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Luxturna EU Approval: Novartis' Lessons For Gene Therapy Success

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The European Commission has officially approved *Luxturna* (voretigene neparvovec), **Novartis AG**'s one-time gene therapy for inherited retinal dystrophy caused by RPE65 gene mutations.

This is the company's first move into gene therapy and the approval is something of a landmark for Novartis. What happens now will have ramifications for how it develops this part of its business. The company told *Scrip* about its launch plans and how its experience regarding pricing, reimbursement and market access will inform its future gene therapy strategy.

Not least the company hopes to learn more about the sort of pricing and reimbursement deals that will be palatable for payers in the future when it comes to the company's gene therapy pipeline, Janneke van der Kamp, Novartis's global head of product and portfolio strategy told *Scrip* in an interview.

Van der Kamp declined to comment on what price the company wants for Luxturna. It is likely to be expensive. In the US, Luxturna's list price is $850,000 for both eyes, though the pricing strategy does include the offer of discounts tied to outcomes. *(Also see "Cell And Gene Therapies Test New Waters In Pricing And Reimbursement" - Scrip, 5 Oct, 2018.)*

Luxturna was developed by **Spark Therapeutics**, which markets the drug in the US. Novartis licensed the development and commercialization rights to the product outside the US in January 2018 in a bid to expand its reach into gene therapy and non-oncology products. *(Also see "Novartis's Luxturna Deal Expands Gene Therapy Ambitions" - Scrip, 25 Jan, 2018.)*

Luxturna, the first gene therapy to be approved for a retinal disease, works by delivering a functional RPE65 gene into the cells of the retina through a single retinal injection. This restores the production pathway for the required enzyme and improves the patient's ability to detect light.

RETHINKING PRICING AND REIMBURSEMENT APPROACHES

As van der Kamp points out, the arrival of gene therapies to the market will mean a rethinking of approaches to pricing and reimbursement. Unlike most other treatments that healthcare systems are used to dealing with, gene therapies offer a one-off treatment with potentially lifelong benefits. "It is a very different way to think about value and pricing compared to basically everything else. Cell and gene therapies are only just starting out and it is something that healthcare systems are not yet used to," she said.

To help healthcare systems understand and address these challenges, Novartis will be offering different types of payment schemes. These will include schemes to help payers spread payments. Such arrangements would help them deal with "this strange shape of the cost curve where all the cost comes up front and you have all the benefits later," she said. Outcomes-based deals will also be on the table, added van der Kamp. "We are very open here to work with them to make this drug available in a way that works well for all parties. It is new for us and new for

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BROUGHT TO YOU BY THE EDITORS OF **PHARMASIA NEWS, START-UP** AND **SCRIP INTELLIGENCE**

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Winter Is Coming
Buckle in for price increases, starting with Pfizer (p11)

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Milestone week for AML patients as two drugs get FDA approval (p15)

from the editor

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It was wonderful to see so many of our readers gathered for the Scrip Awards at the London Hilton on Park Lane this week. At a time when pharma companies are under repeated attack for the cost of medicines, it is important to recognize the remarkable accomplishments of our industry in having a direct impact on people's quality of life. This is thanks to the major commitment of time, money and talent across the biopharma ecosystem aimed at driving forward R&D. From infectious diseases like HIV and HCV to cancers, inflammatory diseases, genetic conditions and more, new drugs are allowing more and more people to survive and thrive where once they were condemned to death and disability. And innovation is flourishing, as our Awards ceremony amply demonstrated.

Congratulations to all our winners, including Pharma Company of the Year MSD, and the esteemed immunologist and founder of the Wellcome Trust Centre for Human Genetics Sir John Bell, who won Scrip's 2018 Lifetime Achievement Award. For the full list see p12-14.

On that vexed question of pricing, Novartis is once again proving itself to be creative and pro-active as it prepares to launch its single-injection gene therapy to treat blindness (see cover story). As the early pioneers of gene therapies and other advanced treatments forge a path to market, novel arrangements such as outcomes-based deals for reimbursement and payment by instalments are likely to become increasingly commonplace. In contrast, there are occasions when pharma firms must accept that straightforwardly lowering prices is the right thing to do. The PCSK9 inhibitors may be a case in point (p8-10).

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What The New US Cholesterol Treatment Guidelines Mean For Esperion
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Guidelines place high emphasis on low cost, but also outcomes data. Esperion plans to file bempedioc acid next year, but outcomes data won't be available until 2022.

Pharma Products Face Uncertain Future In Boston Scientific's 'Logical' £3.3bn Bid For UK's BTG
https://bit.ly/2AvM8G8
Boston Scientific CEO says US group has been tracking UK-based BTG "for more than two years" and that interventional medicine is a key attraction.

Lundbeck Still Assessing Future Of Antipsychotic After Phase III Failure, Says CEO
https://bit.ly/2Rk8uSb
Deborah Dunsire, Lundbeck's new CEO, talks to *Scrip* about the fallout from its recent Phase III setback, and how she sees the road ahead for CNS clinical research.

Leo Lines Up PellePharm Buy In Rare Skin Cancer Deal
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The Danish dermatology specialist could be hitting the acquisition trail again soon having taken an option to buy BridgeBio's PellePharm and its skin cancer drug patidegib in a deal that could be worth $760m.

Sweden's Combigene Readies Gene Therapy For Epilepsy Trials
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CombiGene CEO tells Scrip the Swedish biotech seeks a big pharma partner to develop its lead asset CG01 as a therapy for drug-resistant epilepsy.

Asia Deal Watch: MEI Partners ME-401 With Japan's Kyowa Hakko Kirin, Following Chinese Deal With BeiGene
https://bit.ly/2FLmIdx
About a month after signing a development and commercialization partnership in China for its PI3K delta inhibitor, MEI signs a deal for Japanese rights to the compound with Kyowa Hakko Kirin. Cue and LG Chem partner to develop targeted T-cell therapies for cancer.

inside:

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them, so we will all learn together on what works best for these type of one off treatments."

These will be important lessons given that gene therapies form part of Novartis's wider strategy of offering transformative treatments, including gene and cell therapies, as well as other types of treatment.

"We expect to learn a lot from [our experience with Luxturna] that will benefit how we bring AVXS-101 to market and the rest of the gene therapy pipeline," van der Kamp said. AVXS-101 is potentially the first one-off gene replacement therapy for spinal muscular atrophy and was the star attraction in Novartis's acquisition of AveXis earlier this year, another move to help it grow its gene therapy footprint.

LAUNCH AND PRICING

The launch sequence for Luxturna is as yet unclear as this will depend on talks in individual markets. "That sequence is not determined by us so much as by those countries and how fast those discussions go, which is faster in some markets."

Van der Kamp expects earlier launches in the "usual suspects" – Germany and the Nordic markets – where processes are swifter. Meanwhile, market access could happen sooner rather than later in France because of the size of the population there, she added. More generally she expects countries to move faster than usual because of the high unmet need and because the condition in question is very rare.

THE FOUR AREAS OF 'VALUE'

Van der Kamp declined to comment on pricing but did say that in line with its usual strategy, the company would pursue a value-based price. Value, explained van der Kamp, breaks down into four different areas: technical value, relating to end points in the clinical study; patient values, for example as measure in quality of life; value to the health system, where costs are offset elsewhere in the system; and the societal value.

In addition, the ultra-rare nature of the condition means the budget impact for payers will be limited, which van der Kamp hopes will make discussions easier.

Meanwhile, there are few lessons that can be applied from the company's experience of delivering its cell therapy, *Kymriah* (tisagenlecleucel) to the market, said van der Kamp. She expects Luxturna pricing and reimbursement talks to be simpler because there are fewer complications in delivering a gene therapy to patients than there are for a cell therapy. "In a way it is easier because you don't have to take cells from patients, modify them and put them back in, which is what is so complicated in cell therapy like Kymriah. For Luxturna, it is the same thing we give to every patient. That makes it logistically a lot easier," she said.

A registry will help the company track outcomes in every patient to address marketing authorization requirements for longer term data.

Mutations in both copies of the RPE65 gene affect approximately 1 in 200,000 people and can lead to blindness.

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Neuroscience Is The Next Oncology: Why Biogen Is Doubling Down

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"What's happening in neuroscience right now is like nothing we've seen before. Neuroscience is at an inflection point. We have seen the signs and Biogen has chosen to step forward and lead." Michael Ehlers, **Biogen Inc.**'s executive vice president, R&D, is convinced that the company is in the right place at the right time, but Biogen's attitude is unusual.

In recent years, other companies – **GlaxoSmithKline PLC**, **Pfizer Inc.**, **AstraZeneca PLC**, **Novartis AG**, **Sanofi** among them – have chosen to exit or scale back their R&D into disorders of the central nervous system (CNS). Biogen, on the other hand, spun out its hemophilia business in 2017 under former CEO George Scangos. The latter's strategy to double down on neurology is now being enthusiastically pursued by his successor Michel Vounatsos as the company enters its fifth decade. So what gives Biogen its confidence, and how is it approaching the neuroscience challenge?

According to Ehlers, speaking at an event in Lucerne to mark the Swiss-born biotech's 40th anniversary, there are "six broad reasons" for the company's belief that "neuroscience is the next oncology" and "the fastest area of ongoing scientific advance."

- Firstly, "arguably there's no area that's advancing as rapidly as neuroscience in terms of understanding of disease biology." This growth in knowledge encompasses areas including how the brain develops, how it is affected by aging, and brain plasticity.
- Second is the growing ability to stratify patients by disease pathology.
- Third is the advent of novel technologies to deliver therapeutic agents, for example using cell or gene therapies, or brain penetrative biologics, or intrathecally, like *Spinraza* (nusinersen), Biogen's recently launched antisense oligonucleotide treatment for spinal muscular atrophy, which booked sales of $1.25bn in the first nine months of 2018 after winning approval in the US in December 2016 and in the EU, Japan and other markets the following year.
- Fourth is the fact that "the genetics of complex CNS disorders is advancing beyond where it would have been imagined just four or five years ago."
- Fifth, there is a "real revolution in the ability to interrogate the pathophysiology of neurological disease," driven by technology-enabled progress in biomarker research. "We see a time that is happening right now where there will be patient stratification and early diagnosis enabled by biomarkers," stated Ehlers.
- And finally, he highlighted increasing openness on the part of regulators to new ideas: "innovative trial design informed by

Michael Ehlers

patient need and experience will allow us to proceed through development more rapidly," he said.

Still, as the company's chief medical officer Al Sandrock admitted, "No-one would consider [neuroscience R&D] low-hanging fruit. It's hard and full of risk."

TRANSFORMING THE MEDICAL ROLE

In recognition of the historically high rate of failure in CNS drug development, Sandrock outlined ways in which Biogen is trying to "greatly improve CNS disease treatment" while doing all it can to de-risk its pipeline work. Some of that springs directly from a reappraisal of his own role within the company. "I have been CMO at Biogen for quite a number of years but the CMO role has evolved. I used to be in charge of all development, starting from R [research] to D [development] transition all the way to Phase III and post marketing. Now my role is mainly medical, so I'm not directly involved in R&D although I sit on a committee called the product development operating council."

According to Sandrock, "medical is one of the areas in biopharma that's transforming the most," notably through the potential to use real-world evidence and big data analytics to quantify clinical experience and "make the clinic more of a place where you can actually learn about disease."

He is ambitious in this regard. "I am going to turn it into something that I think hasn't been seen before. Where we really put the patients in the center and we say how can we improve the practice of medicine with the use of our drugs, with the use of diagnostics, with the use of monitoring tools – how can we maximally improve neurological healthcare on behalf of our patients?"

This will involve shifting from simple static diagnosis – running an MRI scan to confirm the suspected presence of a disease like multiple sclerosis, for example – to quantifying, tracking and ultimately providing optimally tailored treatments for individual patients.

