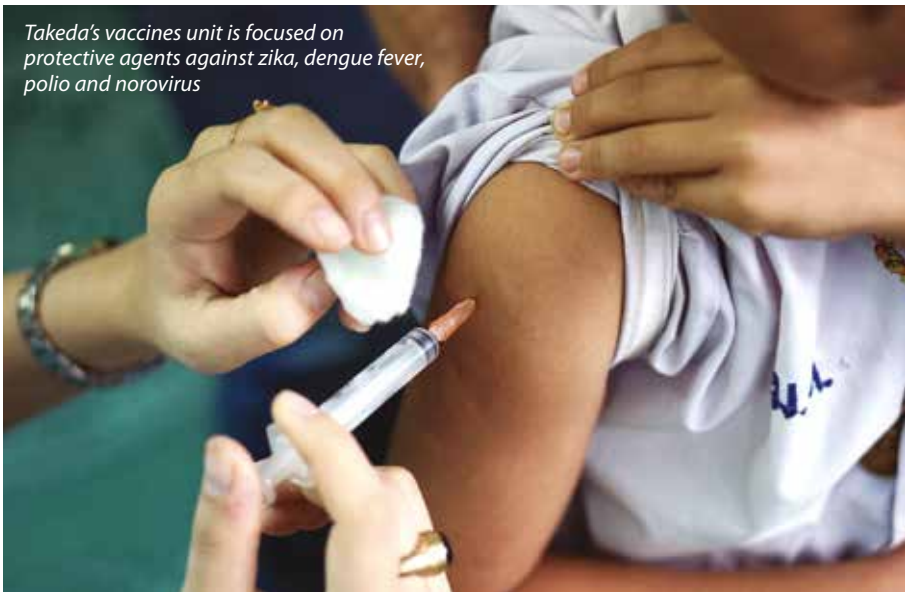
"From our perspective as drug developers, lupus nephritis is easy to diagnose," said Auinia's Solomon. "That doesn't mean it is common or really obvious. It means the diagnoses of lupus nephritis has been well described. You have to have lupus, but you also have to have a kidney biopsy. There's no similar diagnostic test for lupus of the joints."

All of this is not to say there aren't significant challenges to developing new drugs for lupus nephritis, but the focus could pay off and enhance the understanding of lupus more broadly.

Published online 22 August 2017

CONTINUED FROM COVER

"It is difficult to design these studies, to some extent you're at the mercy of the fickle epidemiology," he said. Takeda will await the results of its Phase IIb field efficacy trial before determining the next steps for its norovirus vaccine.



Takeda's vaccines unit is focused on protective agents against zika, dengue fever, polio and norovirus

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> 'One of the critical steps in the eradication of polio is going to involve the transition from live oral polio vaccine to inactivated polio vaccine'

UNMET NEEDS IN POLIO & DENGUE

Takeda's other two disease targets – dengue fever and polio – do have available vaccine treatments, but the company believes it can fill gaps in these markets with its candidates.

In polio, the vaccine unit is developing an inactivated inoculation – a program that is being funded via a grant from the Bill and Melinda Gates Foundation. "Efforts to eradicate polio have evolved over many, many years and to-date we still have not eradicated the disease, although we are getting closer and closer to this goal," Dubin noted. "One of the critical steps in the eradication of polio is going to involve the transition from live oral polio vaccine to inactivated polio vaccine."

Dubin highlighted that there was a global shortage of inactivated polio vaccines. Takeda is working with the Gates Foundation and other public health agencies to develop this vaccine quickly, with the goal of producing at least 50 million doses a year for a period of five years. "We think this will make major inroads into addressing the shortage of inactivated polio vaccine and really help the polio eradication endgame," he said.

In dengue fever, Takeda is developing a vaccine it hopes can be used in younger patients than the current option on the market. **Sanofi's** world-first dengue vaccine, *Dengvaxia*, is currently approved for use in people aged nine and over. Takeda hopes its vaccine candidate will be indicated for use in those as young as four. The company recently completed enrollment for a Phase III pivotal trial that includes children between the ages of four and sixteen. Dubin also noted that in earlier-stage trials, Takeda's dengue vaccine has shown a balanced response across the four dengue serotypes.

He believes dengue will be Takeda's most important vaccine in the coming months, as the company progresses through late-stage development. "There is a large burden of dengue disease in children below the age of nine, so we think population is going to be a very important target for our program."

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Akari To Reboot Tick-Based Group's Prospects

Akari Therapeutics PLC has hired David Horn Solomon, the former CEO of Denmark-based **Zealand Pharma AS**, and given him the challenge of restoring investor trust in the NASDAQ-listed biotech while also designing how to best progress its drug pipeline of tick-derived molecules.

Solomon – who as CEO of Zealand oversaw the development of lixisenatide which is now commercialized by **Sanofi** as *Lyxumia/Adlyxin* – will take on his new role based in New York City from Aug. 28. Solomon had also been the CEO of **Bionor Pharma ASA** and until his appointment at Akari was the managing partner of Sund Capital, a Nordic healthcare investment fund.

Akari's lead molecule is *Coversin*, a recombinant small protein (16,740 Da) derived from a native protein discovered in the saliva of the *Ornithodoros moubata* tick. The protein modulates the host immune system to allow the parasite to feed without alerting the host to its presence or triggering an immune response. Coversin is currently in ongoing Phase II trialing in the rare blood disease paroxysmal nocturnal hemoglobinuria (PNH).

In an interview with *Scrip* in February, Akari's former CEO Gur Roshwalb explained the science behind Coversin and its use of the human immune system's complement system, and why, if successful, the second-generation complement inhibitor would compete with **Alexion Pharmaceuticals Inc.**'s very expensive *Soliris* (eculizumab), currently the only approved complement C5 inhibitor. But Roshwalb was forced to resign three months later after an internal review was conducted amid controversy and litigation launched by Akari shareholders, a storm that also pulled down the biotech's share price.

sten.stovall@informa.com 22 Aug 2017

Sanofi-Backed Voyager Therapeutics Hails Gene Therapy's Arrival

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After many starts and stops, US-based **Voyager Therapeutics Inc.**'s CEO Steven Paul believes gene therapy is finally here.

With a focus on neurological diseases and an ongoing collaboration with **Sanofi**'s **Genzyme Corp.**, Voyager is a gene therapy company developing therapies for Parkinson's disease, a monogenic form of amyotrophic lateral sclerosis (ALS), Huntington's disease, Friedreich's ataxia, frontotemporal dementia, Alzheimer's disease and severe, chronic pain. Its furthest-developed program is VY-AADC01 for Parkinson's in Phase Ib, for which data are expected shortly.

Voyager was founded in 2014 and over the years stacked up $285m, with cash from Series A and Series B private-round investments (totaling $105m) in 2014 and 2015, the collaboration with Genzyme ($100m up front in cash and equity) and the completion of an $80m IPO in 2015. The company hopes to advance not only the Parkinson's program into Phase II early next year, but another of its programs into the clinic by 2018/2019.

Like many gene therapy companies, Voyager is using adeno-associated virus (AAV) as a delivery vehicle. Late last year, Voyager obtained a co-exclusive license to California Institute of Technology (Caltech)'s AAV capsids technology, which has demonstrated enhanced crossing of the blood brain barrier, a feature that can improve central nervous system diseases drug delivery.

Paul says problems with the safety and efficacy of vectors have been why the gene therapy field has taken so long to bear fruit. Advances here, and in the understanding of the genetic underpinnings of certain diseases, mean that the field is now making headway.

"It looks like gene therapy is finally here and we want to be a big part of that," Paul said. "It is a whole new genre of medicine."

PARKINSON'S PROGRESS

Currently there are no approved therapies that can reverse the progression of Parkinson's disease, which is characterized by a loss of neurons in the brain that produce the neurotransmitter dopamine. As levels of this neurotransmitter drop, motor symptoms, such as tremors, slow movement or loss of movement and rigidity, increase. Parkinson's patients have reduced levels of the enzyme, aromatic L-amino acid decarboxylase (AADC), that converts precursor levodopa into dopamine.

Voyager's lead product VY-AADC01, currently in Phase Ib and one of the programs Sanofi has opt-in rights to and is heavily involved with, uses the AAV-2 capsid delivery system and a cytomegalovirus promoter to encourage the expression of AADC. Paul emphasized that this is set to be a 'one-time' treatment, will be surgically administered and has the potential of enhancing the conversion of levodopa to dopamine, thereby improving symptoms.

