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Democrat-Controlled House Will Turn Up The Volume On Drug Pricing

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Drugmakers could see an uptick in congressional investigations, hearings and public pressure to reduce the prices of their products now that the Democrats have regained control of the US House of Representatives, but the prospects for any major legislation aimed at reducing drug prices materializing appear murky at best.

Although the GOP managed to maintain its control of the Senate, Democrats are expected to use their newfound power in the lower chamber to set the stage for the 2020 election cycle.

Drug prices will, therefore, almost certainly stay on their radar in the rhetorical sense. One of the most notable changes likely to come with the Democrat-controlled House is the expected elevation of Rep. Elijah Cummings, D-MD, to the chairmanship of the powerful Committee on House Oversight and Government Reform. Currently the ranking member of the committee, Cummings has been a frequent and harsh critic of biopharma executives, to whom he has routinely cast blame for the "skyrocketing" cost of prescription drugs.

Drug prices have received some degree of bipartisan attention from the Oversight Committee in recent years. Members from both parties have torn into executives from **Turing Pharmaceuticals AG** and **Mylan NV** at a series of hearings on the issue.

But Cummings has also led some more partisan efforts investigating the pricing practices of companies. In November 2016, for instance, Cummings and Sen. Bernie Sanders, I-VT, requested the Justice Department and the Federal Trade Commission (FTC) investigate possible collusion among manufacturers of diabetes products, alleging that "in numerous instances the price increases have mirrored one another precisely."

Similarly, Cummings and fellow Oversight Committee Member Rep. Peter Welch, D-VT, sent letters to a slew of drugmakers in August 2017 requesting information on strategies for pricing their multiple sclerosis products. Now with subpoena power to compel the appearance of witnesses and the production of documents, Democrats on the committee could play a central role over the next two years in dragging drugmakers through the mud.

The House Energy and Commerce Committee, the authorizing committee for the Department of Health and Human Services (HHS) and its various agencies, could also play an investigative role in pressuring drugmakers through its Subcommittee on Oversight and Investigations.

Avalere Health Founder Dan Mendelson told the Pink Sheet in an interview that he believes that there will be "a dramatic increase in investigations" which will focus on topics such as price transparency, alleged collusion on pricing, and rebating policies.

Peter Pitts, president of the Center for Medicine in the Public Interest and a former US FDA associate commissioner, agreed that a Democrat-controlled House will lead to "a litany of hearings and debates on drug pricing under its various manifestations."

Pitts added that discussions of pricing transparency are "entirely appropriate, as

CONTINUED ON PAGE 4

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Headache No More
The migraine market heats up with latest CGPR inhibitor launches (p7)

Specialized Building Blocks
Novartis plans to get ahead of rivals by using innovative technologies (p9)

Soriot Still Standing
First sales growth since 2014 marks turnaround for AZ (p20)

from the editor

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In Switzerland this week, Biogen has been celebrating its 40th anniversary, reminiscing over its formative years in Geneva. Biogen today is rare in having doubled down on CNS at a time when others were taking more measured bets in the field, balancing them with other disease R&D, or getting out altogether. But as the company's executives point out, the advances in understanding neurological diseases, the technologies becoming available to address them and the data analytics to revolutionize research, development, prevention and treatment are driving forward R&D across many different CNS conditions with fresh vigor.

CEO Michel Vounatsos believes CNS is "the new oncology" in terms of investment and progress in the field. The ground-breaking success of its antisense oligonucleotide *Spinraza* (nusinersen, partnered with Ionis Pharmaceuticals), which can enable infants once condemned to a tragically early death from spinal muscular atrophy to live normal lives, is unlikely to be an isolated breakthrough because of wider potential of the science behind it, and because of the multiple other advances that should transform the CNS therapeutic field.