"So we're working with a lot of companies that are doing digital tracking and passive monitoring. Also, in the clinic we have an iPad-based device, for example, where MS patients come into the clinic 30 minutes before their appointment and get their vision, cognition, upper extremity function, ambulation, etc systematically recorded, almost the way we would in a clinical trial. We're also capturing patient-reported outcomes. And we are working with Siemens to quantify the MRI images. We're also getting biological data, and we're combining that with electronic health records," he explained.

"And if you put all that together, you can really transform how we measure change in these patients. One day I'm hoping that we'll get to the point where physicians

have a decision support device where you put all the data – genetics, imaging, clinical, wearable data and so on – and you can then say, based on real-world evidence, for this type of patient, they are most likely to respond to drug A versus drug B, and if they don't respond to drug A, you'd know it quicker, and then you'd know what's the next best drug."

OPTIMIZING NEUROSCIENCE DRUG DEVELOPMENT

Back in drug development, when it comes to maximizing the potential of the pipeline, Biogen is spreading its neuroscience bets over a range of areas with a range of therapeutic approaches and partnerships.

As well as programs to expand its already strong multiple sclerosis franchise, it is looking at Alzheimer's disease, Parkinson's disease and movement disorders, neuromuscular disorders like spinal muscular atrophy (SMA) and amyotrophic lateral sclerosis (ALS), pain, stroke and more. It has a range of biological, small-molecule, antisense and gene therapies under investigation.

The company told *Scrip*: "We continue to be interested in exploring new modalities, such as gene therapy, to expand the target space for neurological diseases. In addition, we expect to remain active in exploring partnering opportunities that would complement our portfolio."

ALZHEIMER'S R&D

Biogen's Alzheimer's pipeline is industry leading, and – with the help of its partnership with **Eisai Co. Ltd.** – it has four separate programs at Phase II or above, including two advanced monoclonal antibodies against the amyloid-beta (Aβ) peptide (aducanumab and Eisai-led BAN2401) and Eisai-partnered elenbecestat, one of the last remaining BACE inhibitors following the failure of a string of others in the class. But recent trial results for BAN2401 prompted widespread confusion and the future of aducanumab hinges on the results of a Phase III trial which is not due to read out until early 2020. *(Also see "Biogen, Eisai Report BAN2401 Seemingly Positive In Alzheimer's; Others Skeptical" - Scrip, 26 Jul, 2018.)*

Despite the ongoing uncertainty, Sandrock believes data so far from the company's double punt on late-stage Aβ-targeting antibodies in Alzheimer's – another field littered with casualties, including Pfizer/**Johnson & Johnson**'s bapineuzumab and **Eli Lilly & Co.**'s solanezumab – suggest it is on the right track.

"Aducanumab and BAN2401 are similar antibodies. They don't bind to the same epitope, but it's very similar. Not just the epitope, but also the specificity for aggregated forms of Aβ versus monomeric forms of Aβ. So here are two different companies with two different antibodies, showing basically the same result: a substantial reduction in amyloid plaque burden and a slowing of cognitive decline. When I used to work in a lab, the highest form of validation was if a different lab used similar reagents and reproduced the result you got in your own lab. I feel like something similar has happened here."

It's a question of using the right biomarkers and designing trials to answer the right questions, Sandrock explained. "This in general applies to neuroscience: it's very risky, but if you use the right biomarkers, conduct the studies in a way that you can learn even from the failures, then I think we won't be wasting our shareholders' investment, we'll be moving the field forward, and then we'll probably still have failures but at least we'll learn from them."

COMBINATION POSSIBILITIES

In the longer term, Sandrock envisages the possibility of combination therapies being developed for Alzheimer's. "One reason we licensed Aβ and tau [the anti-tau antibody BIIB092 was licensed from **Bristol-Myers Squibb Co.**] is that we believe combo is the way to go in future. We have plans to do combinations but we want to get monotherapy data first. We are starting to do animal models. I see a day where you do PET scans to see toxic proteins are building up in a patient's brain. In future we will talk about amyloidopathies, tauopathies, synucleopathies and so on, and that is how we will treat it."

AND THEN...MARKET ACCESS

If the magnitude of the scientific challenge is daunting when it comes to Alzheimer's R&D, success would lead into a new challenge: market access and reimbursement. On this front, Biogen is engaging with payers in different ways, Vounatsos said.

Obliquely, it is enhancing its engagement with policy leaders in Europe via the three anti-TNF biosimilars it has launched under its **Samsung Bioepis Co. Ltd.** joint venture with **Samsung BioLogics**, which "enhance the value proposition and the sustainability of the system" by enabling large savings for public payers and creating "head room for innovation."

But it is also engaging early with policy makers in key markets including in Europe, Japan and the US on the specific issue of preparedness for new Alzheimer's therapies. Vounatsos pointed out that it won't just be about reimbursement – there will be infrastructure needs to provide early diagnosis and monitoring and potentially new treatment modalities. Nevertheless, the already spiraling costs to society of the disease and "the increasingly progressive attitudes of healthcare systems and regulators give us hope that policy leaders will invest in infrastructure to give access to treatments" – although "the amount of work needed in the next five to seven years is staggering if we want to have a meaningful impact."

STAYING AHEAD

Meanwhile, Biogen cannot bask for long in the remarkable success of its **Ionis Pharmaceuticals Inc.**-partnered antisense therapy Spinraza. A competitive threat is looming in the shape of the potentially one-time gene therapy treatment AVXS-101 acquired by Novartis in April, which is under FDA review. Unfortunately, an investigational new drug (IND) application for Biogen's own gene therapy for SMA, under development in partnership with University of Pennsylvania, has been placed on hold by the FDA, after the agency had questions about preclinical data.

In its mainstay area of multiple sclerosis, the outlook is challenging in the face of rising competition and reimbursement challenges. Analysts at Leerink in an Oct. 29 note thought Biogen had "the resources and research to remain at the forefront of the category, but it is still likely to lose share and price over time and faces flat-to-declining sales." Nevertheless, they view Biogen's pipeline for serious neurological diseases as its "most interesting part" which "could unlock tremendous value."

With more than a year to go before the next moment of truth in its late-stage Alzheimer's pipeline, the world's oldest biotech will need to keep its foot to the pedal on building up its other assets (and potentially building them out with acquisitions and partnerships) if it is to make the most of the brave new world of neuroscience for the years to come.

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Winner Takes All: New China Bidding Scheme Marks Price Watershed?

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Shanghai leads China's national "4+7" drug centralized procurement

China is shortly to implement a pilot consolidated, volume-based procurement program that looks likely to set the tone for drug pricing for years to come, and which is already creating worry within the pharma industry as official efforts to rein in rising drug and healthcare costs continue.

A total of 11 cities, including four 'megacities', will participate in the centralized bidding scheme, representing the bulk of the total pharma sector in the country. The program will initially be run for 31 drugs, including some widely prescribed products, and for the first time will cross provincial borders and fully cover China's largest urban pharma markets.

The so-called "4+7 Program" will start in the four top-tier cities of Beijing, Tianjin, Shanghai and Chongqing, plus seven second-tier urban centers of Shenyang, Dalian, Xiamen, Guangzhou, Shenzhen, Chengdu and Xi'an.

BIDDING PROCESS

Under the pilot scheme, the areas will appoint representatives to form a centralized Joint Procurement Office, and will bid for the supply of the drugs at the lowest price on behalf of public hospitals in their areas The overall oversight body will be the Shanghai Pharmaceutical Centralized Bidding Services Management Agency, and a notice released by the agency on Nov. 14 confirmed the public bidding will initially include 31 medicines.

In the past, products from multinationals were able to compete with similar drugs from other companies under China's "one product, two kind (one domestic, one international)" bidding rule.

However, the new. highly centralized procurement scheme will not only break previous provincial pricing boundaries but will mean that the previous premium prices often available to MNCs' drugs, given their generally higher quality, will be affected by head-on competition with cheaper domestic generic medicines that have cleared bioequivalence testing.

MASSIVE VOLUMES AT STAKE

The 4+7 scheme, the first-ever nationwide drug bidding pilot, will bring together demand from the 11 cities; Beijing, Shanghai and Guangzhou represent the top three cities for pharma sales in China, while the others are the largest provincial cities.

The drugs in the centralized bidding process notably include some widely-prescribed medicines, such as cardiovasculars atorvastatin, rosuvastatin, clopidogrel, amlodipine and losartan, antiviral entecavir, CNS drugs paroxetine and risperidone, and anticancer agents gefitinib, imatinib and pemetrexed.

By existing volume, the largest drug to be affected is amlodipine, marketed as *Norvasc* by **Pfizer Inc.** and also dozens of domestic makers, followed by clopidogrel, sold by **Sanofi** as *Plavix* and domestic competitors **Shenzhen Sabrius** and **Henan Shuaike**.

Under the new bidding process, the buyers will procure quantities for one year, and if the quantity is used up before that term, manufacturers will be expected to supply the drug with the same price.

Some notable drugs included in the procurement process, and the total initial quantity subject to the bidding rules, are as below:

BRAND NAME	GENERIC NAME	TOTAL QUANTITY (TABS)	ORIGINATOR
Crestor	rosuvastatin 10mg	15.672m	AstraZeneca
Lipitor	atorvastatin 20mg	8.285m	Pfizer
Norvasc	amlodipine 5mg	29.38m	Pfizer
Cozaar	losartan 50mg	6.281m	MSD
Plavix	clopidogrel 25mg	18.32m	Sanofi
Baraclude	entecavir 0.5mg	4.133m	BMS
Paxil	paroxetine 20mg	1.85m	GSK
Risperdal	risperidone 1mg	3.4m	J&J
Iressa	gefitinib 250mg	491,500	AstraZeneca
Gleevec	imatinib 100mg	2.53m	Novartis
Alimta	pemetrexed 100mg	39,100	Eli Lilly

(Source: Scrip, Shanghai Pharmaceutical Centralized Bidding Services Management Agency

'NOT A RIGHT MOVE'

Already, representatives from research-based multinational drug makers have expressed opposition to the pilot scheme. Jean-Christophe Pointeau, president of the R&D-based Pharmaceutical Association Committee (RDPAC) said "it's not a right move" and hoped the government would reconsider the policy. RDPAC is a major industry trade group representing 40 firms in China.

"Using a 'winner takes all' stance [in the bidding] over certain drugs can't solve [drug pricing] issue," he was quoted as saying during an interview with Bloomberg News. "Because it can cause supply issues and can lead to quality concerns. People can lower drug manufacturing costs, but it should not be at the expense of drug quality, " said the executive, who is also the president of Sanofi Pharma China.

"The industry is communicating with the government to reconsider the policy," he added. "We need to work together to solve the cost-control issue and benefit more patients, the key is how to achieve it."

Compared to the dismay from multinationals, however, domestic companies see some positives from the drastic change to the drug bidding mechanism. "The pilot will certainly lower drug prices but it may not achieve the intended results," Zhou Lin, Vice President of local firm Jingxin Pharmaceutical, told local media. "Volume-based bidding has to ensure fair pricing and good competition, fair and just. Good competition means no irrational price reduction, otherwise the market will be damaged."

STRONG MNC SALES GROWTH

The new bidding process is the latest move to rein in drug prices, especially for large-selling cancer and cardiovascular treatments. The latest quarterly sales figures show many major firms are continuing to grow well from local increases for established products, propelling companies such as Sanofi and Pfizer to double-digit growth in China.

Sanofi saw its sales grow 18% in China compared to last year, and these were up 11% from the previous quarter. The reasons cited included a recent data forgery scandal that drove patients to imported vaccines.

Pfizer grew 24% in the quarter, driven by continued established product growth. "So the growth potential over there [in China] is substantial. And we will continue investing, particularly by relocating our management team and providing autonomy to this business to operate from China," said incoming CEO Albert Bourla, who will replace Ian Read in January.

MOUNTING PRESSURE

Despite the concerns expressed by RDPAC, it seems there will be no relenting from the government in proceeding with the pilot, which is set to be implemented on Dec. 6.