In Dec. 2016, Voyager announced positive interim results from the Phase Ib trial. Paul explained that the study has three cohorts in this trial, with the dosage increasing in each and so far, they have observed improvement in motor symptoms in the first two cohorts. He added that it is their aim to reduce the patients' need to take high doses of levodopa, something that was also observed in the study so far.

"By giving this gene that allows the brain region to start producing dopamine again, one of the goals is to get the dose of the levadopa down and in cohort two, it went down by 35%."

With cohort three a higher dose of gene therapy, the company is hoping for even better results to announce by the end of September.

Voyager plans to start a pivotal registration trial at the end of this year and Paul explained that they will be structuring the trial in an "interesting way". The company expects to start dosing patients for a 'small' Phase II study early next year and will measure the relevant biomarkers before and after administration of the gene therapy. If this brings positive results, Voyager will file a BLA submission for approval, based on that trial, with the following Phase III a confirmatory study.

"We believe we only need one good trial to get this therapy approved by the regulators, the FDA," Paul said. "In the event we should learn something in the Phase II study, that will readout before the Phase III is locked meaning we can change the endpoint based on what we learn, avoiding the risk of starting over."

Voyager is not the only gene therapy company hoping to get a 'one-shot' gene therapy approved, **Oxford BioMedica PLC** is using its *LentiVector* delivery system to produce not one, but three enzymes, including AADC and another that makes levodopa, to increase dopamine levels and reverse symptoms.

Paul described this system as a "more challenging strategy" and one that could be difficult to regulate. "You'd want to reduce the possibility of overreaction and overstimulation of the dopamine receptors," he said, and Voyager's technology is built in a way that the level of levodopa, the substrate for AADC, can be regulated just by controlling the oral dose of levodopa.

OTHER PROGRAMS

In addition to its Parkinson's program, Voyager also has various other products in preclinical development, including VY-S0D101 for monogenic ALS, VY-HTT01 for Huntington's disease, VY-FXN01 for Friedreich's ataxia, VY-TAU01 for frontotemporal dementia/Alzheimer's disease and VY-NAV01 for pain. Although Voyager is handling the main aspects of these programs, Sanofi may opt-in to the Huntington's and Friedreich's programs.

These diseases are caused by mutations that enhance the activity of a protein (known as gain of function) that can be toxic and Voyager aims to use its one-time therapy to silence them. Treatments for these diseases differ from the Parkinson's therapy in that they are made up of the AAV and a transgene with a micro-RNA (miRNA) that selectively silences or knocks down the offending gene.

Voyager is open to partnerships, particularly with those companies that have the right scientific capabilities and an interest in CNS drug development, especially in Alzheimer's disease, Paul said.

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AC Immune Beefs Up Neurodegenerative Pipeline

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Antibodies targeted against pathological processes in one neurodegenerative disease might be effective in other diseases, including Alzheimer's, according to the Swiss biotech **AC Immune SA** which is beefing up its early discovery pipeline with such "next-generation" antibodies.

AC Immune uses a proprietary technology, *SupraAntigen*, that displays antigens on the surface of liposomes and is thought to be ideal for producing antibodies for the treatment of diseases like those of the CNS caused by pathological proteins that differ only slightly from healthy proteins, i.e., they have different shapes or are not folded in the correct manner.

"We can quickly identify molecules that are directing the disease state. I am hoping the molecules will have the disease-modifying properties we are looking for," said Andrea Pfeifer, CEO of the Lausanne, Switzerland-based company, which completed an IPO on US NASDAQ just over a year ago. *(Also see "IPO Update: Novan, AC Immune End Summer Slowdown As Market Improves" Scrip, 29 Sep, 2016.)*

Pfeifer is not downhearted by other companies' failed investigational products in neurodegeneration, saying she is "absolutely convinced we will be seeing some positive data coming out of this research." The European company executive is not alone in having that conviction: pharma companies like **Biogen** and **Roche** are also continuing to pursue research into antibodies and other molecules in Alzheimer's disease *(Also see "Alzheimer's Update: Amyloid Hypothesis Lives On At Biogen, Lilly, Merck, Pfizer, Roche" Scrip, 11 Dec, 2016.)*.

Even **Eli Lilly & Co.**, which was dismayed by the failure of solanezumab in Phase III studies, has more recently reported the start of Phase I studies with a new antibody selective for amyloid beta-42, MEDI1814, in collaboration with its partner **AstraZeneca PLC.**

The new antibodies made by AC Immune are targeted against alpha-synuclein, a well-established target in Parkinson's disease and other Lewy body diseases, and against TDP-43 (TAR DNA binding protein 43), a recently identified target of interest in neuro-orphan indications such as frontotemporal lobar degeneration. The antibodies bind to the pathological forms of alpha-synuclein and TDP-43, and as these targets may also play a role in other neurodegenerative diseases like Alzheimer's disease, the antibodies may be useful in those diseases too.

A THREE-PILLAR STRATEGY

AC Immune is pursuing what it is calling a three-pillar strategy. "We have Alzheimer's disease as one major pillar, the next is neurodegeneration and neuro-orphan indications, and the third is diagnostics," Pfeifer noted. Diagnostic products in particular are considered key for future growth of the company: "they enable clinical trials in the other two pillars, and are a means of creating revenues in partnerships with other companies." AC Immune is collaborating with **Genentech Inc.** (Roche) which is conducting two Phase III studies (CREAD1 and CREAD2) with the Swiss company's Abeta antibody, crenezumab, in patients with prodromal or mild Alzheimer's disease, with CREAD1 expected to read out in 2020.

> The antibodies bind to the pathological forms of alpha-synuclein and TDP-43

Since the IPO, AC Immune has reported encouraging data on a potential anti-Abeta therapeutic vaccine, ACI-24, that is in early clinical studies. And next year AC Immune expects to have interim Phase Ib data on the use of ACI-24 for addressing Alzheimer's in people with Down's syndrome who have a higher risk of developing the disease.

Also in early clinical studies is ACI-35, an anti-pTau therapeutic vaccine for Alzheimer's disease being developed in collaboration with **Janssen Biotech NV**, and an anti-Tau antibody, R07107505, for Alzheimer's disease in development with Genentech, with the later expected to enter Phase II studies in the coming months.

Published online 25 August 2017

TITANS OF PHARMA

A snapshot of the industry's top leaders and the businesses they oversee

	Johnson & Johnson US	Pfizer US	Merck & Co US	Gilead Sciences US
				
CEO	**Alex Gorsky**	**Ian Read**	**Kenneth Frazier**	**John Milligan**
Appointed To Role In	**2012**	**2010**	**2011**	**2016**
Previous Position	Chair, J&J Medical Devices	Pfizer SVP, Group President, Worldwide Biopharmaceuticals	President, Merck & Co, Inc	President and COO, Gilead Sciences
Background	Began career as sales rep at Janssen Pharmaceutical, J&J. Defected to Novartis as head of pharma for North America 2004-2008 before returning.	Career spent at Pfizer, joined as an auditor. Has chemical engineering and accounting qualifications.	Legal: joined Merck in 1992 as general counsel.	Joined Gilead in 1990 as research scientist. Studied biochemistry.
2016 Compensation[1]	**$26.9m** (+12.9%)	**$17.3m** (-3.7%)	**$21.8m** (-10.0%)	**$13.9m** (+68.4%)[2]
2016 Company Sales	$71.9bn	$52.8bn	$39.8bn	$30.4bn
2016 Company Net Profit	$16.5bn	$7.2bn	$5.7bn	$13.5bn
Market Cap (June 30, 2017)	$355.9bn	$200.5bn	$175.6bn	$92.5bn
R&D Head	**Paul Stoffels**	**Mikael Dolsten**	**Roger Perlmutter**	**Norbert Bischofberger**
Appointed To Role In	**2009**	**2010**	**2013**	**2007**
Previous Position	Worldwide Chairman, Pharmaceuticals (J&J)	Head of Wyeth R&D, previously at Boehringer Ingelheim and AstraZeneca	Head of R&D, Amgen	EVP, R&D, Gilead
2016 Compensation[1]	**$12.7m** (+18.0%)	**$8.2m** (+35.8%)	**$7.1m** (-14.5%)	**$6.2m** (-11.3%)