Society will want access to these advances, whether it be in rare conditions like SMA or in common and devastating illnesses like Alzheimer's disease, and companies will need to work with governments around the world to ensure the broader societal benefits are factored into cost-benefit analyses. Otherwise, accounts of the biopharma industry at loggerheads with governments over drugs bills as described in this issue (see cover story, p5) will become the discordant soundtrack to the otherwise happy tale of the triumph of scientific perseverance over once apparently intractable and tragic medical realities.

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Strong Xtandi Drives Astellas To Brighter Outlook
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Japanese firm unveils new capital investment program for novel biologics including antibodies and cell therapies as it ups full-year forecasts on strong US and global growth for Xtandi after a solid first half.

Lilly's CVOT Success With Trulicity Causes Bullish Outlook For Diabetes Franchise
https://bit.ly/2DmjTNe
Lilly reported strong sales growth for many of its recently launched products, but news of the potentially differentiating REWIND cardiovascular outcomes trial data dominated the pharma's third quarter earnings call.

Daiichi Sankyo Seals Speedier Europe Review For Quizartinib
https://bit.ly/2B6oUYB
The acute myeloid leukemia drug is the lead candidate in the strong oncology pipeline the Japan-headquartered company has assembled over the past couple of years.

Mylan Sees Generic Advair Marathon Nearing FDA Finish Line
https://bit.ly/2QHm1mv
Company management expressed confidence its application for the first generic Advair is approvable, although the US agency didn't clear it in October as Mylan had hoped.

Deal Watch: Amgen Outsources Celiac Drug To Provention; Lilly, NextCure Will Co-Discover IO Drugs
https://bit.ly/2PvrdgR
Through its Provention collaboration, Amgen partnered with the team that worked on AMG 714 at Celimmune, which the big biotech bought in 2017. Lilly will partner with NextCure to use the latter's FIND-IO platform for immuno-oncology drug discovery.

Coherus Gears Up For January Udenyca Launch, Prices Biosimilar At 33% Discount To Neulasta
https://bit.ly/2DkM9zA
Buoyed by the market share held by biosimilars of the short-acting neutropenia drug Neupogen, Coherus hopes its Udenyca price, contracts and services will give its biosimilar a significant share of the market for the longer-acting Neulasta.

inside:

COVER / Democrat-Controlled House Will Turn Up The Volume On Drug Pricing

5 'Drastic' Japan Price Reforms Hitting R&D Incentives, Plans – EFPIA

7 Migraine Market Gets Competitive With Second, Third CGRP Inhibitor Launches

9 Narasimhan: Novartis' Specialized Portfolio Will Lead To Bigger Breakthroughs And Greater Value

11 Gilead's FXR Agonist Posts Questionable Results In NASH, But Offers Hope In PSC

14 China Set To Become Global Drug Innovation Center

16 Better Together: New Deal Adds Weight To China Biosimilar/ Biobetter Swap

18 Yuhan Strikes Long-Awaited Lung Cancer Deal Through Huge Janssen Alliance

20 AstraZeneca Q3 Sales Rise 'Is Milestone', CEO Soriot 'Not Leaving'

21 Genentech's Immunology/Infectious Disease Deal Maker On Following The Science

22 **Pipeline Watch**

23 **Appointments**

CONTINUED FROM COVER

long as they include the entire drug pricing ecosystem" that includes the role of pharmacy benefit managers (PBMs) in addition to the pharmaceutical industry.

LEGISLATIVE ITEMS FACE UNCERTAIN FUTURE

But while investigations will likely take a prominent position in the Democrat-led house, the prospects of tangible legislative items related to drug pricing are unclear.