Drug pricing issues in general have been high on the central government's agenda due to continued public outcry over the pricing of, and access to, effective medicines for life-threatening conditions including cancer. In August, the newly established Medical Insurance Agency lowered the prices of 14 widely prescribed cancer drugs by 3-7.8%, with an average cut of 4.8%. *(Also see "China Vs. Cancer: Seven Companies Given Price Cuts, Roche Gets New Approval" - Scrip, 21 Aug, 2018.)*

The majority of the products affected are from multinationals, which accounted for seven out of the nine companies hit by the new cuts, perhaps adding to such companies' concerns about the new bidding process.

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From the editors of PharmAsia News.

New US Cholesterol Guidelines Hit PCSK9s Hard On Pricing, Value

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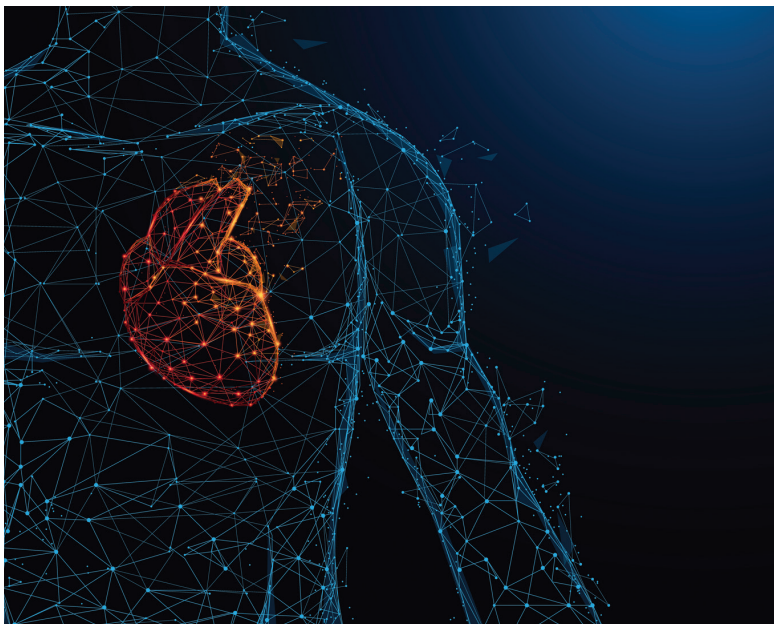
New US treatment guidelines for cholesterol management include branded injectable PCSK9 inhibitors for the first time along with mainstay generic oral statins, but also flag high list pricing and demand cost-effectiveness.

Joint guidelines on managing cholesterol from the American Heart Association (AHA) and American College of Cardiology (ACC) were released on Nov. 10 at the AHA annual meeting in Chicago and published in *Circulation*. It's the first update since 2013, though some consensus documents to help guide use of new therapies have been released in the last five years. *(Also see "PCSK9 Sales Still Slow, But May Get Boost From Label, Guideline Changes" - Scrip, 4 Aug, 2017.)*

One general change from 2013 is more of a focus on treatment goals, **Massachusetts General Hospital** cardiologist Amit Khera explained in a Nov. 13 editorial in *Circulation*.

High cholesterol traditionally has been managed according to LDL-cholesterol goals, but the 2013 version de-emphasized numeric targets in favor of treating based on calculation of risk. Statins were preferred as they were supported by extensive randomized, controlled outcomes data and nonstatin therapies were de-emphasized,



due to the lack of supporting outcomes data. "The new guidelines represent a comeback of sorts for both LDL-C thresholds and non-statin therapies. The authors recommend additional nonstatin therapy predominantly for those at higher-risk with explicit LDL-C thresholds at which to consider these therapies," Khera said.

Since the last version was released, a lot has changed in the landscape of cholesterol management. **Merck & Co. Inc.**'s IMPROVE-IT study showed positive results for *Zetia* (ezetimibe) in 2014, though not positive enough for the US FDA to approve an outcomes claim for preventing cardiovascular events. Zetia is now available as a generic.

The focus on prices and cost-effectiveness for nonstatin therapies is a new feature for the guidelines

Two PCSK9 inhibitors – **Amgen Inc.**'s *Repatha* (evolocumab) and **Sanofi/Regeneron Pharmaceuticals Inc.**'s *Praluent* (alirocumab) – were approved in mid-2015; they're indicated for patients with familial hypercholesterolemia (FH), a genetic condition, and on top of diet, statins and/or other cholesterol-lowering therapies to lower LDL-C. Positive outcomes data were released later – as a result, Repatha has a cardiovascular outcomes claim in US labeling and a similar claim is now under review for Praluent. *(Also see "PCSK9 Inhibitor Labeling Parity Is Within Reach As Praluent And Repatha Strive To Make Commercial Case" - Pink Sheet, 20 Aug, 2018.)*

And, positive outcomes data in the REDUCE-IT study were released at the AHA meeting on Nov. 10 for **Amarin Corp. PLC**'s prescription fish oil product *Vascepa* (icosapent ethyl).

There wasn't time to consider the Vascepa data for the 2018 guidelines update and there have not yet been discussions about when the next guidelines for cholesterol will be released; it may be another five years, according to the AHA.

WHAT THE GUIDELINES SAY

Suggested use of nonstatin therapies is focused on very high-risk patients with atherosclerotic cardiovascular disease (ASCVD) and LDL-C ≥70 mg/dL despite maximal statin therapy.

The guidelines advise that in very high-risk patients (that is with a history of multiple major ASCVD events or one major ASCVD event and multiple high risk conditions) it is "reasonable to add ezetimibe to maximally tolerated statin therapy when the LDL-C level remains ≥70 mg/dL (≥1.8 mmol/L)."

In very high-risk patients whose LDL-C remains ≥70 mg/dL on maximally tolerated statin and ezetimibe therapy, "adding a PCSK9 inhibitor is reasonable, although the long-term safety (>3 years) is uncertain and cost effectiveness is low at mid-2018 list prices," they note.

"The requirement for ezetimibe first was based on generic availability, tolerability, safety and lower cost and appreciating that a significant proportion of individuals would achieve an LDL-C <70 mg with this strategy. However, if ASCVD event reduction is proportional to the absolute change in LDL-C, PCSK9 inhibitors would be more effective at event reduction than ezetimibe in these higher-risk groups," Khera's article states.

The list price in mid-2018 was in the $14,500 range for both Repatha and Praluent. However, in October, Amgen lowered its list price to $5,850, in an effort to help Medicare patients with out of pocket expenses, which are based on the list price. The company took the step of lowering the list price for all payers, though it may take time to roll this out across the board, due to existing contracts. *(Also see "Amgen Drops Repatha List Price 60% To Cut Medicare Co-Pays And Boost Use" - Scrip, 24 Oct, 2018.)* Sanofi/Regeneron previously pledged to lower Praluent's net price and have been aggressive with discounts in negotiations with payers to secure favorable reimbursement. *(Also see "Let's Make A Deal: Sanofi/Regeneron Extend A Hand On Praluent, Express Scripts Takes It" - Scrip, 1 May, 2018.)*

Per the guidelines, for patients with severe primary hypercholesterolemia who have LDL-C of 100 mg/dL or more while on statins, adding ezetimibe is reasonable. After that, adding PCSK9 is reasonable for those with multiple risk factors, with the same caveats about long-term safety and low cost-effectiveness. These patients would typically have familial hypercholesterolemia (FH).

For those with FH, guidelines advise that for those with no clinical evidence of ASCVD, PCSK9 inhibitors "provide uncertain value" at mid-2018 US list prices.

NEW FOCUS ON COST

The focus on prices and cost-effectiveness for nonstatin therapies is a new feature for the guidelines.

"The new guidelines included an explicit value statement about PCSK9 inhibitors, stating that at mid-2018 list prices, they have a low value (>$150,000 per quality-adjusted life-year)," Khera noted.

"All models project higher lifetime cost from use of PCSK9 inhibitors because the cost will exceed any savings from prevention of cardiovascular events. To be cost-effective by conventional standards, the cost of PCSK9 inhibitors will have to be reduced on the order of 70% to 85% in the United States," the guidelines explain.

Stanford University cardiologist Mark Hlatky, a member of the guidelines writing committee, told *Scrip* that the value statement in the new treatment guidelines was based on a rigorous review of evidence from published cost-effectiveness studies.

"That was not just a matter of opinion. It was a very careful review of the cost-effectiveness in seven different models," he said.

Khera concluded that the new inclusion of value considerations in the guidelines is a positive step, but the challenge in "embedding the calculations in treatment algorithms is that value changes with pricing."

Indeed, the price point of both PCSK9 inhibitors is coming down, although not yet to the level where they would be considered to offer high value, that is with a quality per adjusted life year of <$50,000, Khera said.

PRICE A PROBLEM FROM BEGINNING

Despite robust LDL-lowering, the PCSK9 inhibitors have had a tough time getting established. Amid wide availability of cheap and proven oral statin generics, insurers balked at the annual wholesale acquisition cost of about $14,500 a year. Furthermore, the drugs launched without outcomes data.

In the third quarter of 2018, more than three years after the launch in the US, Sanofi reported that Praluent sales were up 64.3% to €68m

($78m) of which €41m was generated in the US (+46.4%) and €22m in Europe (+83.3%). Amgen reported $120m in sales (+35%) for Repatha in the same period.

The demonstration of outcomes benefits has helped the drugs, as have lower costs. When outcomes data from the ODYSSEY study were released in March, Sanofi/Regeneron announced they would lower pricing for Praluent in line with findings of the third-party Institute of Clinical and Economic Review (ICER).

ICER had concluded that the range for the net price for Praluent for high-risk patients with LDL of at least 100 mg/dL despite intensive statin therapy should be $4,500 to $8,000 per year, depending on risk, with the highest-risk patients at the upper end. *(Also see "PCSK9 Turning Point? Sanofi/Regeneron Dangle Lower Price Carrot For Praluent " - Scrip, 12 Mar, 2018.)* For those who have had an acute coronary syndrome and event in the past year and an LDL-C ≥70 mg/dL, ICER concluded the value price range was $2,300 to $3,400 per year.

Amgen told *Scrip* that since it announced its new lower price for Repatha in the US at the end of October, five large statewide and national plans have added the lower priced version of Repatha at a fixed tier copay for both commercial and Medicare plans.

Amgen views the guidelines as a direct result of positive outcomes data for PCSK9 inhibitors and as confirmation of cost effectiveness for very high risk patients," Amgen said.

"We look at the guidelines as they stand as a positive step for patients," in that they clearly articulate that high-risk patients, similar to the population enrolled in the FOURIER outcomes study, benefit from treatment, Scott Wasserman, head of cardiovascular development at Amgen, said in an interview.

However, Wasserman said that he personally does disagree with the guidelines' advice to add ezetimibe first before a PCSK9 inhibitor. That may not be the right choice for everybody, as with ezetimibe you get an additional 20% reduction in LDL-C, but some patients need more, he said. Wasserman also said that he was a little surprised by the focus on cost-effectiveness in the new guidelines as cost-effectiveness modeling is complex and based on a lot of assumptions that change with time. For example, the mid-2018 $14,500 list price is already outdated when it comes to Repatha.

Sanofi/Regeneron said in a statement that with the new guidelines and the ODYSSEY Outcomes study, "there is an increasing body of clinical evaluation and evidence reinforcing the need for high-risk patients to be able to access PCSK9 inhibitors, including Praluent."

However, the guidelines make it clear that statins are the primary treatment and that Zetia is the first choice as an add-on therapy to statins. The document notes the volumes of cholesterol-lowering data supporting statins for primary and secondary prevention, and describes the randomized controlled data for nonstatins as add-on drugs to statin therapy as "important" but "limited."

The guidelines say that more data are needed to determine the full scope of the benefit of nonstatin drugs. For example, additional randomized controlled trials are needed to show whether a lower limit for LDL-C attainment exists, "beyond which the incremental benefit attained is worth neither the risks nor the cost of additional therapy."