[1] base salary, bonus & long-term incentives (including equity awards), [2] assumed CEO position Mar. 10, 2016

AbbVie US	Roche Switzerland	Novartis Switzerland	Sanofi France	GlaxoSmithKline UK	AstraZeneca UK
					
Richard Gonzalez	**Severin Schwan**	**Joseph Jimenez**	**Olivier Brandicourt**	**Emma Walmsley**	**Pascal Soriot**
2013 *(at company inception)*	**2008**	**2010**	**2015**	**2017**	**2012**
Head of Pharmaceutical Products Group at Abbott Laboratories	CEO, Roche Diagnostics	Division Head, Novartis Pharmaceuticals	CEO, Bayer Healthcare	CEO, GSK Consumer Healthcare	COO, Roche Pharmaceuticals
Spent 30 years at Abbott.	Economics, Law degrees, joined Roche as trainee in corporate finance in 1993.	Bachelor's degree in economics then MBA; prior to Novartis had senior leadership roles at HJ Heinz Co.	Physician by training, had leadership roles at Pfizer before Bayer.	Before joining GSK in 2010 was with L'Oréal for 17 years in marketing and general management.	Formerly CEO of Genentech, doctor of veterinary medicine and MBA holder.
$21.0m (+0.8%)	**CHF11.6m** (-2.6%)	**CHF12.0m** (+3.4%)	**EUR9.7m** (-42.3%)	**n/a**[3]	**£9.8m** (+22.6%)
$25.6bn	CHF52.6bn	$48.5bn	EUR33.8bn	£27.9bn	$23.0bn
$6.0bn	CHF9.7bn	$6.7bn	EUR4.5bn	£1.1bn	$3.5bn
$115.4bn	CHF206.7bn	CHF207.3bn	EUR105.6bn	£80.4bn	£65.0bn
Michael Severino	**n/a** **no single R&D chief**	**Vasant Narasimhan**	**Elias Zerhouni**	**Patrick Vallance**	**n/a** **no single R&D chief**
2014	**n/a**	**2016**	**2011**	**2012**	**n/a**
SVP, Global Development and Corporate Chief Medical Officer, Amgen	n/a	Global Head of Development, Novartis Pharmaceuticals	Scientific Advisor to CEO Christopher Viehbacher	SVP, Medicines Discovery and Development, GSK	n/a
$7.2m (+9.7%)	n/a	**CHF3.6m** (from Feb 2016)	n/a	**£0.78m** base salary	n/a

[3] Overall 2017 package will be c.25% less than the £6.8m received by Sir Andrew Witty in 2016

The Price Is Right: Amgen Defends Repatha At $9,669 Against More Critics

EMILY HAYES emily.hayes@informa.com

A new study funded by **Amgen Inc.** finds that the company's PCSK9 inhibitor *Repatha* is cost effective at the annual net price of $9,669, though an editorial accompanying the study questions whether the findings are based on "best-case scenarios" and feeds into a familiar refrain that the class still costs too much.

Results from the cost-effectiveness study were published by investigators from Amgen's FOURIER outcomes study of *Repatha* (evolocumab) in the *Journal of the American Medical Association (JAMA) Cardiology* on Aug. 23, and Amgen believes they represent the view of cholesterol specialists on the value of PCSK9 inhibitors.

"We hope this economic analysis from experts will actually be an important perspective to show that the value-based prices for these drugs in the right patients is largely consistent with the average net price in the market today," Joshua Ofman, senior vice president of global value, access and policy at Amgen, commented in an interview.

Once projected to be big blockbusters, PCSK9 inhibitors – Repatha and **Sanofi/Regeneron Pharmaceuticals Inc.**'s *Praluent* (alirocumab) have struggled to get off the ground since approval in 2015, largely due to payers' restrictions on access. For the second quarter, Amgen reported sales of $83m for Repatha while competitor reported €42m ($50m) in sales for Praluent.

Meanwhile, criticism about high pricing has continued to mount. Both drugs have a list price of about $14,500 annually, though this does not include rebates and Amgen has indicated in the past that the net annual price for Repatha is in the range of from $7,700 to $11,200 per year. *(Also see "Is Amgen's FOURIER Enough For Physicians, Payers To Expand Repatha Use?" Scrip, 17 Mar, 2017.)*

For Amgen's Repatha, the release of the FOURIER outcomes study in March was a major event, with potential to turn performance around. But to some, the results were mixed even though the trial met the primary endpoint. Repatha demonstrated an added 15% reduction in risk for major cardiovascular events, including cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina or coronary revascularization, but it did not show a significant reduction in cardiovascular mortality on its own. *(Also see "Is Amgen's FOURIER Enough For Physicians, Payers To Expand Repatha Use?" Scrip, 17 Mar, 2017.)*

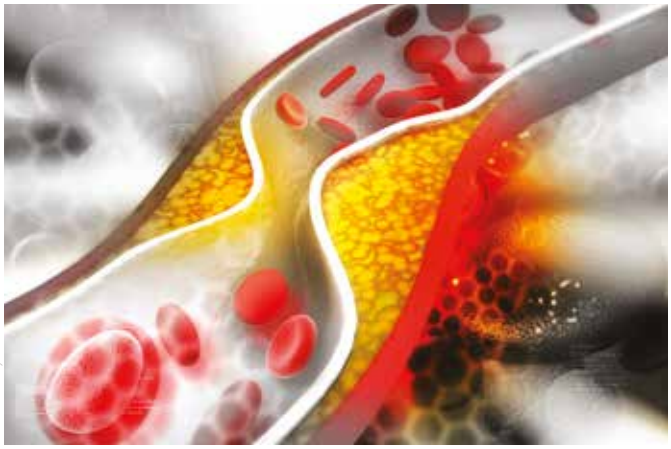
In June, the Institute for Clinical and Economic Review (ICER), a nonprofit organization that issues reports used by payers to make reimbursement decisions, highlighted the lack of mortality benefit in a new evidence update and concluded that Repatha with statins are "comparable or better" than treatment with statins alone; before it had deemed the benefit promising, but inconclusive.

ICER previously set a benchmark of $5,404-$7,735 annually as the appropriate price for treatment of patients with atherosclerotic cardiovascular disease whose LDL-C levels were not at the target of 70 mg/dL or lower with statin therapy alone. It will release a new benchmark reflecting FOURIER shortly.

ARGUING OVER CV MORTALITY

While ICER's main concern seems to be the lack of the cardiovascular mortality benefit, Amgen is standing by its argument that it is not a realistic expectation given the current state of cardiac care and the relatively short duration of FOURIER (26 months).

"No one would expect a trial of that duration to have a mortality benefit," Ofman said. He also pointed out that none of the outcomes trials of intensive statin therapy showed a mortality benefit. When FOURIER was presented at the American College of Cardiology annual meeting in March, clinicians noted that CV death has become less common with contemporary medicine, and the event rates in FOURIER were much lower than in earlier outcomes trials.



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The academic group that ICER has worked with on its PCSK9 reports published a research letter on Aug. 22 in JAMA that updated a value-based pricing analysis of Repatha versus **Merck & Co. Inc.**'s now-generic *Zetia* (ezetimibe) as an add-on therapy to statins, using the same modeling applied in other ICER reports for the class and including the FOURIER data. The letter was co-authored by ICER chief scientific officer Daniel Ollendorf.

To make their analyses, lead author Dhruv Kazi of the Zuckerberg General Hospital in San Francisco, et al., used a simulation group of 8.9m US adults who had similar characteristics as the FOURIER participants and compared against Zetia plus statins to assess cost per quality-adjusted life-year (QALY) gained, using $100,000 per QALY gained as its willingness-to-pay threshold for cost effectiveness.

They concluded that relative to adding Zetia, the PCSK9 inhibitors would be cost effective if their list price was cut by 71% to $4,215 or less. This assumes a cardiovascular survival benefit – without a late survival benefit, the calculations change dramatically. But Amgen's Ofman defended that expectation, as the FOURIER results track with the Cholesterol Treatment Trialists' Collaboration (CTTC) meta-analysis of intensive statin therapy, which experts accept as indicative of a mortality benefit.

ICER believes that the more policy-relevant comparison for PCSK9 inhibitors is against statins alone and will soon issue a new value-

based price range that is different from the Kazi study, but uses the same economic modeling.