HHS Secretary Alex Azar has explained that there are several aspects of the Trump administration's drug pricing blueprint he believes could be acted on administratively, but there were also several items for which he requested legislative support from Congress, such as the required disclosure of list prices in direct-to-consumer (DTC) advertisements. *(Also see "How Drug Promotion Might Change Under Trump's Rx Pricing Plan" - Pink Sheet, 14 May, 2018.)*

Azar has also sought congressional support for moving drugs from Medicare Part B to Part D to bring some degree of price negotiation to medications administered by a physician. The HHS secretary has stressed that his department has the power to conduct a demonstration or a pilot, although he also said he hopes for additional statutory authority in the future. *(Also see "Part B Drugs Could Be Switched To Part D Under Trump Pricing Plan" - Pink Sheet, 14 May, 2018.)*

An area of the blueprint for which Azar has said definitively necessitates legislation is the end of gaming of the 180-day first generic exclusivity clock, where a first generic sponsor sits on its exclusivity and prevents the entry of additional generics. *(Also see "Congressional Action On Drug Pricing Blueprint Likely To Be Modest" - Pink Sheet, 14 Jun, 2018.)*

However, broader, more partisan healthcare issues will likely take priority over any items related to biopharma policy, as the Democrats will seek to develop a platform to battle Trump in the 2020 presidential election.

"The focus is really going to be on pre-existing conditions and 'Medicare for All,'" Mendelson said. "And the goal really will be to set the stage for the next election."

With the Democrats controlling only one house of Congress, "really what they get is a megaphone," Mendelson continued. "They don't get the ability to shape the policy in a way that is meaningful without giving the president legislative victories."

Nevertheless, it is possible that Democrats could join with Trump in passing legislation that fits his drug pricing agenda if enough Republicans in the Senate get on board, says Dan Judy, a research analyst at North Star Opinion Research.

"It's not crazy to imagine Democrats in Congress putting something together pulling a few Republicans over from the Senate who have been working on these issues for a long time, passing something that the president will sign," Judy said Oct. 24 at an Alliance for Health Reform reporter's breakfast. "If it's a comprehensive solution [to drug pricing] that remains to be seen."

Legislation for list price disclosure in DTC advertisements could be one of the areas where the stars align, as Democrats – and to a smaller extent Republicans – have made legislative efforts in the past on the issue.

The Senate initially approved an appropriations bill in August with an amendment sponsored by Sen. Chuck Grassley, R-IA, Dick Durbin, D-IL, and Angus King, I-ME, that would authorize HHS to develop regulations requiring the disclosure of list prices in DTC advertising, although the provision was ultimately stripped from the final bill. *(Also see "DTC Ad Price Disclosure Provision Stripped From US Funding Bill" - Pink Sheet, 19 Sep, 2018.)*

Congress is unlikely to develop bipartisan support for moving drugs from Part B to Part D. Several Democrats from the Senate Committee on Health, Education, Labor and Pensions have expressed skepticism about whether the B-to-D shift would work. *(Also see "Shifting Medicare Part B Drugs To Part D: Legislative Prospects Cloudy" - Pink Sheet, 14 Jun, 2018.)*

If Democrats decide not to hand Trump any legislative victories, it will likely stymie the extent to which Azar can carry out the blueprint and limit any further moves to those that can be accomplished through regulatory action.

In the Senate, there is likely to be little change in the general approach to drug pricing. However, biopharma will lose one steadfast champion with the retirement of Sen. Orrin Hatch, R-UT. *(Also see "Sen. Hatch, Biopharma Industry Champion, Ready To Hang Up His Gloves" - , 3 Jan, 2018.)* Grassley has been floated as his potential replacement as chairman of the Finance Committee.

POTENTIAL DEMOCRATIC ITEMS

Pitts predicts that with Democrats in charge of the House, the lower chamber will put forward what he calls "a banner of bad ideas." One such policy would be a renewed push for a broad drug importation program, Pitts says.

FDA is currently exploring a narrow drug importation program targeting sole-source products that are off-patent and off-exclusivity. Although agency commissioners have historically opposed drug importation, FDA has stressed that any resulting policy would be narrowly tailored. *(Also see "Drug Importation Can Be Triggered By 'Excessive' Price Increases; Now US FDA Has To Decide What That Means " - Pink Sheet, 19 Jul, 2018.)*

Any broader importation program would also likely fail to get passed the Senate, as Republicans have consistently shot down such proposals.