Also, additional trials are also needed to show either they are safe for those with statin-associated side effects and safe and effective in those over 75 is unclear, the document notes.

University of California San Francisco cardiologist Rita Redberg, a critic in the past of what she believes is over-treatment with statins, views the new ACC/AHA guidelines as very cautious with respect to PCSK9 inhibitors – reflecting both concerns about the cost and the outcomes data for Repatha and Praluent.

In FOURIER, Repatha demonstrated an additional 15% reduction in risk for major adverse cardiovascular events (MACE), including cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina or coronary revascularization. But it did not show a significant reduction in cardiovascular or overall mortality.

In ODYSSEY Outcomes, Praluent was associated with a significant, 15% lower rate of MACE, which included death from coronary heart disease, nonfatal heart attack, fatal or nonfatal stroke and unstable angina requiring hospitalization.

Praluent was associated with a 22% lower risk of death from any cause (hazard ratio 0.78, 95% confidence interval 0.65 to 0.94; nominal p=0.01). This was enhanced in patients followed for at least three years and those with LDL-C of at least 100mg/dL at baseline, the companies noted in a presentation of updated data at the AHA meeting in November.

However, Redberg said that the very small benefit on mortality in ODYSSEY isn't really that convincing. "I would say the jury is still out," she added.

WILL PCSK9 PRICING COME DOWN EVEN MORE?

Amgen says that lowering its list price for Repatha to $5,850 was a hard decision, but one that it had to take, since 75% of Medicare patients were walking away from their scripts. As to whether that will be low enough, the company said it is still early days and the US system is very complex.

"This is a unique solution for this unique situation and we need to see how the situation evolves over time with this change," Wasserman said. Regeneron noted that its net price of Praluent of $4,500 to $8,000 was designed for payers that allow more straightforward, affordable patient access, though its list price of $14,600 per year has stayed the same.

"In this dynamic market, we'll continue to thoughtfully look for sustainable solutions that will break down the barriers to patient access and affordability," Regeneron said.

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The Inevitable Is Coming: Price Increases, Starting With Pfizer

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As 2019 approaches, a big question is how drug makers will handle annual US price increases, usually taken on marketed drugs in January, in an increasingly hostile political environment. Even with the industry in President Trump's crosshairs on the issue of high drug prices, some amount of drug price hikes seems inevitable given how reliant the industry is on them to drive top-line growth.

Pfizer confirmed Nov. 16 that it is raising prices on some of its medicines, although the announcement wasn't particularly surprising given that CEO Ian Read had indicated as much during the company's third quarter sales and earnings call.

But the big pharma appears to be trying to balance on a tightrope, driving growth where it can while hoping to minimize the damage when it comes to public perception.

The company said it would raise list prices on 41 medicines representing just 10% of its portfolio, effective Jan. 15. The company will maintain current prices on the other 90% of the portfolio. Additionally, the price increases will be rather modest versus prior years, just 5% with the exception of four products, three of which will have a 3% price increase and of one which will go up 9%.

The company would not disclose which product the 9% increase will be on, but argued the increase is warranted due to the completion of two development programs that led to new FDA-approved uses for the medicine.

The list price increases will be offset by higher rebates and discounts to payers, Pfizer said. The net effect on revenue growth in the US in 2019 will be flat, the company added.

Pfizer's transparent update on drug pricing is a notable change for a leader in an industry that has long taken multiple, double-digit price increases on marketed drugs that have flown under the radar of the public. Granted, the company went public with a statement on its 2019 drug pricing plans after news broke in the business media. Nonetheless, Pfizer's statement highlights just how much the company is looking to mitigate damage from taking price increases.

> 'At the very least, threatening to raise prices gives industry a bargaining chip to negotiate some of these policies away' – Ronny Gal

There has been a lot of focus on Pfizer's pricing plans because the company was targeted by Trump in a Tweet earlier this year for taking price increases in July. Read then walked back the decision after a phone conversation with Trump and vowed to hold off on raising prices on any drugs until the new year or until there was action on Trump's drug pricing blueprint.

A lot of other pharmaceutical manufacturers followed Pfizer's lead at the time, agreeing to hold off on price increases for a time, and they may follow the company's lead again now.

PHARMA SQUEEZED BY BOTH PAYERS AND POLICY

Drug makers are in between something of a rock and a hard place when it comes to taking price increases, at least in certain drug categories. The industry has for many years relied on substantial – sometimes even double-digit – price increases on US list prices to help offset higher rebates promised to payers to secure formulary access so that net price increases grow modestly, but don't decline.

Despite the growing outcry over drug price increases, a report from IQVIA earlier this year showed that net price growth was only 1.9% on average in 2017, while price increases on an invoice-price basis grew 6.9% on average. *(Also see "Rebates And Discounts Have A Big Impact On US Drug Prices, IQVIA Report Shows" - Scrip, 19 Apr, 2018.)*

Pfizer said in the statement that the net impact of price increases on its 2018 revenue growth is projected to negative 1% in the US compared with 2017.

"The drug industry kind of has to come back to increasing prices," Bernstein analyst Ronny Gal said in a Nov. 19 research note. "If they don't, they will start missing numbers."

Plus, now that the Trump administration has released some policy ideas that are antithetical to the industry, there is less incentive for the industry to play nice, Gal pointed out.

"At the very least, threatening to raise prices gives industry a bargaining chip to negotiate some of these policies away," Gal wrote.

In October, the Centers for Medicare and Medicaid Services (CMS) announced Medicare Part B reforms, including a proposal to use an international drug price index to determine reimbursement, a daunting threat from industry's perspective. *(Also see "Part B's Foreign Price Bench-marking Will Only Hurt Bad Negotiators, HHS's Azar Argues" - Scrip, 25 Oct, 2018.)*

The US Department of Health and Human Services (HHS) also came forward with a proposed rule that would require drugs and biologics reimbursed through Medicare or Medicaid to include a product's wholesale acquisition cost in direct-to-consumer TV ads, something the industry would like to avoid.

Industry is advocating for a more balanced way to get pricing information to patients. The Pharmaceutical Research and Manufacturers of America (PhRMA) have proposed a voluntary measure requiring members to include in DTC ads information about where patients can go to learn more balanced pricing information, like the wholesale acquisition cost and the cost for the patient after insurance. *(Also see "Industry Makes A Drug Price Transparency Push In DTC Ads, But Is It Too Little Too Late? " - Scrip, 15 Oct, 2018.)*

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Novartis And MSD Triumph At the 14th Annual Scrip Awards

The pharma, biotech and allied industries came together to celebrate another year of excellence at the 14th Annual Scrip awards in London on 28 November hosted by the Right Honourable Lord (William) Hague.

The past year has been another one of change. Those in the industry know that R&D innovation is driving more activity in the sector than ever before. As biosimilars gradually increase their place on the market and payers worldwide demand price restraints, we've seen industry renewal through the development and launch of a number of new therapy modes that truly offer tremendous value to patients and society, from gene and cell therapies to continuing advances in immuno-oncology. Meanwhile, data and artificial intelligence tools are helping to drive transformation across the industry's activities. A glance at the winners of the 2018 Scrip Awards show that the future is bright for biopharma.

The Scrip Awards categories range from those that reward the broader achievements of companies, to those for innovation in deal making, advances in R&D and the more personal accomplishments of teams and individuals. New this year, we introduced the Best Use of Real-World Evidence category to witness to the increasing importance of proving the benefits of new drugs in the market.

Novartis was the night's biggest winner, taking home two trophies: **Syneos Health's Best New Drug Award** for Kymriah, and **Executive of the Year – For Large & Medium Cap Companies (sponsored by Lachman Consultants)** for Vas Narasimham, who took up the role of CEO from Global Head of Drug Development and Chief Medical Officer for Novartis during the qualifying 12 months. Gene therapy company AveXis, which Novartis acquired during the year, also won **WuXi AppTec's Biotech Company of the Year Award**.

The other big winner was MSD, which took home the coveted **Pharma Company of the Year** award **(sponsored by CMIC)** and shared with AstraZeneca the **Licensing Deal of the Year (sponsored by Worldwide Clinical Trials)** for their deal for covering *Lynparza* (olaparib) and selumetinib.

But the night belonged to **Scrip's Lifetime Achievement Award (sponsored by ICON)** winner Sir John Bell.

COMPANIES

The winner of the **Pharma Company of the Year (sponsored by CMIC)** award is chosen each year by *Scrip*'s senior editorial team, based on a variety of key metrics, including its financial performance in the previous year, strategic advances, progress in the emerging markets, and advances in the drug pipeline.

Scrip was impressed by MSD's performance in a most areas, from the political leadership of its CEO Kenneth Frazier, to its financial performance, particularly of its lead immuno-oncology drug *Keytruda* (pembrolizumab), which more than doubled its sales in the 12 months to June 30 this year to $5.5bn, almost surpassing its diabetes franchise. Keytruda also shone in the clinic, where it pulled ahead of its rivals in indications such as lung cancer.

Then there were MSD's deals. In addition, to the alliance with AstraZeneca for the anticancers Lynparza and selumetinib, it entered into a multi-cancer global strategic oncology collaboration with Eisai centered around *Lenvima* (lenvatinib), while in M&A has committed more than $900m to acquire two innovative biotech companies Rigontec and Viralytics. And in terms of giving back, MSD donated more than $2.7bn in grants and product donations in 2017. Indeed, in the qualifying period, the company announced its commitment to donate, through to 2025, an additional 100 million doses a year of its river blindness treatment to eliminate that parasitic disease.

WuXi AppTec's Biotech Company of the Year Award (sponsored by WuXI AppTec) went to gene therapy company AveXis. AveXis published ground-breaking Phase I clinical results with its proprietary gene therapy AVXS-101 for the one-time treatment of spinal muscular atrophy, the number one genetic cause of infant mortality. In May, AveXis was acquired by pharmaceutical giant Novartis for $8.7bn – a deal which "spoke volumes," the judges said, while noting that the firm had produced some of the "most compelling gene therapy results ever."

For the CRO categories, new giant IQVIA won the **Best Contract Research Organization – Full-Service Providers** category in a close race. The judges came down for IQVIA because of its de-identified patient records and expertise in virtual trials.

Combining the strengths of its parent companies, this year IQVIA launched new

offerings to further enhance protocol design, site selection, patient enrolment and data quality. It has improved enrolment rates by 60%, and IQVIA Virtual Trials now allows it to recruit patients virtually – removing geographic and logistical barriers.

For **Best Contract Research Organization – Specialist Providers**, the trophy went to Cytel. Cytel has demonstrated its core expertise in trial design and planning as well as expertise in helping sponsors optimize their programs. The judges commended its specialist focus and thought leadership in adaptive clinical trials.

Masters Speciality Pharma's Best Company in an Emerging Market Award (sponsored by Masters Speciality Pharma) went to WuXi Biologics. Working with the proceeds of its June 2017 IPO, China's WuXi Biologics has started constructing three new drug development and manufacturing sites, including one in Ireland. The judges particularly highlighted the fact that it has passed a significant milestone by being approved by the US FDA to manufacture a commercial biologic drug. "An incredible company," they said.

R&D PROGRESS

This year a new category was added to the R&D-based categories, **Best Use of Real-World Evidence**, which went to PAREXEL International for its Multiple Sclerosis Algorithms Development and Validation project. The project overcomes the historical barriers to the use of real-world data in MS research, distinguishing and characterizing MS subpopulations to enable future research. The judges described it as a "new and useful approach to RWE."

Syneos Health's Best New Drug Award (sponsored by Syneos Health) was jointly awarded to Novartis and Kite Pharma/Gilead Sciences for their pioneering CAR-T therapies. *Kymriah* (tisagenlecleucel) and *Yescarta* (axicabtagene ciloleucel), respectively.