AMGEN FLAGS STUDY FLAWS

Amgen's Ofman sees the analyses of ICER and some other groups as flawed. First, he notes that the ICER model used by Kazi et al. assumed an event rate of 3% per 100 patient-years, which he notes is much lower than high-risk patients in the real world who really need PCSK9 inhibitors. And, the $100,000 threshold is lower than the $150,000 per QALY value accepted by leading American cardiology associations and the World Health Organization.

A new cost-effectiveness study funded by Amgen and published in *JAMA* on Aug. 23 by Greg Fonarow, co-chief of the UCLA Division of Cardiology, and colleagues, used $150,000 as a willingness-to-pay benchmark. Researchers analyzed data using two different event rates (6.4 per 100 patient-years for the real-world population with ASCVD and LDL of 70 mg/dL or above and 4.2 per 100 patient-years for a population similar to FOURIER).

The study funded by Amgen and the model used by ICER both assume a mortality benefit over time, based on the reduction in events, and considered cost savings associated with prevention of cardiovascular events. The Amgen-backed researchers noted that at the current list price of $14,523, adding evolocumab to standard background therapy in patients with ASCVD "exceeds generally accepted cost-effectiveness thresholds." At this price, for a population with a 6.4 per 100 patient-years event rate, the incremental cost-effectiveness ratio per QALY gained would be $268,637.

However, the cost-effectiveness value would be substantially higher ($483,800) at the list price and $290,601 at a discounted net price – if a cardiovascular mortality benefit did not emerge

Evolocumab would meet the $150,000 per QALY threshold at an annual net price of $9,669 for the real-world scenario Amgen tried to define (or $6,780 for the FOURIER trial population, which matched the label but wound up showing a low event rate), Fonarow and colleagues noted.

Treatment could be targeted at patients with even higher risk to improve the cost-effectiveness picture. In patients with ASCVD and LDL-C of at least 80 mg/dL, evolocumab therapy would be cost-effective with an [incremental cost-effectiveness ratio] of $100,193 per QALY for a US clinical practice ASCVD population, with an event rate of 6.4 per 100 patient-years, but only at a net price of $10,311, Fonarow and colleagues concluded.

CHORUS OF CRITICAL VOICES

PCSK9 inhibitors' dramatic LDL-lowering and other qualities were originally hailed as a breakthrough, "but these features have been overshadowed by another breakthrough of PCSK9 [inhibitor] therapy: its high cost," according to a *JAMA Cardiology* editorial accompanying the Amgen study results by Daniel Mark (Duke University), Ilana Richman (Yale University) and Mark Hlatky (Stanford University).

"With list prices more than $14,000 per year, these drugs have achieved the dubious distinction of being the most expensive preventive therapies by far in the history of cardiovascular medicine," the editorial states.

In the past, cardiologists have embraced expensive new therapies, but their willingness to do so depends on improvements in clinical outcomes.

PCSK9 inhibitor therapy "creates a conundrum for clinicians who see innovative drugs that might help their patients but that are much too expensive to justify using," the editorial says.

"Unfortunately, things may be even less favorable than they seem. The unfavorable incremental cost-effectiveness ratios estimated by Fonarow et al. likely represent best-case scenarios, with several model assumptions that are more optimistic than the available data warrant," it notes.

For example, the study assumed a survival advantage after five years of therapy, and the level of any reduction in mortality greatly effects the estimated cost-effectiveness, the authors explained.

"The evidence from FOURIER, with a median follow-up of just 2.2 years, cannot settle this question, and the results of the cost-effectiveness models are exquisitely sensitive to the assumptions about long-term effects," the editorial concludes.

Mark and colleagues advocated careful consideration of costs and efficiency for PCSK9 inhibitors versus allocation of resources to other prevention strategies.

This is just the latest article in the medical press to flag exorbitant PCSK9 pricing. In a JAMA editorial on July 24, biostatistics expert John Ioannidis of the Stanford Prevention Research Center noted, based on the list price, that "treatment of fewer than 20 million US adults with evolocumab at the cost of this single drug would match the entire cost for all other prescription pharmaceuticals for all diseases in the United States combined."

On Aug. 7, *JAMA Internal Medicine* published a research letter by Immaculada Hernandez, University of Pittsburgh, questioning the real value of outcomes-based contracts for evolocumab. Even after discounts and outcomes-based refunds, the annual price for evolocumab is "double the prices at which these studies predicted evolocumab would be cost effective [$4,250-$4,500]," she wrote.

Hernandez suggested payers should make realistic assessments about the value of Repatha, taking into account the high turnover of the insurance market, which means payers are unlikely get refunds for patients who switch plans. She also warned that there is a "risk that outcomes-based contracts will become the latest complicated artifact used in the reimbursement of pharmaceuticals without providing any additional value to the current mechanisms."

Amgen's Ofman takes issue with the focus on pricing as a distraction from the real value of Repatha in people with ASCVD at high risk of an event. For those with an average LDL-C of 120 mg/dL, a PCSK9 inhibitor is extremely cost-effective even at the list price, and while access has improved, it is still being restricted.

"There is great rationale for payers to begin to work with Amgen on value-based contracts to make sure we are getting high-risk patients who need these products," the exec said.

Since releasing the FOURIER results, Amgen has been offering value-based contracts that offer a refund if Repatha fails to prevent heart attack or stroke – signing the first, with Harvard Pilgrim Health Care, in May. *(Also see "Amgen's Repatha Contract With Harvard Pilgrim Includes A Full Refund" Scrip, 3 May, 2017.)*

In a statement provided to Scrip, Regeneron commented that the research "only included data pertaining to Amgen's Repatha, failing to mention – or analyze – Sanofi and Regeneron's Praluent." The partners expect to release the findings of their ODYSSEY OUTCOMES trial in the first quarter of 2018.

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UK Charity Starts Early-Stage Clinical Studies Of Lilly's Cdc7 Inhibitor

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Team work is essential in cancer research

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The Centre for Drug Development of the UK's leading cancer charity, **Cancer Research UK**, announced on Aug. 23 it will start testing a novel type of anticancer from **Eli Lilly & Co.** under its partnership scheme that aims to make sure promising compounds don't fall through the cracks of industry's development processes.

It will evaluate the tolerability of Eli Lilly's LY3143921 in a Phase I study of oral doses given daily for 21 days, and repeated up to 12 times. It will also establish the recommended dose in patients with various cancers including advanced bowel, lung ovarian, urothelial, pancreatic, breast, head and neck, and oesophageal cancer.

The Centre's mission is to find new ways to treat cancer, and the charity sponsors and funds the early clinical development of compounds that it believes are of interest because of their mode of action, although the originating company retains all underlying rights to their programs. The compounds usually come from companies that are not prioritizing their development, and Lilly does seem to have a full plate when it comes to potential novel anticancers.

As well as waiting US approval for the cyclin-dependent kinase (CDK) 4/6 inhibitor, abemaciclib, in two breast cancer indications, Lilly also outlined a revamped oncology R&D strategy a month ago, which included an ERK1/2 inhibitor that is in Phase I, a CHK1 inhibitor, prexasertib, under evaluation for ovarian cancer, and a TIM-3 checkpoint inhibitor monoclonal antibody.

Under Cancer Research UK's clinical development partnership scheme, companies can decide after the completion of the charity's clinical studies if they want to develop the product or to allow the charity to search for another development partner, whilst retaining a share in any future revenues.

Selected CDc7 Inhibitors In Development

COMPANY	COMPOUND	STAGE OF DEVELOPMENT
Takeda Pharmaceutical Co. Ltd.	TAK-931	Phase I
Eli Lilly & Co./Cancer Research UK	LY3143921	Phase I
Eli Lilly & Co.	LY3177833	preclinical
SBI Biotech Co. Ltd./Sierra Oncology Inc./ Carna Biosciences Inc.	AS-141/SRA141	preclinical
Lin BioScience Inc.	LBS-007	preclinical
Exelixis Inc./Bristol-Myers Squibb Co.	XL-413	discontinued
Nerviano Medical Sciences SRL	NMS-1116354	discontinued
Nerviano Medical Sciences SRL	RXDX-103	no development reported
Roche	Cdc7 inhibitors	no development reported
Amgen Inc.	Cdc7 inhibitors	no development reported
AbbVie Inc.	Cdc7 inhibitors	no development reported

Source: Informa Pharma's Pharmaprojects.