Pitts further posits that House Democrats will likely call for banning DTC advertising or removing the tax write-offs for it. They may also facilitate discussions on the Bayh-Dole Act, which permits universities to seek ownership of inventions made with federal funding, Pitts says.

Democrats are also expected to renew their push for authorizing HHS to negotiate drug prices directly with manufacturers in Part D. But congressional Republicans have consistently opposed the idea, as has Azar himself, which makes any possibility for legislative traction inconceivable.

The Trump administration instead has touted its allowing of Medicare Part D plans to negotiate indication-specific pricing for prescription drugs starting with the 2020 benefit year, as well as Medicare Advantage plans to use step therapy to manage Part B drugs, as ways to lower costs. *(Also see "Medicare Part D Plans Can Start Negotiating Indication-Based Pricing This Fall" - Pink Sheet, 30 Aug, 2018.)* and *(Also see "Step Therapy For Medicare Part B Drugs Will Lower Costs By 20%, HHS Projects" - Pink Sheet, 8 Aug, 2018.)*

With a Democrat-controlled House, industry is expected to face greater challenges in promoting its own legislative priorities than

it would have if Republicans held their majority in both chambers. One of biopharma's top priorities is legislation reducing the discount for branded drugs provided to beneficiaries in the Medicare Part D coverage gap. An increase in the discount from 50% to 70% was slipped into a funding bill in March, catching industry lobbyists off guard.

The Pharmaceutical Research and Manufacturers of America (PhRMA) has been working to reduce the increase ever since, so far unsuccessfully. *(Also see "Part D Coverage Gap Discount Relief Misses Ride On Opioids Bill" - Pink Sheet, 30 Sep, 2018.)* But industry is expected to make a big push in the coming weeks.

In other Part D reforms, PhRMA wants lawmakers to attend to the pending coverage gap "cliff" with legislation that would correct, or at least delay, an upcoming surge in out-of-pocket spending requirements for seniors in the gap. The increase is scheduled to begin in 2020. The Affordable Care Act changed the way that the Part D out-of-pocket spending threshold had originally been indexed in order to slow its trajectory. But that was a temporary fix that expires at the end of 2019.

PhRMA has also been pushing for reforms of the 340B drug discount program. The group's aim is to rein in the scope of the program, which has grown exponentially in recent years without a corresponding increase in regulatory oversight. Both chambers of Congress have held hearings on 340B but consensus on legislation to reform it may take time. *(Also see "340B Reform: US House Bills Mark The End Of The Beginning" - Pink Sheet, 12 Jul, 2018.)*

POTENTIAL PHARMA CHAMPIONS DEFEATED

Although the Republicans held onto their majority in the Senate, there were two notable GOP candidates who lost that biopharma would have liked to see in the upper chamber: Bob Hugin in New Jersey and Patrick Morrisey in West Virginia.

Celgene Corp.'s former CEO, Hugin lost his bid to unseat the incumbent Democrat Bob Menendez. Hugin spent 19 years at Celgene working in several different capacities, most recently serving as the company's executive chairman. *(Also see "Appointments: Celgene, Merck KGaA, Ipsen, Ablynx, Advicenne, Dragonfly, Ritter And The ABPI" - Scrip, 31 Jan, 2018.)*

Hugin has publicly echoed industry's frequent argument on drug pricing, which is that the list price does not reflect the price that consumers pay for their medication amid a complex supply chain.

Morrisey, for his part, lost out to incumbent Democrat Joe Manchin. Currently Attorney General of West Virginia, Morrisey previously worked as a lobbyist for the pharmaceutical industry during his time in private practice. A victory for either candidate would could have meant a new lawmaker to fill Hatch's shoes in the Senate as the biopharma sector's biggest cheerleader.