These first two chimeric antigen receptor T cell therapies are at the forefront of immunocellular therapy in which a patient's own T cells are engineered to seek and destroy cancer cells, and has been touted as the new frontier of cancer therapy.

Kymriah was approved for pediatric acute lymphoblastic leukemia, a rapidly progressing disease that becomes fatal within a few months if left untreated, and for which previous options were suboptimal. Yescarta was approved for the treatment of adult patients with relapsed or refractory large B-cell lymphoma.

In a very closely fought category, the judges felt these two pipped the competition and that there was little to choose between them. "Outstanding clinical results revolutionizing treatment."

IQVIA's Clinical Advance of the Year Award (sponsored by IQVIA) went to GW Pharmaceuticals' Phase III GWPCARE4 trial of *Epidiolex* for refractory epilepsy.

GW's pharmaceutical formulation of purified cannabidiol Epidiolex (CBD) demonstrated its anti-convulsive effects in refractory forms of pediatric-onset epilepsy – an area with an acute unmet need. In this study, Epidiolex significantly reduced the median monthly drop seizure frequency compared with placebo when added to existing treatment, and was generally well-tolerated.

The judges described this as a "breakthrough" and added: "The recent approval in the US is a remarkable achievement on many levels."

This year the Best Technological Development in Clinical Trials awards were split into two to acknowledge those advances made by larger clinical sponsors, and those by tech companies.

Best Technological Development in Clinical Trials – Clinical Sponsor-focused went to Covance's Xcellerate CRA Dashboard, in another tight category.

Covance has developed the Xcellerate CRA Dashboard to help clinical research associates access to near real-time site-level data anywhere, at any time. The mobile and web-enabled application gives CRAs enhanced visibility to site performance data, reducing the complexity of site monitoring and enabling more effective management. The judges said it was a "significant tool for efficiency and effectiveness."

Meanwhile, the **Best Technological Development in Clinical Trials – Tech Sponsor-focused** was awarded to Medidata's Medidata Rave Engage. This technology is at the forefront of clinical trial virtualization, providing a novel trial platform to enable large, virtual clinical trials, with huge cost savings. "The practicality of this solution is what clinical trials (especially large simple patient registries) needs," the judges said.

DONE DEALS

Deal-making is at the heart of the pharma and biotech industries and the categories here seek to reward the full range of activities.

Licensing Deal of the Year (sponsored by Worldwide Clinical Trials) went to AstraZeneca and Merck & Co (MSD) for Lynparza and selumetinib.

This deal worth up to $8.5bn aims to maximize the potential of two anticancers, AZ's PARP inhibitor Lynparza and Merck's MEK inhibitor selumetinib, by exploring the growing scientific evidence that combining each of these two drugs with other drugs could offer even greater benefits to patients in multiple indications. The strategic collaboration is expected to further increase the number of treatment options available for patients.

The judges lauded this huge deal as highly unusual for two large pharmas, for its size and for the fact it was signed and closed simultaneously. "An unusual aspect is the focus on enabling a combination with each party's own checkpoint inhibitor. Very beneficial for both parties and shows that two big pharmas can work together," they said.

The **Best Partnership Alliance** award went to F-star and Denali Therapeutics for developing a multi-specific platform for delivery of medicines across the blood-brain barrier.

The alliance brings together Denali's expertise in blood-brain barrier (BBB) biology and the development of CNS therapies with F-star's capabilities in engineering antibody Fc-regions. Together, the partners are developing Fcabs (Fc-domains with antigen-binding) against up to three different transporters in the BBB that have the potential to deliver biologic therapies into the CNS.

"Through this structure, F-star is able to realize the full value of its platform and individual program assets and to provide short term returns to its investors. Both parties have a practical and solution-oriented approach to discover and develop targeted molecules for significant unmet needs. The same shared values and mutual respect are evident in the scientific collaboration," the judges said.

Moving to fundraising, this year the **Financing Deal of the Year (sponsored by MC Services)** was split into public and private financings. **The Financing Deal of the**

Year – Public trophy went to Ablynx for its $200m US IPO on NASDAQ.

On October 27, 2017, Ablynx issued its US IPO on the NASDAQ market raising $200m. On October 30, an extra $30m was raised through closing of the underwriters' option. The $230m raised represented the largest biotech IPO in the US for 2017 and closely followed positive Phase III data for Ablynx's lead Nanobody drug candidate, caplacizumab.

One judge commented, "Now that's what I call a public fundraising, US IPO followed by an acquisition by Sanofi, It's academic now on the use of proceeds."

Financing Deal of the Year – Private was awarded to BioNTech's $270m Series A financing. The Series A significantly broadened its investor base to global institutional and other international investors that complement BioNTech's existing investors. It was reported as the seventh largest Series A worldwide ever for a biotech company, and the second largest ever in Europe. "The scale, continuing enhancement of valuation, and ability to avoid bankers deserves recognition," said the judges.

Another important kind of collaboration is that between industry and partners that aim to give back to the wider community.

The **Community Partnership of the Year** award **(sponsored by Medidata)** went to Beximco Pharma with DSM Nutritional Products and Sight & Life Global Nutrition Research Institute to improve nutrition in rural Bangladesh.

This tripartite effort aims to support, for free, community nutrition and health research intended to test, discover, inform and guide policies that can lift the health burden of micronutrient deficiencies from women, infants and children in impoverished regions of rural Bangladesh and South Asia.

This is an "excellent example of public private academic collaboration seeking to explore new models a of care in resource poor settings," said the judges. "This project should be widely supported. It will help improve, as shown by results of research, rate-lowering of pre-birth, lowering rate of still birth and weight of infants born in north-west Bangladesh's rural villages. The outcome of all these efforts by all parties – in Bangladesh, Switzerland and USA – is clearly visible."

PEOPLE AND TEAMS

Finally, the pharma, biotech and allied industries are nothing without the excellent people working within them, and the Scrip Awards has a number of categories to celebrate both individual and team achievement.

The **Business Development Team of the Year (sponsored by Skipta)** was awarded to Evotec's business development team.

"This team has done a large number of substantive and strategic transactions," including a major strategic collaboration with Sanofi to establish a new open innovation platform near Lyon to accelerate infectious disease research and development. "I've been stunned by the value they have created for a discovery and services platform where you normally don't expect those sort of fireworks," commented one judge.

Once again, the highly contested **Executive of the Year (sponsored by Lachman Consultants)** category was divided into two to recognize executives at large and smaller firms.

Executive of the Year – For Large & Medium Cap Companies went to Novartis's new CEO Vas Narasimhan.

During the qualifying year, the then global head of drug development and chief medical officer for Novartis was announced as CEO designate, ahead of the departure of former CEO Joe Jimenez. Since taking the helm, Narasimhan quickly signaled his intention to further Novartis's commitment to digital health, with the goal of achieving a "productivity revolution" by transforming Novartis from a traditional healthcare company into a medicines and data sciences company with a series of bold moves.

The judges said he had a "major influence on future of Novartis, especially his spearheading digital health and technology. Vas is obviously accomplished and now has a perch to dramatically impact the biopharma business model, but needs to demonstrate over the coming years how much his innate strengths as well as Novartis platform can deliver."

The **Executive of the Year – For Small Cap & Private Pharma Companies** went to Raman Singh, CEO of Mundipharma Singapore.

Under Singh's leadership over the past year, Mundipharma achieved an unprecedented expansion of its treatment portfolio through a combination of strategic licensing deals and new product launches. He has driven rapid growth in all metrics, including performance, number of medicines, country presence and number of personnel. Singh has shown "outstanding success in licensing deals and is a key industry opinion leader," the judges said.

SIR JOHN BELL

The highlight of the evening was **Scrip's Lifetime Achievement Award (sponsored by ICON)**, which was bestowed upon Sir John Bell for a career that has spanned academia and industry.

The Canadian immunologist and geneticist – who holds the Regius Chair of Medicine at the University of Oxford – studied first in Canada and then medicine at Oxford on a Rhodes scholarship.

In 1993 he founded the Wellcome Trust Centre for Human Genetics, one of the world's leading centers for complex trait common disease genetics.

He was also a founding director of three Oxford-based biotech start-ups: Avidex, which was initially acquired by MediGene in 2006 and subsequently spawned Immunocore and Adaptimmune; Oxagen; and PowderJect Pharmaceuticals, which was acquired by Chiron Corp, now part of Novartis, in 2003.

He is non-executive chairman of Immunocore, and Sensyne Health, a clinically focused artificial intelligence company. He also serves on the boards of Roche and Genentech and had a previous role on the scientific advisory board at AstraZeneca.

Sir John chairs the scientific committee of UK Biobank and the Global Health Scientific Advisory Board of the Bill and Melinda Gates Foundation, as well as being an advisor to other humanitarian foundations. He served as President of the Academy of Medical Sciences from 2006 to 2011 and was responsible for the working party that produced the Academy's highly influential report Strengthening Clinical Research, which highlighted the need for the UK to focus attention on developing expertise in translational research.

In 2008, he was knighted for his services to medicine, is now one of three UK life sciences champions, and in the 2015 New Year Honours was appointed Knight Grand Cross of the Order of the British Empire for services to medicine, medical research and the life sciences industry.

More Good News For AML As Pfizer And AbbVie/Roche Drugs Get FDA Okay

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The number of drugs approved in the US for acute myeloid leukemia (AML) has gone up by two with the news that the FDA has given the thumbs-up to **Pfizer Inc.**'s *Daurismo* (glasdegib) and **AbbVie Inc.** and **Roche**'s *Venclexta* (venetoclax).

The green lights for Daurismo and Venclexta mean that seven therapies for the disease have now been approved by the FDA since 2017

First up, the agency has approved Daurismo, a once-daily oral hedgehog pathway inhibitor, to be used in combination with low-dose cytarabine (LDAC) for the treatment of newly diagnosed AML in adults aged 75 or older who are unable to have intensive chemotherapy because of its toxicities and comorbidities – almost half of adults diagnosed with AML do not receive chemo for these reasons. The green light was based on data from the Phase II BRIGHT 1003 trial which showed that median overall survival was 8.3 months for patients treated with Daurismo plus LDAC compared with 4.3 months for those on LDAC only.

The approval comes with a boxed warning in case of off-label use rather than relevance to the target population. The FDA noted the risk of embryo-fetal death or severe birth defects, adding that Daurismo should not be used during pregnancy or while breastfeeding.

Daurismo is the second Pfizer medicine to be approved in the US in the last 14 months for AML. *Mylotarg* (gemtuzumab ozogamicin), withdrawn from the market by the company in 2010, got the green light last year from the FDA in combination with daunorubicin and cytarabine for the treatment of adults with previously untreated, de novo CD33 positive AML. *(Also see "Pfizer's Mylotarg Finally Gets CHMP Nod But No New Indication For Sutent" - Scrip, 26 Feb, 2018.)*

POTENTIAL SALES

Granted a priority review at the end of June and now the only FDA-approved hedgehog pathway inhibitor for AML, Daurismo could have sales of around $450m by 2020, according to analysts at Credit Suisse. These could rise substantially with approvals in other indications such as myelodysplastic syndrome (MDS) and acute lymphoblastic leukemia; it is also being studied in patients with myelofibrosis previously treated with JAK inhibitors.

It has been a very successful few months on the regulatory front for Pfizer's oncology projects. Earlier this month, it got the go-ahead for *Lorbrena* (lorlatinib) for ALK-positive metastatic non-small cell lung cancer (NSCLC), while in October the FDA backed its PARP inhibitor *Talzenna* (talazoparib) for advanced breast cancer. In September, the kinase inhibitor *Vizimpro* (dacomitinib) was approved for first-line NSCLC. *(Also see "Pfizer Expands In Breast Cancer With Talazoparib Approval" - Scrip, 16 Oct, 2018.)*

VENCLEXTA

On the same day (Nov. 21) the FDA also granted accelerated approval to Venclexta with LDAC, azacitidine or decitabine for the same indication as Daurismo. The green light was based on results from two studies in people over 75 newly diagnosed with AML regardless of subtypes, including those who were ineligible for intensive induction chemotherapy.