CDC7 INHIBITORS

The cell division cycle 7 (Cdc7) protein is a serine-threonine kinase that is required to start DNA replication in cells, and its inhibition in healthy cells usually leads to the cells staying in a viable state. However, cancer cells appear more sensitive to Cdc7 inhibitors and proceed to apoptosis (cell death). Moreover, tumor cells with defective *p53* genes appear to be more susceptible to Cdc7 inhibitors, including patients with metastatic bowel cancer, squamous non-small cell lung cancer and high-grade serous ovarian cancer.

The industry has **Takeda Pharmaceutical Co. Ltd.**'s TAK-931 as an example of another Cdc7 inhibitor in early clinical studies. **Sierra Oncology Inc.** has a compound, SRA141/AS-141 in preclinical studies.

Companies such as **Roche**, **AbbVie Inc.** and **Amgen Inc.** have had research programs in the area, but have not reported any progress. Informa Pharma's Pharmaprojects reports the industry's Cdc7 inhibitor pipeline as follows:

The charity's Drug Development Centre has been involved in the development of a number of marketed agents, including the PARP inhibitor rucaparib (**Clovis Oncology Inc.**'s *Rubraca*), the prostate cancer therapy abiraterone (**Janssen Biotech NV**'s *Zytiga*) and the brain cancer therapy temozolomide (**Merck & Co. Inc.**'s *Temodar*). Currently it has more than 30 potential new agents in preclinical, Phase I and early Phase II studies, in collaboration with companies that include **AstraZeneca PLC**, Amgen, **Bicycle Therapeutics Ltd.** and **Merck Serono SA.**

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Topas Bags Big Pharma Partner With Lilly Pact

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Topas leverages powerful tolerance induction capabilities of the liver

Just under a year and a half after being spun off from **Evotec AG**, Germany's **Topas Therapeutics GMBH** has signed a deal with **Eli Lilly & Co.** in the field of antigen-specific tolerance induction.

The multi-year collaboration will have an initial focus on external antigens thought to induce inflammation and/or autoimmune disease. Topas will be responsible for conducting preclinical studies and Lilly has an option on all candidates produced for in-licensing and further development.

Financial details of the deal have not been disclosed, but Topas will receive the usual package of an upfront fee, R&D funding, milestone payments and royalties. For its money, Lilly is getting access to the Hamburg-headquartered group's technology platform which induces antigen-specific immune tolerance by harnessing the liver's natural immunology capabilities.

The technology involves peptide-loaded nanoparticles that are selectively targeted towards liver sinusoidal endothelial cells (LSECs), which Topas notes is "one of the body's premier sites to induce tolerance against blood-borne antigens by generating peptide-specific regulatory T cells." Chief executive Timm Jessen told *Scrip* that "we utilize the tolerogenic potential of the liver - no other company is going down that route."

He added that "we can dose our tolerizing agent very precisely as the uptake of our peptide-loaded nanoparticles from blood by the LSECs is an active and very efficient process." Furthermore, "we expect to treat patients only once or twice per year to induce and sustain tolerance," Jessen noted.

Lilly is impressed and its head of biotechnology and immunology research, Thomas Bumol, stated that Topas "has a very novel approach to immune tolerance induction, which we would like to see successfully applied to certain disease relevant antigens."

The deal is clearly a boost for Topas, which was spun out in March 2016 from Evotec's subsidiary Bionamics, itself acquired in March 2014. It launched with a Series A financing of €14m from Epidarex Capital, EMBL Ventures and Gimv, as well as Evotec, which is its largest shareholder.

Jessen told *Scrip* that the Series A financing has one remaining open slot, where an amount in the single-digit million euro range will be raised and "we aim to fill that slot by the end of the year". He also said of the Lilly tie-up that "the interest from such an important pharmaceutical company in our technology, we believe, supports the strong commercial potential of our work."

'We expect to treat patients only once or twice per year to induce and sustain tolerance'

Topas has two programs ready to enter the clinic next year - one for multiple sclerosis and one for an undisclosed orphan disease. Jessen said the company is looking to partner those projects and it also has a co-development program in Type 1 diabetes that is currently in pre-clinical testing.

Other companies looking at immune tolerance include **Parvus Therapeutics Inc.** which signed a major type 1 diabetes deal with Novartis in April, and **Anokion SA**, a Swiss firm with an antigen-specific immune tolerance platform that Celgene has an option to acquire.

Published online 22 August 2017

Apellis Eyes Progress For Lead AMD Product

Apellis Pharmaceuticals Inc., a company focused on autoimmune and inflammatory diseases, has reported that APL-2, its complement C3 inhibitor in development for geographic atrophy (GA) linked to age-related macular degeneration (AMD), has met its primary endpoint in a Phase II trial (FILLY). The company now plans to use recently raised funds to initiate a Phase III trial in late 2018, in addition to progressing other pipeline products.

Apellis was founded in 2009 and closed a $60m Series E preferred stock financing earlier this month. Having licensed its technology from the University of Pennsylvania, the company believes that APL-2, which is a synthetic cyclic peptide conjugated to a polyethylene glycol (PEG) polymer, can control GA and late-stage AMD by binding to and blocking C3 and C3b, effectively blocking all three pathways of complement activation (classical, lectin, and alternative).

AMD itself is a disorder of the macular, the central part of the retina, and can progress into GA, eventually resulting in irreversible loss of vision. There are currently no approved therapies for this advanced form of AMD. Apellis estimates that there are a million GA patients in the US alone.

The primary endpoint for the FILLY trial, a 246-patient sham-controlled study, was to assess the change in GA lesion size from baseline to month 12 in comparison to sham. A 29% reduction in the rate of the lesion growth was observed, in comparison to sham, at 12 months when APL-2 was administered monthly through intravitreal injection (p=0.008). For administration every other month, there was a non-significant 20% reduction (p=0.067).

lubna.ahmed@informa.com 25 Aug 2017

Read about Apellis' compeition here: http://bit.ly/2wQdreG

Quite A Range: Adamas Ponders $10,000-$30,000 Price Tag For Gocovri

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Adamas Pharmaceuticals Inc. has not finalized the pricing for its newly-approved *Gocovri* in the treatment of levodopa-induced dyskinesia in Parkinson's disease, but the company is using other Parkinson's therapies priced between $10,000 and $30,000 per year as benchmarks.

Emeryville, Calif.-based Adamas announced the US FDA approval for its extended-release formulation of amantadine (formerly ADS-5102) on Aug. 24, noting that Gocovri is the first medicine specifically approved for the orphan indication. The company will have no competition other than the immediate-release generic predecessor for at least a year, since the next drug in the pipeline for levodopa-induced dyskinesia hasn't been submitted yet for the FDA consideration.

Meanwhile, Adamas is preparing to finalize its Gocovri price and make the drug available later this year, with an official launch and promotion by 59 sales representatives slated for January 2018. The company's stock rose 38.4% in after-hours trading to $19.71 per share based on the approval and launch news.

A million people in the US are diagnosed with Parkinson's disease and about 90% experience dyskinesia related to the standard of care therapy – the levodopa component of levodopa-carbidopa – at some point as doctors increase dosing to combat the symptoms of the neurodegenerative disease. Adamas notes that about 150,000 to 200,000 Parkinson's patients in the US report that their daily life is impacted by levodopa-induced dyskinesia (LID).

ORPHAN APPROVAL, BUT BROADER EFFICACY

Gocovri was approved to treat dyskinesia experienced by Parkinson's patients on levodopa-based therapies with or without concomitant use of dopaminergic medications. Adamas founder, chair and CEO Gregory Went said in an interview that the FDA approved the drug based on the company's entire Phase I, II and III data package, including two Phase III studies that showed statistically significant improvements versus placebo in reducing dyskinesia as measured by the Unified Dyskinesia Rating Scale (UDysRS).

The drug also reduced "off" times that Parkinson's patients experience with short-acting levodopa-based therapy and increased "on" times – data points that are included in Gocovri's label. That made some analysts speculate in 2015 when the first set of Phase III results were revealed that Adamas could win a broader Parkinson's disease label. However, Went told *Scrip* that "we always sought an indication for Parkinson's patients who suffer from dyskinesia."