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'Drastic' Japan Price Reforms Hitting R&D Incentives, Plans – EFPIA

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The European research-based pharma industry federation EFPIA is warning that the "drastic" new criteria for the price-setting of original drugs adopted in Japan in April are unduly focused on short-term government cost savings, and are already prompting some its local members to revise their R&D strategies given increased business uncertainty.

Dr Jean-Christophe Tellier, vice president of EFPIA globally, warned at a press conference in Tokyo that the 2018 reforms to the country's reimbursement price calculation system under its national health insurance scheme are causing a loss of predictability, and in some respects are "ignoring" the need to sustain the industry's costly innovation.

While the European group "is very conscious about the importance of Japan's universal healthcare system," the tightening of eligibility requirements for the price maintenance premium system (PMP) in particular – which exempts certain original drugs from regular price cuts for their patent life – is "putting innovation at risk," he cautioned.

"These changes may create a fear of an unstable environment" within the industry, the chairman and CEO of **UCB Group** told the meeting, something that could call into question companies' investment plans at a time when Japan is facing a rapidly ageing population and rising overall healthcare costs.

HIGHER ELIGIBILITY HURDLES

The PMP system was first adopted in April 2010 on a trial basis, and originally granted all new drugs exemption from Japan's regular biennial price cuts until patent expiry. However, the April 2018 changes raised the bar and narrowed the scope for eligibility, being applicable to only the first three best- or first-in-class products, while a new "company scoring" system is also now taken into account.

In addition, there was a shift towards annual (rather than biennial) regular price revisions based on actual market prices, expanded repricing of big-selling drugs, and the adoption of a trial cost-effectiveness assessment scheme. However, uncertainties and a lack of clarity remain around how some of these will be implemented and managed.

Tellier praised Japan's "wonderful track record" in speeding up approvals, describing its ability to provide a reimbursement price (and thereby national access) very soon after an approval as the "best in the world." But he cautioned that the changes this year mean "the 'drug lag' [in approvals versus the US and EU] may resurface due to corporate worries."

Dr Ole Mølskov Bech, chairman of EFPIA Japan, added that many of the group's local members are receiving planning queries from their head offices over the shape and implementation of the planned April 2019 price revision, but are not able to provide much guidance at the moment due to a lack of policy clarity.

ALREADY IMPACTING R&D PLANS

Bech, who is president of **Novo Nordisk AS** in Japan, told the Tokyo media briefing – part of an 'EFPIA Day' in Japan – that the future impact of last April's policy revisions is likely to follow a 2017 EFPIA Japan simulation that predicted a 1.5% compound annual decline in the country's prescription new drug market over the 2015-26 period.

Stating that the old PMP system had served patients well, he said "the balance between the sustainability of Japan's NHI system and support for innovation was lost in the reforms."

In terms of the actual impact on EFPIA Japan members so far, as determined through a survey in September, Bech disclosed that 14 out of 15 respondents said they had had products excluded from the PMP, with 65 active ingredients pushed out of the scheme in total for all local EFPIA members (an average of 4.6 per company, but ranging up to 11).

Two of five respondent companies said they no longer get full price protection for relevant drugs due to the new company eligibility criteria, with two saying that more than half of their total sales had been impacted by the exclusion of products from the PMP.

"These policies are already affecting current and future company R&D policies for Japan," Bech stated. 50% of 14 local EFPIA members said they had already changed their strategy, with 11 out of 14 saying they would do so in the future.

"A key problem with the scheme is that it does not recognize [non-PMP-qualifying] products launched later but that may have significant patient benefits," Bech said. There is now no pricing evaluation of factors such as improved dosing convenience or improved safety/efficacy, providing little development incentive for such products, he added.

Against this background, EFPIA proposed that the PMP criteria be reviewed so that innovation with clear patient benefits can be accurately recognized within the system.

CEA WORRIES

Another facet of the April 2018 reforms was the formal introduction of a pilot cost-effectiveness assessment (CEA) scheme, which initially will be applied only to a limited group of seven selected products with potential high budget impact and on a post-approval basis, to determine if calculated prices are appropriate.