In the M14-358 trial, the rate of complete remission (CR) was 37% (n=25/67) for those who received Venclexta plus azacitidine, while for those on the AbbVie/Roche drug plus decitabine, the rate of CR was 54%(n=7/13). The M14-387 study showed a CR rate of 21% (n=13/61) for those who received Venclexta in combination with LDAC.

The latest approval of Venclexta, an oral B-cell lymphoma-2 (BCL-2) inhibitor, marks the third clearance for the drug granted under priority review by the FDA. It is already available for patients with

chronic lymphocytic leukemia or small lymphocytic lymphoma, with or without 17p deletion, who have received at least one prior treatment and is also being studied in other hematologic malignancies including multiple myeloma, non-Hodgkin lymphoma and MDS. *(Also see "CLL Sector Heats Up, AbbVie/Roche Upbeat About First-Line Venetoclax Combo" - Scrip, 1 Nov, 2018.)(Also see "After MURANO: Roche/AbbVie Map Venclexta's Expansion Past CLL" - Scrip, 12 Dec, 2017.)*

SEVEN AML APPROVALS IN TWO YEARS

The options for AML are on the rise after decades of nothing coming to the market and the green lights for Daurismo and Venclexta mean that seven therapies for the disease have now been approved by the FDA since 2017.

Novartis AG's *Rydapt* (midostaurin) led the way with FDA approval in April last year for FLT-3 mutated AML, while **Agios Pharmaceuticals Inc.** has two drugs on the market – **Celgene Corp.**-partnered *Idhifa* (enasidenib) for the treatment of AML patients with an IDH2 mutation, approved in August 2017 and *Tibsovo* (ivosidenib) for patients who test positive for an IDH1 mutation, which got the nod in July this year. The other approved therapy is **Jazz Pharmaceuticals PLC**'s *Vyxeos* (daunorubicin and cytarabine), which got the FDA okay in August last year for therapy-related AML or AML with myelodysplasia-related changes. *(Also see "Novartis' Rydapt: Two Indications, Two Prices" - Scrip, 1 May, 2017.) (Also see "Tibsovo Approval Makes Agios' Second AML Approval In A Year; Priced At $26k For 30 Days" - Scrip, 20 Jul, 2018.)*

There is hopefully more to come. In September, **Astellas Pharma Inc.**'s *Xospata* (gilteritinib) received its first approval globally, in Japan, for FLT3 mutation-positive relapsed or refractory AML, and as the news about Daurismo and Venclexta hit the wires, the FDA granted priority review status to **Daiichi Sankyo Co. Ltd.**'s closely-watched AML therapy quizartinib, setting an action date of May 25, 2019. *(Also see "First Approval Globally For Gilteritinib, In Japan For AML" - Scrip, 28 Sep, 2018.) (Also see "Daiichi Sankyo Seals Speedier Europe Review For Quizartinib" - Scrip, 5 Nov, 2018.)*

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Bavencio Loses An Opportunity In Ovarian Cancer

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Merck KGAA and **Pfizer Inc.**'s *Bavencio* (avelumab) lost an opportunity to crack the ovarian cancer market early with the anti-PD-L1 checkpoint inhibitor's failure as monotherapy and in combination with chemotherapy in the Phase III JAVELIN Ovarian 200 study of tough-to-treat platinum-resistant or refractory disease.

The companies announced in a Nov. 19 top-line release that the drug missed progression-free survival (PFS) and overall survival (OS) endpoints when tested alone or with pegylated liposomal doxorubicin (PLD) chemotherapy against PLD alone in the three-arm study of 556 women with cancer resistant or refractory to platinum chemotherapy.

Bavencio is one of the more advanced checkpoint inhibitors in development for ovarian cancer and the companies have hoped to be the first in the PD-1/L1 class approved for this indication. *(Also see "Immuno-Oncology Outlook: Bavencio Leads PD-1/L1 Pack In Ovarian Cancer" - Scrip, 18 Jul, 2017.)*

The trial's failure means a delayed regulatory filing for this second-line indication, in turn creating opportunities for competing checkpoint inhibitors in this space, Biomedtracker analysts noted. Meanwhile, Phase III first-line studies in earlier-stage disease are ongoing – the JAVELIN Ovarian 100 study tests Bavencio with chemotherapy and JAVELIN Ovarian PARP 100 tests Bavencio with chemotherapy and Pfizer's PARP inhibitor *Talzenna* (talazoparib). The primary completion dates for these trials are September 2019 and February 2022, respectively.

Many other studies of competing combinations are running at the same time. For instance, **Bristol-Myers Squibb Co.** is studying its PD-1 inhibitor *Opdivo* (nivolumab) in combination with **Clovis Oncology Inc.**'s PARP inhibitor *Rubraca* (rucaparib) in the first-line maintenance setting in the ATHENA study. **Roche** is testing the combination of its PD-L1 inhibitor *Tecentriq* (atezolizumab), its VEGF inhibitor *Avastin* (bevacizumab) and chemotherapy as a first-line treatment in the Phase III IMagyn050 study and in platinum-sensitive relapsed patients in the Phase III ATALANTE study.

SOME POSITIVE EFFICACY SIGNALS REPORTED

Although the just-reported refractory/resistant study of Bavencio missed its efficacy endpoints, there were some positive trends. The hazard ratio for avelumab with PLD versus PLD alone on PFS was 0.78, and the hazard ratio for the OS endpoint was 0.89. Neither of these were statistically significant.

Also, avelumab alone was associated with numerically worse outcomes compared to PLD alone – with a hazard ratio of 1.68 for PFS and 1.14 for OS.

Furthermore, the objective response rate (ORR) secondary efficacy endpoints reported in the study were disappointing at 13.3% for Bavencio/PLD, 3.7% for avelumab alone and 4.2% for PLD alone.

Safety was in line with prior reports in the overall JAVELIN development program, Pfizer and Merck KGAA reported.

The companies explained in a statement that the study enrolled women with aggressive refractory disease and no response to prior platinum-based chemotherapy – patients that are challenging to treat and not typically included in Phase III ovarian cancer studies.

The sponsors believe that while negative overall, study results indicate activity for the combination in these hard-to-treat patients.

Although the companies indicated that efficacy signals were observed in the combination arm compared to PLD, "the limited efficacy and potential for increased adverse events are likely to prohibit use in these patients as they are typically very sick and may experience excessive toxicity," Biomedtracker analysts said.

About 295,000 women are diagnosed worldwide every year with ovarian cancer. Current treatment options include platinum-based chemotherapy, which is given repeatedly in succession, PARP inhibitors

and Avastin. The disease typically is diagnosed late and most patients eventually become resistant to platinum-based chemotherapy. About 70% of those treated with standard of care frontline platinum-based chemotherapy relapse in the first three years and after the first relapse, 20% to 25% have platinum-resistant disease, the sponsors note. The five-year survival rate for those with metastatic disease is lower than 20%.

Interest in applying PD-1/L1 checkpoint inhibitors in ovarian cancer is intense, but while they haven't shown much benefit as single agents, there have been some promising early results for combinations.

JUST THE LATEST BAD NEWS

As a new market entrant in the PD-1/L1 family – having received its first US FDA approval in March 2017 for metastatic Merkel cell carcinoma and now also cleared for locally advanced or metastatic urothelial carcinoma, a crowded indication – Bavencio has not had an easy time making its own way. *(Also see "Pfizer's Avelumab Makes Its Debut, In Rare Form Of Skin Cancer" - Scrip, 23 Mar, 2017.)*

Merck KGAA reported sales of only €19m ($22m) in the third quarter, up from €7m in the year-ago period. Pfizer did not report sales for the drug in the third quarter.

The JAVELIN program includes 30 clinical programs enrolling more than 9,000 patients in greater than 15 tumor types, the companies note.

Prior to the ovarian cancer announcement, the sponsors announced that Bavencio failed in the Phase III JAVELIN Lung 200 study in second-line non-small cell lung cancer (NSCLC). *(Also see "Pfizer/Merck KGAA's Bavencio Fails OS Endpoint In Second-Line Lung Cancer" - Scrip, 15 Feb, 2018.)*

Merck KGAA's R&D chief Luciano Rossetti said at the time that second-line NSCLC and second-line ovarian cancer are minor commercial opportunities.

Previously, in late 2017, Bavencio failed as a single agent third line agent against chemotherapy in the Phase III JAVELIN Gastric 300 study. *(Also see "Pfizer/Merck KGAA's Bavencio Gastric Cancer Failure Not As Bad As It Seems" - Scrip, 28 Nov, 2017.)*

However, the sponsors look well positioned in renal cell carcinoma after reporting positive PFS data for Bavencio with Pfizer's tyrosine kinase inhibitor *Inlyta* (axitinib) in the Phase III first-line JAVELIN Renal 101 study, which was reported at the European Society for Medical Oncology annual meeting in October, though overall survival data are still immature. *(Also see "Pfizer Well-Placed To Lead First-Line Advanced RCC Market" - Scrip, 30 Oct, 2018.)*

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Immunocore Expands IO Pact With Genentech To Target MAGE-A Antigens

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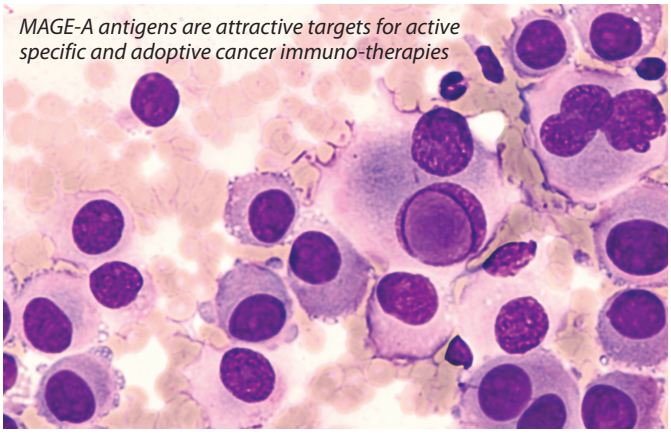
Building on an existing multi-target R&D collaboration, **Genentech Inc.** and **Immunocure** will now co-develop the UK-based T-cell receptor specialist's therapeutic candidate IMC-C103C, a proprietary molecule targeting tumors expressing the protein MAGE-A4 (melanoma-associated antigen A4), with first-in-human clinical trialing set for early next year.



MAGE-A antigens are attractive targets for active specific and adoptive cancer immuno-therapies

Under the terms of the agreement, announced on Nov. 19, Immunocore will lead the clinical study to establish safety and preliminary efficacy of IMC-C103C as both monotherapy and in combination with **Roche**'s PD-L1 inhibitor *Tecentriq* (atezolizumab).

The companies said regulatory applications to support first-in-human clinical studies were in advanced stages of preparation and that clinical trialing was set to start in early 2019 and involve patients across a number of solid tumor types.

The research collaboration centered on IMC-C103C expands an initial partnership, signed in June 2013, to discover and develop multiple novel cancer targets under which Immunocore received an initiation fee of between $10m and $20m per program plus the possibility of receiving more than $300m in development and commercial milestone payments for each target program, along with tiered royalties. That research collaboration agreement is still in effect.

The latest collaboration will see Genentech pay Immunocore $100m in upfront and near-term milestone payments.

If testing successfully establishes proof-of-concept data for IMC-C103C, the UK biotech has an option to continue co-developing IMC-C103C through to commercialization, or to fully license the candidate to Roche-owned Genentech in return for royalty and milestone payments.

MAGE-A human tumor-associated antigens belong to the larger family of cancer/testis antigens (CTA). Melanoma-associated antigen A4 as a CTA is overexpressed in a variety of cancers.