Patients enrolled in the Phase III clinical trial known as Study 1 experienced a 37% reduction in UDysRS total score versus a 12% reduction in the trial's placebo arm at week 12. Similarly, in Study 2 UDysRS scores were reduced by 46% for Gocovri-treated patients versus 16% for the placebo group. "On" times increased by 3.6 hours for Gocovri in Study 1 and by four hours in Study 2 versus 0.8-hour and 2.1-hour increases, respectively, for placebo-treated patients.

"It was nothing but a pleasant surprise here in having dyskinesia as well as the 'off' time reduction and the 'on' time given back to patients in the label," Went said.

The most common side effects in the Phase III studies were hallucinations, dizziness, dry mouth, peripheral edema, constipation, fall and orthostatic hypotension. The label advises doctors to monitor patients for depression and suicidal ideation; watch for dizziness and orthostatic hypotension, especially after starting treatment or increasing the dose; and to look out for hallucinations and psychotic behavior. Patients already diagnosed with major psychotic disorder should not begin treatment with Gocovri.

The label also advises doctors to discontinue treatment if patients report falling asleep during daily activities and to reduce dosing or discontinue Gocovri therapy if patients experience increased gambling or sexual urges, uncontrolled spending or other urges. However, physicians are advised against sudden discontinuation, due to withdrawal-emergent hyperpyrexia and confusion.

COMMERCIAL PREPARATIONS UNDER WAY

Adamas brought in chief operating officer Richard King in April to lead the Gocovri commercial launch, but the company has been preparing for commercial manufacturing and marketing for the past year and a half. King previously was COO at the Scripps Research Institute in San Diego, but his prior experience includes the launch of the aesthetic and neurology drug *Dysport* (abobotulinumtoxinA) and the growth drug *Increlex* (rhIGF-1) at **Tercica Inc.** (acquired by Ipsen) as well as sales of *Niaspan* (niacin) and the launch of *Advicor* (niacin/lovastatin) at **Kos Pharmaceuticals Inc.**

"We intend to bring the drug into the distribution channel in the fourth quarter of this year to serve a community that's been aware of and waiting for this," Went said. "We will put our sales force on the ground in January with about 59 representatives. That gets us to about 85% of [the doctors responsible for] initiations of Parkinson's treatment."

Adamas has not announced a price for Gocovri yet, but the CEO said the company will make decision about the drug's list price in time to prepare distributors. Adamas has said, however, that pricing will fall somewhere between the $10,000 annual cost of dopaminergic therapies for Parkinson's disease and the $30,000 per year charged for other drugs approved to treat movement disorders.

"We want to make sure we provide access and assistance to commercial and Medicare Part D patients," Went said. "We also want to recognize the value of this novel treatment and the 3.6 hours of on-time we're giving back to patients. Making sure that the value that we've created is recognized by all stakeholders has been an important part of our culture."

He said all payers are aware of the important efficacy provided by levodopa and the fact that at some point dosing is increased until it can't be adjusted anymore and still reduce Parkinson's symptoms. He also noted that about half of the payers contacted

by Adamas are aware of the dyskinesia associated the levodopa therapy as dosing increases.

"When go in with data about reducing dyskinesia, you have a good start. When you show you improve both dyskinesia and off-time, it really gets their attention, and when add in the effect on on-time, the conversation gets more enjoyable," Went said. "This dyskinesia, it's diagnosed at the prime of life. Payers want to have the ability to use levodopa as efficiently as you can."

Adamas has set up a patient assistance program called Gocovri Onboard to help patients, families and physicians via reimbursement support, prescription fulfillment and financial assistance.

BRANDED COMPETITION COMING, BUT LIMITED

The company is likely to have a year or more without brand-name competition for Gocovri in its approved levodopa-induced dyskinesia indication, since the next drug in the pipeline is **Osmotica Pharmaceutical Corp.**'s *Osmolex ER*, another extended-release amantadine product, which Biomedtracker expects Osmotica to submit for the FDA approval this month.

Next up is the Phase II candidate dipraglurant, an mGluR5 negative allosteric modulator developed by **Addex Therapeutics**, which is expected to begin a Phase III program in LID during the fourth quarter, according to the Biomedtracker database. **Novartis AG** discontinued development of a similar compound in 2013.

Vanda Pharmaceuticals Inc. also has a Phase II alpha-7 nicotinic acetylcholine receptor partial agonist called AQW-051 in development for LID, Biomedtracker notes.

Adamas is considering other Parkinson's disease indications for Gocovri based on the drug's effects on "on" and "off" time, but the company hasn't announced specific clinical trial or supplemental filing plans in that area. More details will be revealed when Adamas hosts an analyst day in September, Went said, but noted that a Phase III trial looking to improve walking for multiple sclerosis patients will begin in early 2018. Gocovri produced a 17% placebo-corrected improvement in walking speed in a Phase II study completed last year. The company is examining the drug's potential in epilepsy as well.

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Merck KGaA's MS Drug Mavenclad May Defy Doubters

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Now that **Merck KGAA**'s oral multiple sclerosis drug *Mavenclad* (cladribine) has finally got European approval, the German group is now looking at how to make inroads into what is already a crowded market.

Mavenclad has been given the green light for the treatment of highly active relapsing MS and Merck notes that it is the first oral short-course treatment to provide efficacy across key measures of disease activity including disability progression, annualized relapse rate and magnetic resonance imaging activity. The approval comes after the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency issued a positive opinion in June.

The approval is based primarily on the two-year Phase III CLARITY trial which showed that Mavenclad cut the annualized relapse rate by 67% and the risk of six-month confirmed EDSS (expanded disability status scale) progression by 82% versus placebo. An extension study demonstrated that no further treatment with Mavenclad was required in years three and four.

Some analysts have been skeptical about the prospects of Mavenclad, which was rejected by European regulators in 2010 and again in 2011, amid malignancy concerns. Since then, the MS field has changed dramatically and already has three established oral disease-modifying therapies - **Novartis AG**'s *Gilenya* (fingolimod), **Biogen Inc.**'s *Tecfidera* (dimethyl fumarate) and **Sanofi**'s *Aubagio* (teriflunomide).

However, Mavenclad has the backing of Gavin Giovannoni, professor of neurology at Barts and The London School of Medicine and Dentistry, Queen Mary University of London (QMUL) and an influential voice in the MS world. He said that the approval was "an exciting moment and one that will change the way we treat MS".

He noted that Mavenclad is a selective immune reconstitution therapy (SIRT) which simplifies treatment administration by giving patients just two short annual courses of tablets in four years. As such, "patients can benefit from the treatment over a longer period of time without having to continually take medication and without the need for frequent monitoring," Giovannoni added.

Merck is looking to hit the ground running, saying that initial launches in Germany and UK are expected as early as September. No pricing information is available as yet.

Giovannoni's enthusiasm is mirrored by colleagues at QMUL. They have cited previously unpublished clinical trial data they gained access to through a Freedom of Information request to the European Medicines Agency which revealed the benefits of Mavenclad on quality of life.

The QMUL researchers say that "for a number of reasons, including a perceived increase in cancer risk later shown by QMUL research to be an anomaly", the EMA rejected license applications from Merck, prompting a halt in development of the drug in 2011. This was followed by its withdrawal from markets where it had been licensed (Russia and Australia) and ongoing trials were terminated.

STOPPING DEVELOPMENT WAS 'TRAGIC'

Lead researcher Dr Klaus Schmierer, reader in clinical neurology at QMUL, said in a statement that "cladribine seemed to have such excellent potential as a treatment for MS that we thought it was tragic the development programme was shelved, and significant parts of the clinical trial data remained unpublished.

"In addition to the drug being highly effective, well tolerated and safe as far as short term studies can show, we now know it also improves patients' quality of life. The new results seemed so clear, we felt it was extremely important to publish and share these data."

The new analysis, published in the *Multiple Sclerosis Journal*, stated that after nearly two years, the benefits for people with relapsing MS taking the Merck drug were particularly significant for self-care, and a positive effect on mobility was detected.

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Samsung Looks Beyond Biosimilars Via Takeda Tie-Up

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Samsung Bioepis Co. Ltd. has joined hands with **Takeda Pharmaceutical Co. Ltd.** to develop novel biologics, moving beyond its core focus on biosimilars.