But both Tellier and Bech highlighted the focus in this process on the cost of drugs, rather than a more holistic view of the wider societal and longer-term value of medicines. CEA needs to be transparent and involve all stakeholders, especially patients, Bech said - "They can highlight what is important and what outcomes are most valuable to them."

EFPIA is concerned that the routine adoption of the process could lead to delays in new product launches, and is proposing a "careful review" before full implementation to make sure the process "serves the right purpose."

The European group also believes the system should not be used to make reimbursement decisions, and that it be only a supplement to the current pricing system (into which certain CEA elements are already built in). It would also like to see an expansion of the "sakigake" scheme, that grants expedited reviews to pioneering new products, and the conditional early approval scheme, to make these "competitive" with the US and EU.

GREATER COLLABORATION

The executives were also careful to re-state EFPIA's willingness to participate in discussions n Japan's healthcare challenges, with Tellier suggesting the creation of knowledge exchange platforms and support for alliance building and research.

"There is a need to maintain a good balance in health spending and we want to stimulate this" the CEO said, pointing to the industry-academia-government Innovative Medicines Initiative in Europe as a successful example.

Globally in the pharma industry, "the science today is as vibrant as ever," he observed, while in Japan the quality of science, the healthcare system and clinicians remain very high. "Everything is there to support science and innovation," but there is room to improve the collaborative approach.

Addressing a question from *Scrip* on how this might be achieved practically, Bech said that EFPIA had no specific proposals but that "it would make sense to do something similar in Japan along the lines of the IMI. This could generate value to address some of the needs, and this could be something to discuss with Japanese health authorities" as part of ongoing dialog.

REGIONAL COMPETITIVE POSITION

Both EFPIA representatives emphasized that Japan does not operate in isolation, and in senior Big Pharma management's eyes it is competing with other big global markets for its share of strategic investment, adding to the need for supportive, patient-centric policies.

This is particularly true given forecasts that Japan will be the only major prescription market globally to decline in the 2017-22 period.

Bech highlighted the raft of recent regulatory reforms in China that are encouraging innovation, aligning regulatory requirements with global norms, accelerating reviews, expanding reimbursement for high-need drugs, and more strongly protecting intellectual property.

"But it is not only the big markets. Singapore for example, with fewer than six million people, has also been highly successful in attracting significant investment from global pharma companies through corporate R&D incentives and tax breaks" that have built employment and increased output, he observed. *Published online 11 November 2018*

From the editors of PharmAsia News.

Migraine Market Gets Competitive With Second, Third CGRP Inhibitor Launches

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The launch of the CGRP inhibitors marked the biggest shakeup in the migraine market since the triptans started going generic – and the sponsors were pushed during their third quarter earnings calls for details that can help clarify the competitive landscape.

Amgen Inc.'s and **Novartis AG**'s *Aimovig* (erenumab), which the FDA approved in May, is the only CGRP inhibitor that's been on the market long enough to generate significant sales. Its $22m third quarter figure was notable since the company still is negotiating many of its contracts with payers and patients are receiving the subcutaneously administered biologic for free until their health plans or pharmacy benefit managers (PBMs) agree to cover the drug. *(Also see "Amgen's Aimovig Aims To Capture As Many Migraine Patients As Possible With $6,900 Price" - Scrip, 17 May, 2018.)*

Amgen and Novartis had a short-lived lead in the race to commercialize the injectable migraine prevention treatments. **Teva Pharmaceutical Industries Ltd.**'s *Ajovy* (fremanezumab) won FDA approval on Sept. 14 and launched in the US about two weeks later. *(Also see "Is Quarterly Dosing For Teva's Ajovy Enough To Differentiate It From Other CGRP Inhibitors?" - Scrip, 17 Sep, 2018.)* The agency endorsed **Eli Lilly & Co.**'s *Emgality* (galcanezumab) on Sept. 27 and the product launched in October. *(Also see "Lilly Looks To Emgality Access, Injector And Data To Differentiate Its CGRP Inhibitor " - Scrip, 28 Sep, 2018.)*