IMMUNOCURE'S IMMTAC PLATFORM

Privately held Immunocore seems to have hit on a successful business model. Its proprietary TCR (T-cell receptor) technology generates a novel class of bi-specific biologics called immune mobilising monoclonal TCRs Against Cancer, or ImmTAC, that combine high-affinity T-cell receptors with an anti-CD3 antibody fragment to activate the immune system to recognize and destroy cancer cells.

The Oxford-based group enjoys biotech 'unicorn' status a start-up valued at more than $1bn and has a number of high-profile collaborations.

'We're excited to move this first molecule forward, both as a single agent and in combination with Tecentriq, and to further explore the role of T cell receptor-directed medicines in fighting cancer' - James Sabry

HAS OTHER PARTNERSHIPS TOO

Besides Genentech, Immunocore also has separate collaborations with **GlaxoSmithKline PLC**, **AstraZeneca PLC**, **Eli Lilly & Co.**, and the **Bill and Melinda Gates Foundation**.

In August, Immunocore announced that its first potential cancer candidate to come out of its collaboration with GSK, named IMCnyeso, had entered Phase I testing in patients with non-small cell lung cancer, bladder cancer, melanoma and synovial sarcoma.

Immunocore also has a co-discovery and co-development collaboration with Eli Lilly to research and potentially develop novel T cell-based cancer therapies. *(Also see "Lilly to trial kinase inhibitors with Immunocore's TCR candidate in melanoma" - Scrip, 29 Jun, 2015.)*

Immunocore and AstraZeneca have a broad program of immuno-oncology combination trials underway. IMCgp100, Immunocore's lead ImmTAC program, is currently in a clinical combination study with **MedImmune LLC**'s PD-L1 checkpoint inhibitor *Imfinzi* (durvalumab) in patients with metastatic cutaneous melanoma who no longer respond to anti-PD-1 therapies.

In 2017, the Bill and Melinda Gates Foundation announced the investment of $40m into Immunocore to support development of Immunocore's ImmTAV (immune mobilising monoclonal TCRs against virus) and ImmTAB (immune mobilising monoclonal TCRs against bacteria) therapeutics for infectious diseases. *(Also see "Gates Foundation's $40m Incentivizes Cancer Specialist Immunocore To Develop TB, HIV Drugs" - Scrip, 18 Sep, 2017.)*

Commenting on the latest research collaboration pact with Genentech, Immunocore CEO Andrew Hotchkiss said: "MAGE-A4 is a known cancer-associated antigen expressed in a wide range of malignancies. Genentech is a leader in oncology with extensive immunology expertise, with whom we've had a good collaborative relationship for several years. We look forward to embarking upon this new partnership to investigate whether IMC-C103C could ultimately improve the lives of people with MAGE-A4 positive cancers."

James Sabry, who heads global pharma partnering at Roche in a statement said Genentech has so far had "a very productive collaboration with Immunocore. We're excited to move this first molecule forward, both as a single agent and in combination with Tecentriq, and to further explore the role of T cell receptor-directed medicines in fighting cancer."

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Takeda/Shire Clears Last Antimonopoly Hurdle – Shareholders Up Next

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The European Commission (EC) has given formal antitrust clearance to **Takeda Pharmaceutical Co. Ltd.**'s proposed acquisition of **Shire PLC**, removing a potential final regulatory hurdle to the deal and further paving the way for this to be completed in early January.

As expected – and already offered by the Japanese company - the Commission's approval was given on condition of fulfillment of a commitment by both companies to divest Shire's Phase III pipeline asset SHP647.

The EC saw future potential overlap for this with Takeda's marketed drug *Entyvio* (vedolizumab), given that both are indicated for inflammatory bowel diseases such as ulcerative colitis and Crohn's disease.

Takeda and Shire have now formally committed to divesting this along with certain associated rights, although Takeda stressed in a statement that the move is not a condition for the completion of the $62bn acquisition of its larger target.

Despite the overnight news from Europe, Takeda's share price fell by about 3.6% in morning trading in Tokyo on Nov. 21, apparently reflecting some lingering investor uncertainty over the upcoming shareholder approval of the deal.

In the meantime, Takeda apparently sees few problems with the process for shedding SHP647, saying it "is an exciting pipeline compound and Takeda expects the asset to attract interest from a number of potential buyers," adding that it remains committed to Entyvio as the "cornerstone" of its specialty gastrointestinal portfolio.

SHAREHOLDERS UP NEXT

Following smooth antimonopoly nods from other major jurisdictions such as the US and Japan, the EC approval was the last such regulatory clearance needed to proceed with the acquisition. While this has lifted some of the remaining uncertainty surrounding the deal, it still needs to be approved by the shareholders of both companies, a process towards which attention is now turning.

Both Takeda and Shire have now set shareholder meetings for Dec. 5, and Takeda re-confirmed that, subject to approvals at these and the court sanction of a Shire scheme of arrangement, formal completion of the deal - the biggest ever overseas M&A transaction in Japanese corporate history - is set for Jan. 8.

While there are still some pockets of shareholder resistance, mainly centered around a group linked to members of Takeda's founding family that together holds an estimated 10% stake, Takeda President

Japan's largest overseas M&A edges closer

and CEO Christophe Weber said in a statement that "we are optimistic that our shareholders recognize the significant long-term value creation potential of this powerful combination."

A two-thirds majority shareholder vote would be needed to move ahead with the deal, which will involve the issue of new shares as part of funding arrangements and result in the merged entity being 50% owned by current Takeda investors.

The dissident group, which excluding the Takeda family is thought to hold around 1%, has expressed its intention to continue pushing against the deal until the end, but there has so far been little apparent support for this stance from retail investors, which currently hold around a quarter of all Takeda shares.

In other developments related to funding arrangements, Takeda recently announced the issue price of $5.5bn in unsecured, US dollar-denominated senior notes and €7.5bn in unsecured Euro-denominated senior notes.

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Santhera To Snap Up Second DMD Drug As Idorsia Climbs Aboard

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With one Duchenne muscular dystrophy (DMD) candidate already on its hands in *Raxone* (idebenone), **Santhera** is close to getting hold of another one – vamorolone – through a option deal inked with fellow Swiss group Idorsia.

Santhera has bought the rights to sublicense vamorolone, which was discovered and is being developed by **Reveragen BioPharma Inc.** of the US. **Actelion Pharmaceuticals Ltd.** had acquired an option to license the product in 2016 but that was subsequently transferred to Idorsia, when it was spun off following J&J's acquisition of Actelion in 2017.

Under the terms of the pact, which covers all indications and territories except Japan and South Korea, Idorsia will receive one million new shares, representing a 13.3% equity stake in Santhera, and an upfront cash payment of $20m, of which $15m will compensate the company's investment in the pivotal Phase IIb VISION-DMD trial of vamorolone being conducted by ReveraGen.

Thomas Meier, Santhera's CEO, told *Scrip* that vamorolone "has been on my radar for quite some time," noting that he formally approached fellow DMD specialist and ReveraGen CEO Eric Hoffman in late 2015 about working together. However, "he said 'you've come too late my friend, we are just about to sign a deal'," Meier noted, and Actelion beat him to it.

> "Thomas Meier, Santhera's CEO, told Scrip that vamorolone 'has been on my radar for quite some time'"

Meier did not give up and contacted Idorsia CEO Jean-Paul Clozel in February this year. The latter firm has four compounds in late-stage clinical development so both parties have now decided Santhera is best placed to maximize the potential of vamorolone.

Vamorolone binds to the same receptors as glucocorticoids but modifies the downstream activity of the receptors, Santhera noted. This has the potential to 'dissociate' efficacy from typical steroid safety concerns, the firm argued and therefore could replace existing glucocorticoids such as **PTC Therapeutics Inc.**'s *Emflaza* (deflazacort), the current standard of care in children and adolescents with DMD which at high doses has severe side effects which limit long-term usage.

The VISION-DMD trial, which is being conducted at 30 sites across North America, Europe, Israel and Australia and will enrol 120 boys, began in August 2018 and is expected to last about 24 months. If successful, Santhera can exercise its option after receiving the data, triggering a one-time $30m payment. Assuming Santhera does take up the option on vamorolone,

Idorsia will be eligible for $80m in regulatory and commercial payments for DMD and four sales milestones totaling $130m, as well as regulatory milestones of up to $205m for three additional indications, plus tiered royalties.

If all goes well, an FDA filing is anticipated by the end of 2020, where vamorolone has fast-track status, with a European submission the year after. Santhera estimated the peak sales potential for vamorolone for the DMD indication at $500m.

Meier said that he was very happy with the way the trial has been designed and praised ReveraGen for "doing the right thing, getting scientific advice from both the European and US regulators. They have done everything the regulators recommended them to do" which should lead to approval if the study goes well.

Meier told *Scrip* that the vamorolone deal "really is a gamechanger, making us the European company in DMD on a par with PTC and Sarepta." The latter has the other DMD drug along with Emflaza to have been approved by the FDA, namely *Exondys 51* (eteplirsen), which addresses a mutation present in an estimated 13% of patients, and "while we are not on the market yet, we have two late-stage assets that are not limited to mutation types."

The other drug he referenced was Raxone, which is already approved for Leber's hereditary optic neuropathy (LHON) but has had repeated knockbacks from European regulators for DMD. The European Medicines Agency's evaluation committee, the CHMP, initially rejected Santhera's request for the DMD indication in September 2017 and following a re-examination said no again in January this year. *(Also see "Definitive Data Hopes Keep Santhera's Duchenne Drug Alive in UK Despite EMA No" - Pink Sheet, 1 May, 2018.)*

The agency repeating its concerns as to whether the observed treatment effect on respiratory function in the company's Phase III DELOS trial translated to a real benefit for DMD patients. However, Meier said the firm has been busy collecting data and is preparing for DMD filings of Raxone in Europe in the first quarter of 2019.

At the same time the Idorsia deal was unveiled, Santhera also announced it is hosting an extraordinary general meeting on Dec. 11 in connection with plans to raise up to CHF50m through the sale of up to 3.5 million shares.

Meier agreed with *Scrip* that the company is going to need more than that to fund its growing pipeline which also contains POL6014, a selective inhibitor of human neutrophil elastase licensed from Polyphor to treat cystic fibrosis and other neutrophilic pulmonary diseases. He said that the financing was prudent and manageable at the moment "to put wood under the keel" to cover activities over the next six months and the initial $20m payment to Idorsia. *(Also see "Santhera Expands Pipeline With Polyphor Cystic Fibrosis Deal" - , 16 Feb, 2018.)*

Once the spring comes next year, more long-term financial solutions will come into play, Meier concluded.

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Multinationals Eye Divesting Established Products In China Amid Fierce Competition, Shifting Focus

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The golden days for some drugs in China seem to be passing, and manufacturers are preparing to battle sizzling competition by raising cash and focusing more on profitable innovative therapies as demand for such products rises.

US giant **Eli Lilly & Co.** has seemingly become the latest multinational pharma firm to decide to divest maturing products in this market, against a background of intense competition for some of its past core products. The company is reported to be looking for potential buyers for multiple products including the best-selling CNS drugs *Zyprexa* (olanzapine) and *Prozac* (fluoxetine), among others. The value of the portfolio to be divested stands at $200-300m.

Lilly has four major CNS treatments in China, comprising *Cymbalta* (duloxetine) and *Strattera* (atomoxetine) in addition to Zyprexa and Prozac. Early this year, medical sales reps in charge of Zyprexa and Prozac were reportedly re-assigned to focus more on the marketing of Cymbalta.

The moves are said to be to raise funds to support the launch of Lilly's innovative new products in China, where encouraging policies for the introduction of new therapies have resulted in a wave of approvals in recent months. One of these is a new indication for Cymbalta for chronic musculoskeletal pain.

Previously approved in China in 2006, Cymbalta is used mainly in depression and anxiety, and the new indication approval will enable it to enter a broader market.

GOLDEN DAYS PAST?