Under the strategic collaboration, the two companies will jointly fund and co-develop multiple novel innovative biologic therapies in unmet disease areas. The partnership brings together Samsung Bioepis' agile biologics development platform with Takeda's "best-in-class experts" in drug development. The two will collaborate in exploring novel drug substance, clinical development, regulatory approval and commercialization. Financial terms of the deal weren't disclosed.

Samsung Bioepis has been considering partnerships with global pharma companies to enter the novel drug development business as part of its long-term goal to become a leading global biopharma firm.

"Takeda's extensive knowledge and expertise in drug development makes the company an ideal partner for us as we open a new chapter at Samsung Bioepis," said Christopher Hansung Ko, president and CEO of Samsung Bioepis, in a statement.

The agreement is also in line with Takeda's R&D strategy and comes amid a series of deals by the Japanese company this year, which includes a licensing agreement for **Tesaro**'s *Zejula* (niraparib), a PARP inhibitor for cancer. Takeda has made major changes to its R&D strategy last year after deciding to focus on three core drug development areas: gastro-intestinal, oncology and CNS.

RIGHT TIME TO CO-WORK

The latest deal will enable the two companies to build synergies in terms of cost and time.

Samsung expects to "minimize risks" in diversifying into novel drugs through the collaboration with Takeda and expand its research and development capabilities in biosimilars into novel drug development.

Capitalizing on Takeda's strength in gastro-intestinal therapies, the two will initially co-develop Takeda's TAK-671, which is intended for the treatment of severe acute pancreatitis.

"So far, there isn't any therapy developed for acute pancreatitis. The program is in pre-clinical stage, which we believe is the right time to co-work and create synergies," said Samsung.

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According to Biomedtracker, several companies including **GlaxoSmithKline PLC**, **Stason Pharmaceuticals**, **D-Pharm Ltd.** and **Sun BioPharma Inc.**, are progressing development of pancreatitis drug candidates ranging from preclinical to Phase II, although there weren't any particular acute pancreatitis therapies in the pipeline.

In the US, 24.2 people out of 100,000 suffer from acute pancreatitis, while in South Korea, the disease affects about 20 out of 100,000.

For the time being, Samsung plans to pursue novel drug development in the form of co-development, rather than licensing deals, due to high risks.

Samsung Bioepis, which is a joint venture between **Samsung BioLogics** and **Biogen Inc.** , has a broad pipeline of biosimilars that includes six "first wave" candidates in immunology, oncology and diabetes.

Samsung Bioepis has so far launched biosimilar etanercept in Australia, Canada, South Korea and Europe, while launching biosimilar infliximab in the US, Europe, Australia and South Korea.

Its biosimilar adalimumab has received CHMP's recommendation and is awaiting approval in Europe, while its biosimilar trastuzumab is undergoing regulatory approval in Europe.

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From the editors of PharmAsia News.

Destiny Advances First-In-Class Antibiotics

Destiny Pharma is banking that increased awareness of the need to tackle antimicrobial resistance will draw investors to its shares when it makes a scheduled listing on the London's AIM stock market on Sept 4.

The British biotech's lead asset, dubbed XF-73, targets antibiotic-resistant bacterial infections in hospitals. Destiny Pharma's proposition to investors is that the XF drug platform offers potential to generate a new range of anti-microbial drug products which kill bacteria quickly, using a unique mechanism of action that bacteria seem unable to resist.

No resistance emergence

Supporting that are studies showing XF-73 is the only antibacterial drug to resist 55 repeat exposures to the superbug methicillin resistant *Staphylococcus aureus* (MRSA) without resistance emerging, the firm says.

"This type of feature – and this extreme resistance to bacterial resistance emergence – means that we foresee a long clinical lifetime for our products, and the ability to go into areas where resistance and antibiotic resistance is an issue for existing antibiotics, so we are clearly differentiated," said Bill Love, founder and chief science officer at Destiny Pharma.

IPO

The biotech's CEO, Neil Clark told *Scrip* that its initial public offering "should allow Destiny to progress XF-73 to the cusp of Phase III pivotal studies in the prevention of post-surgical *S. aureus* infections during 2019."

He noted that the recent high-profile and multi-faceted review on antimicrobial resistance and the international crisis it poses should offer a receptive backdrop for Destiny Pharma's AIM listing.

sten.stovall@informa.com 21 Aug 2017

Novartis Plays Access Card As Kisqali Gets EU Approval

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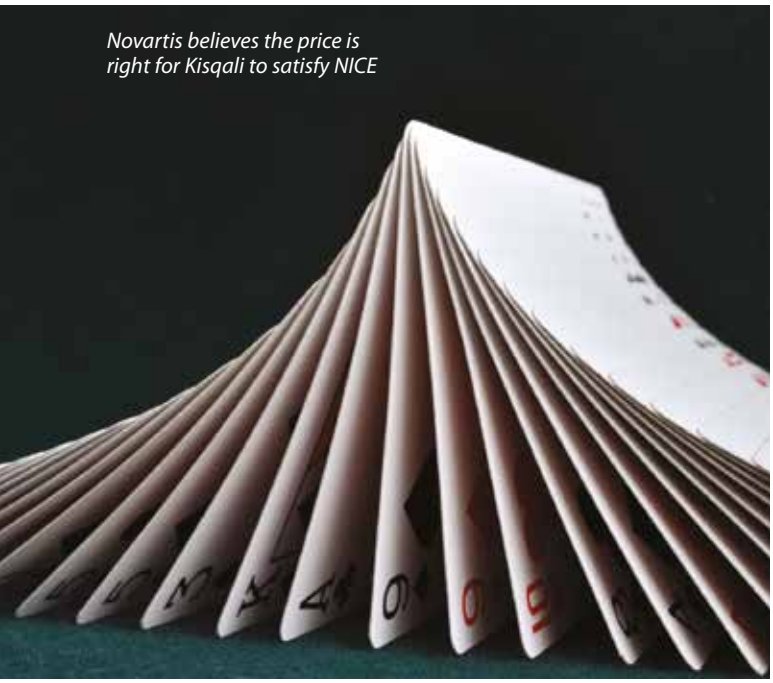

Novartis believes the price is right for Kisqali to satisfy NICE

Shutterstock: Markus Pfaff

Novartis AG is making optimistic noises about getting reimbursement and quick access for patients in the UK to *Kisqali* (ribociclib), its advanced breast cancer treatment which has just been approved in Europe.

Kisqali is now licensed for use in Europe as a first-line treatment in combination with an aromatase inhibitor in postmenopausal women with hormone receptor positive, human epidermal growth factor receptor-2 negative (HR+/HER2-) locally advanced or metastatic breast cancer. Approval of the cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitor, which was given the green light in the US in March, was expected after the European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) issued a positive opinion in June.

The approval is based on data from the Phase III MONALEESA-2 trial showed that Kisqali plus Novartis' *Femara* (letrozole), an aromatase inhibitor, reduced the risk of progression or death by 43% over placebo plus letrozole. More than half of patients (55%) with measurable disease taking ribociclib plus letrozole experienced a tumor size reduction of at least 30%.

HOPES FOR 'SWIFT AGREEMENT' WITH NICE

Novartis' thoughts have now turned to getting Kisqali into the various European markets and it has addressed the thorny issue of access in the UK. In a statement, the company quotes Dr Mark Verrill at the Freeman Hospital in Newcastle, who says that "the availability of treatments such as ribociclib is a significant clinical advance for women living in the UK with this type of breast cancer".

He adds that he has "first-hand experience" of using Kisqali, an oral treatment that can be taken at home, in the MONALEESA-2 trial, and looks forward to "a swift agreement with the National Institute for Health and Care Excellence (NICE) so that access is not an issue for postmenopausal women in England and Wales who could be offered this new treatment".

Recent history suggests that discussions with the UK cost watchdog over innovative cancer treatments can be quite fraught. However, Barak Palatchi, general manager of Novartis Oncology UK & Ireland, seems confident, saying, "The new NICE process to assess funding cancer medicines on the NHS is a welcome development and we are working closely with NICE to ensure eligible patients in England and Wales have access to ribociclib at the earliest opportunity."

NECK AND NECK WITH PFIZER'S IBRANCE AT NICE

If Palatchi's optimism is justified, Novartis could be in a position to leapfrog **Pfizer Inc.**'s rival CDK4/6 inhibitor *Ibrance* (palbociclib) in getting reimbursed. In February, NICE issued draft guidance rejecting Ibrance in combination with an aromatase inhibitor for the same indication as Kisqali, saying the estimated incremental cost-effectiveness ratios for the drug were estimated to be between £132,872-£150,869 per quality-adjusted life year (QALY) gained - well above the £20,000-£30,000 range NICE usually considers to be cost-effective.

Earlier this summer, Pfizer made a fresh submission, including a patient access scheme that will involve a price discount. According to NICE, Ibrance costs £2,950 for 21 capsules and a full course of treatment comes in at just under £80,000, although Pfizer is currently offering the drug for free to the National Health Service until a final decision on routine funding is made.

As for Kisqali, while a quick reimbursement in the UK would be welcome at Novartis, it is the US that will drive the product's growth, although Ibrance's second-quarter sales across the pond leapt 45% to $727m. In terms of other European markets aside from the UK, Novartis has not responded to enquiries about launch plans or pricing. *(Also see "Novartis Sets 'Flexible Pricing' For Kisqali To Compete Against Pfizer's Ibrance" Scrip, 14 Mar, 2017.)*

Published online 25 August 2017

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

CLICK
Visit scrip.pharmamedtechbi.com for the entire pipeline with added commentary.

Selected clinical trial developments for the week 18–24 August 2017

LEAD COMPANY/PARTNER	COMPOUND	INDICATION	COMMENTS
Phase III Suspended			
Ultragenyx Pharmaceutical Inc.	*Ace-ER* (aceneuramic acid)	GNE-related myopathy	GNEM; primary endpoint of improving upper extremity muscle strength not met.
Phase III Results Published			
Amgen Inc.	*Kyprolis* (carfilzomib)	multiple myeloma	ENDEAVOR; *The Lancet Oncology* online, Aug. 23, 2017.
Celldex Therapeutics Inc.	rindopepimut	glioblastoma	ACT IV; *The Lancet Oncology* online, Aug. 22, 2017.
Updated Phase III Results			
AstraZeneca PLC	*Brilinta* (ticegrelor)	acute coronary syndrome	PEGASUS TIMI 54 subanalysis; extended treatment reduced risk of CV mortality post-MI.
Phase III Interim/Top-line Results			
Genmab AS/Johnson & Johnson	*Darzalex* (daratumumab)	multiple myeloma, front line	ALCYONE; improved PFS, reduced risk of death.
Phase III Initiated			
CytoDyn Inc.	PRO 140 (a viral entry inhibitor)	HIV/AIDS infection	With antiretroviral therapy.
Astellas Pharma Inc.	gilteritinib	acute myeloid leukemia, FLT3 mutation-positive	MORPHO (maintenance); the 4th Phase III study.
Intra-Cellular Therapies Inc.	lumateperone	schizophrenia	Switch study; long-term safety study.
Phase III Announced			
Otsuka Holdings Co. Ltd./ H. Lundbeck AS	*Rexulti* (brexipiprazole)	acute manic episodes in bipolar disorder	Versus placebo, in just over 300 patients.
Phase II Interim/Top-line Results			
Apellis Pharmaceuticals Inc.	APL-2, a complement C3 inhibitor	dry age-related macular degeneration	FILLY; slowed disease progression.
Isofol Medical AB	*Modufolin* ((6R)-5, 10-methylenetetrahydro-folate	colorectal cancer, metastatic	ISO-CCC-005; initial efficacy signs.
Teikoku Pharma USA Inc.	TPU-006 (dexmedetomide) 3-day patch	pain following bunionectomy surgery	Pain controlled, no unexpected safety events.

Source: Biomedtracker

Novartis Starts 'Complex' Trial of Novel Malaria Therapy

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Novartis AG and the **Medicines for Malaria Venture** (MMV) have begun a Phase IIb trial of what it hopes will be a game-changing antimalarial therapy, KAF156.

KAF156 belongs to a new class of antimalarial compounds called imidazolopiperazines, and is believed to have the potential to clear malaria infection, including resistant strains, as well as to block the transmission of the malaria parasite.

In a Phase IIa proof-of-concept trial published in the *New England Journal of Medicine* last year, the compound was shown to act quickly and strongly across multiple stages of the parasite's lifecycle, rapidly clearing both *Plasmodium falciparum* and *P. vivax* parasites, including infections with artemisinin-resistant parasites.

Artemisinin-based combination therapies (ACTs) are currently the standard of care against *P. falciparum* infections. They combine artemisinin, which quickly kills the parasite, with a longer-acting partner drug, such as mefloquine, lumefantrine (as in Novartis's *Coartem*), piperaquine, amodiaquine and pyronaridine. However, rising resistance to artemisinin and decreasing efficacy of partner drugs are causing problems, especially in Asia. Reduced sensitivity to artemisinin has also been sporadically reported in Africa.

> Being able to cure patients with a single dose is seen as the pinnacle of malaria drug R&D

The new trial has begun in adults Mali and will expand to adolescents and children in 16 other centers in a total of nine countries in Africa and Asia over the next few months.

It will test KAF156 in combination with a new, improved formulation of lumefantrine using multiple dosing combinations and dosing schedules of the two drugs, including the feasibility of a single-dose therapy in adults, adolescents and children, making the study "particularly complex", Novartis said. Being able to cure patients with a single dose is seen as the pinnacle of malaria drug R&D as this will ensure compliance, minimize the risk of resistance and reduce costs.

Novartis hopes to get children on board quickly, following safety review of the data generated in adults, to accelerate the development of a pediatric formulation.

"To build on the gains made against malaria since the turn of the century, we need new medicines that are effective across all types of resistance patterns and geographies, and that are easy to administer, especially to children," said Dr David Reddy, CEO of MMV.

KAF156 is the result of a Wellcome Trust, MMV and Singapore Economic Development Board supported joint research program with the Novartis Institute for Tropical Diseases, the Genomics Institute of the Novartis Research Foundation, and the Swiss Tropical and Public Health Institute.

Published online 21 August 2017

APPOINTMENTS

Almirall has appointed ***Peter Guenter*** CEO – effective Oct. 1. Guenter joins the company from Sanofi where he held various senior positions over the past 22 years, most recently as executive vice president diabetes and cardiovascular global business unit. ***Ron Menezes*** will also be joining Aqua Pharmaceuticals, an Almirall company, as president and general manager in September. Most recently, Menezes was vice president of sales and sales operations, pain and CNS portfolio at Depomed Pharmaceuticals.

Axial Biotherapeutics, a company focused on neurological diseases, has appointed ***Srinivas G. Rao*** chief medical officer (CMO), ***Bridget M. Cole*** vice president of medicinal chemistry and ***Ryan Barrett*** vice president, corporate development and intellectual property. Rao has more 17 years of experience in the pharmaceutical and biotechnology industries and most recently, he was senior vice president and CMO at DepoMed Inc. Barrett joined Axial from OvaScience, where he was vice president and senior corporate counsel. He previously held financial and business positions, including senior business development associate at BioEnterprise Corp. Cole assumed her position as vice president of medicinal chemistry in July 2017, before which she was vice president at Flatley Discovery Lab.

Christian Meyer has joined ***Therachon AG*** as chief medical officer (CMO) and will be succeeding **Maarten Kraan**, who will remain as an advisor to the company. Meyer began his career at Novo Nordisk AS and most recently, he was the CMO at uniQure BV.

Theranexus, a company focused on the central nervous system, has named ***Werner Rein*** chief medical officer. Rein has held various roles in the management of drug development programs in the pharma industry and most recently, he was Sanofi's global vice president for clinical research in psychiatry.

Fredrik Järrsten will join **Karolinska Development AB** as chief financial officer later this year from Bactiguard Holding AB, where he currently is chief financial officer and business development director. Before Bactiguard, Järrsten was director business development, including M&A, at Aleris.

Carrick Therapeutics has named ***Burt Adelman*** and ***Clive Dix*** to its board. Adelman will serve as the chair of the board and brings over 35 years' experience to the company, with his most recent position being executive vice president and chief medical officer at Dyax Corp. Dix is CEO of C4X Discovery Holdings and has been named a non-executive director of Carrick's board. He co-founded and CEO of Convergence Pharmaceuticals Ltd. and PowderMed Ltd.

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