One underlying reason for Lilly's planned product divestments could be the fierce competition facing both Zyprexa and Prozac, which are without patent protection in China and domestic rivals are catching up fast. A total of 17 domestic makers have launched generic versions and one of these, **Jiangsu Hansoh Pharma**'s *Oulanning*, being the first generic now has a market share of 68%, data compiled by local media Menet show.

Fierce competition aside, pricing pressure could be another consideration. The Chinese government recently issued its first-ever nationwide "4+7" centralized drug bidding process, and the "winner takes all" approach is causing concerns among MNCs. *(Also see "Winner Takes All: New China Bidding Scheme Marks Price Watershed? " - Scrip, 20 Nov, 2018.)*

One of the products subject to the bidding process will be olanzapine, and the volume-based bidding is expected to bring prices further downward, especially given that more domestic generics are now clearing mandatory bioequivalence testing.

In a bid to improve the quality of domestic generics, the government has set the end of 2018 as the deadline for 75 commonly used oral drugs to clear such testing, confirming they are as equally effective as originators' products. As an incentive, producers that have passed the BE testing will be able to compete directly with multinationals in the new bidding process.

Multinationals in China divest established products to focus on innovative new products

Similar to Zyprexa, Prozac is also now facing competition from nearly two dozen domestic makers.

NEW PRODUCT ON THE WAY

What may be even more significant to Lilly's strategy is the approval of *Elunate* (fruquintinib), an anticancer agent developed by **Hutchison China Meditech Ltd.** (Chi-Med) and commercialized by Lilly in China. Indicated for colorectal cancer (CRC), Elunate is expected to compete head-on with **Merck KGAA**'s *Erbitux* (cetuximab). *(Also see "New Drug Bonanza as Chi-Med, Eisai, Alexion Harvest Big Wins In China" - Pink Sheet, 7 Sep, 2018.)*

"The approval marks a success for Lilly's partnership with local biopharma to jointly develop innovative new drugs," commented Senior Vice President and head of Lilly China's Oncology business Wang Yizhe. "We hope to launch Elunate soon to benefit late-stage colorectal cancer patients in China." The product has just been launched, a step described as "a major milestone for Chi-Med" by company chairman Simon To.

Elunate is indicated for the treatment of patients with metastatic CRC that have been previously treated with fluoropyrimidine, oxaliplatin and irinotecan, including those who have previously received or are unsuitable for anti-vascular endothelial growth factor (VEGF) therapy and/or anti-epidermal growth factor receptor (EGFR) therapy (Ras wild type). The highly selective VEGFR inhibitor is the first domestically developed treatment for CRC in China, where around 380,000 people are newly diagnosed with the disease annually, making it the fifth most prevalent cancer type in the country.

FROM R&D TO HEALTH MANAGEMENT

There may also be some other broad factors behind Lilly's changing focus in China. In addition to the new approvals, Lilly like other multinationals is increasingly turning to artificial intelligence to transform itself digitally, switching from being centered on R&D to focusing more on total health management.

As evidence of this, in September Lilly China and Microsoft signed a deal to use the latter's AI and cloud computing technology to build a health ecosystem driven by AI, AI+Health. The goal is to become a healthcare solutions provider, via the digitization of current platforms, building a new platform to leverage Lilly's own value proposition, and ecosystem partnership.

Some of the specific measures include online meetings and interactions with physicians, a mobile phone diabetes management tool, and the *iDoctor* physician social network to facilitate discussions. Partnering with one of China's internet giants, Tencent and Tencent-backed DXY, Lilly is providing a mobile diabetes management solution that covers diagnosis to treatment and personalized services.

"AI has been elevated to become a national priority in China, and healthcare is one area with the most potential for AI," said Lilly China GM Julio Gay-Ger in a statement. "Lilly intends to accelerate the use of AI and cloud computing via the collaboration with Microsoft and explore new technology-enabled healthcare to aid [the central government's] Health China 2030 Plan and benefit patients."

ROCHE DIVESTS PEGASYS TO ASCLETIS

The trend for multinationals to ally with local firms for their older established products in China started with **AstraZeneca PLC** and doesn't stop at Lilly.

On Nov. 20, **Roche** China announced that it had entered a partnership for *Pegasys* (peginterferon alfa-2a) for hepatitis B and C infections, granting **Ascletis Pharma Inc.** exclusive sales and marketing promotion rights in Mainland China, starting from Dec. 2019.

First approved in 2003, Pegasys has been on the market for 15 years and the tie-up follows a previous partnership with Ascletis in which Roche licensed its HCV asset danoprevir to the company. The Shaoxing, Zhejiang-based startup developed it within five years and launched in as Ganovo in China.

For its part, Ascletis is aiming to become a specialty pharma centered on infectious diseases, hepatitis and HIV/AIDS, and it has several pipeline products under development for HCV and HIV. Ravidasvir, its leading hepatitis C candidate, is licensed from US-based **Presidio Pharmaceuticals Inc.** and has been filed for marketing approval in China.

Also in the Ascletis pipeline are HIV drug ASC09 and ASC06 targeting liver cancer. The company teamed up with Swedish firm **Medivir AB** in August to obtain Greater China rights to MV-802, a pan-genotypic nucleotide inhibitor for HCV.

Ascletis went on to become the first biotech to go public in Hong Kong under the local stock exchange's revised listing rules. *(Also see "Finance Watch: Ascletis First Biotech To List Under New Hong Kong Rules, BeiGene Joins In" - Scrip, 3 Aug, 2018.)*

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From the editors of PharmAsia News.

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.

PIPELINE WATCH, 16–22 NOVEMBER 2018

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

Phase III

Event Stage	Lead Company/Partner	Drug Name	Indication	Comments	Change To LOA (%)	LOA (%)
Phase III Published Results	Aimmune Therapeutics, Inc.	AR101	Food Allergies	PALISADE; NEJM, Nov. 22, 2018	2	73
Phase III Published Results	Acacia Pharma Group plc	Barhemsys (iv amisulpride)	Emesis	Prior Prophylaxis; Anesthesiology, Nov. 19, 2018	0	93
Phase III Final Results	AstraZeneca PLC	Imfinzi (durvalumab) w/tremelimumab	Non-Small Cell Lung Cancer	MYSTIC; Missed OS Primary Endpoint	0	100
Phase III Updated Results	VBL Therapeutics	VB-111	Brain Cancer	GLOBE; Missed OS Endpoint, Well Tolerated	0	0
Phase III Updated Results	Glenmark Pharmaceuticals Limited	Ryaltris (olopatadine/mometasone)	Allergic Rhinitis	GSP 301-303; Improved Symptoms	0	86
Phase III Updated Results	DBV Technologies	Viaskin Peanut	Food Allergies	PEPITES; Increased Peanut Reactivity Threshold	0	87
Phase III Updated Results	Formycon AG/Bioeq IP AG	FYB201 (ranibizumab biosimilar)	Wet Age-Related Macular Degeneration	COLUMBUS-AMD; Comparable To Reference Product	0	59
Phase III Interim/Top-Line Results	Hutchison MediPharma/Lilly	fruquintinib	Non-Small Cell Lung Cancer, Third-Line	FALUCA; Missed Primary OS Endpoint, Improved PFS	0	6
Phase III Interim/Top-Line Results	Shire Pharmaceuticals Group PLC	Takhzyro (lanadelumab)	Hereditary Angioedema	HELP Study Ext.; Reduced Attacks	0	100
Phase III Interim/Top-Line Results	Merck KGaA/Pfizer	Bavencio (avelumab)	Ovarian Cancer	JAVELIN Ovarian 200; Missed OS And PFS Endpoints	-10	29
Phase III Interim/Top-Line Results	Aimmune Therapeutics, Inc.	AR101	Food Allergies	RAMSES (4-17 Years); Reduced Reaction Severity	0	73
Phase III Interim/Top-Line Results	Stallergenes SAS	Actair (House Dust Mite Allergens)	HDM-Induced Allergic Rhinitis	SL75.14 (EU/US); Met Primary Endpoint	5	67
Phase III Trial Initiation	Corcept Therapeutics Inc.	relacorilant	Cushing's Syndrome	GRACE; In US, Canada And Europe	36	62
Phase III Trial Initiation	Kolon TissueGene, Inc.	Invossa cell and gene therapy	Osteoarthritis Pain	TGC123, TGC15302; In The US	38	67

Source: Biomedtracker | Informa, 2018

Fresh Funding Pushes Inflazome Into Clinic With Inflammation Inhibitors

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"This could be a new paradigm for treating multiple inflammatory diseases," Matt Cooper, CEO of **Inflazome Ltd.** told *Scrip*, when discussing the potential for the company's assets, which are about to enter the clinic in 2019. "And what's exciting is that if it works in several diseases, it may work in several more."

Inflazome is developing in-house small-molecule inhibitors of the NLRP3 inflammasome to stop the cycle of chronic inflammation that drives diseases such as inflammatory bowel disease, gout, osteoarthritis, liver, kidney and cardiovascular diseases.

The Dublin, Ireland-based company has just closed a Series B financing round of €40m ($46m). The oversubscribed financing round was led by Forbion, with Longitude Capital and founding investors, Novartis Venture Fund and Fountain Healthcare Partners, also participating.

"While reviewing the inflammation/autoimmune space for new investments from our recently closed €360m Forbion Fund IV fund, we were specifically attracted to companies developing modulators of the inflammasome for their key regulatory properties in the inflammation process and hence their role in many inflammatory diseases," Marco Boorsma, general partner at Forbion, explained to *Scrip*.

"Our specific interest in Inflazome stems from the founders' and management's vast expertise and experience in immunology, inflammasome biology and inflammasome modulation, their expertise in the discovery and development of a diversified pipeline of NLRP3 inhibitors, and their foundational IP position in the area of NLRP3 inhibition," he continued.

The two-year-old company now holds 29 patents, stemming from the collaborative work of its co-founders, Cooper and its chief scientific officer Luke O'Neil, who is also professor of Biochemistry at Trinity College Dublin, and an academic founder of the recently launched **GlaxoSmithKline PLC**-backed biotech **Sitryx**.

The Series B proceeds will be funneled back into R&D, and to also advance the company's proof-of-concept trials for its first-in-class NLRP3 inflammasome inhibitors into multiple clinical trials in 2019 and 2020.

The company has two programs, a brain penetrative series which could be suitable for Alzheimer's, Parkinson's, Huntington's, motor neurone disease, and even traumatic brain injury. "The target validation for NLRP3 is enormous," Cooper explained. The second program is full of "periphery restrictive molecules" that don't go in the brain, and there the diseases range from non-alcoholic steatohepatitis (NASH), to osteoarthritis to cardiovascular disease.

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APPOINTMENTS

Executive	To Company	New Role	From Company	Previous Role	Effective Date
Stephan Jackman	Alzamend Neuro Inc	Chief Executive Officer	Ennaid Therapeutics	Chief Operating Officer	19-Nov-18
Adam Townsend	Apellis Pharmaceuticals Inc	Chief Commercial Officer	Biogen	Leader, Commercial and Corporate Development	20-Nov-18
Robert Brown	Brickell Biotech Inc	Chief Executive Officer	Eli Lilly & Co.	Chief Marketing Officer	1-Jan-19
Jason Ryan	Magenta Therapeutics	Chief Operating and Financial Officer	Foundation Medicine	Chief Financial Officer	1-Jan-19
Fabio Baschiera	Oculis ehf	Vice President, Clinical Development	Novartis Ophthalmic Franchise	Global Clinical Operations Lead	20-Nov-18
Peter Sallstig	Santen Inc	Senior Vice President, Global Product Development	InsMed Inc	Vice President, Head, Clinical Development	15-Nov-18
Reza M. Haque	Santen Inc	Senior Vice President, Global Research and Development Strategy	Shire plc	Vice President, Medical Affairs and Senior Ophthalmologist in Residence	15-Nov-18

Click here for all appointments: https://bit.ly/2oHWRYn

Source: Medtrack | Informa, 2018

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