Market access was top of mind, as **Express Scripts Holding Co.** announced in mid-October that it would cover Aimovig and Emgality, but exclude Ajovy, from its formulary. *(Also see "Teva Stands By Migraine Strategy After Ajovy Misses Boat On Express Scripts Deal" - Scrip, 17 Oct, 2018.)*

Apart from the new launches, **Allergan PLC** defended its blockbuster *Botox* (onabotulinumtoxinA) and the company's growing migraine franchise, which includes a pair of CGRP inhibitors, and **Alder Biopharmaceuticals Inc.** hyped its intravenous anti-CGRP biologic eptinezumab, which is on track for a first quarter 2019 FDA filing.

Lilly also noted the recent submission of an additional on-demand migraine treatment for US FDA approval, lasmiditan, which could be the first of a new wave of entrants to the migraine market.

LOOKING FOR PAYER UPDATES

During its Oct. 18 call, Amgen's partner Novartis projected confidence about the launch to date, and Amgen filled in some of the blanks during its Oct. 30 call, noting that in addition to the partners' nearly exclusive deal with Express Scripts they are in active discussions with several other payers, including **Kaiser Permanente** and **Anthem Inc.** Amgen also noted that about 70% of free prescriptions have been converted to paid drug.

Teva had to reassure investors that Ajovy sales will not fall significantly short of its competitors because of its exclusion from the Express Scripts national preferred formulary, which covers 15% of commercially insured lives.

Executives insisted during Teva's Nov. 1 earnings call that the company is in the midst of negotiations with multiple payers, and it expected each agreement to look different – though it signaled discounts could be in the 25%-30% range. Some health plans and PBMs will cover one or two drugs, while others will cover all three CGRP inhibitors, and discounts will vary in each scenario, executives noted.

Amgen is making progress with payers beyond Express Scripts, including Anthem and Kaiser, and about 70% of free prescriptions have been converted to paid drug

Teva reported positive reception for Ajovy's primary distinguishing feature, a quarterly dose on top of the monthly dosing common across the class. The company noted that about 20% of Ajovy prescriptions are for the quarterly dose, which was more than Teva expected, and boosted expectations that availability of both monthly and quarterly doses would be a differentiating factor compared with the product's rivals, which are approved only as monthly treatments.

But while more than 1,600 doctors prescribed Ajovy during its first four weeks on the market, Amgen noted that about 12,000 prescribers and 100,000 patients have experience with Aimovig. However, the first-in-class product's growth trajectory is expected to moderate with the launch of competing CGRP inhibitors, Amgen told investors.

"We would expect a marketing battle to begin as each of the drug companies plots a strategy to 1) gain share of new patients, and 2) generate meaningful sales down the road," BTIG analyst Timothy Chiang said in a Nov. 2 note about Teva's earnings call.

BTIG estimates that Ajovy's sales will total $160m in 2019 and more than double to $380m in 2020, with sales exceeding $1bn by 2023.

Oppenheimer's Esther Rajavelu forecast $5m in 2019 and $58m in 2020 sales, growing to $617m in 2022.

"In our view, Amgen/Novartis has the benefit of being the first product to gain FDA approval in May. Since its introduction in May, Aimovig prescription volumes have ramped with 41,125 new and 67,348 total prescriptions dispensed in September, according to Symphony Health," Chiang wrote.

Leerink's Geoffrey Porges said in an Oct. 31 note that it may be difficult to assess the success of CGRP inhibitor sales for some time, given the amount of free drug Amgen, Teva and Lilly are providing to get patients started on their products and since significant discounts are being given to payers – as much as 40%-60% under the Express Scripts deals – to win reimbursement. BTIG's Chiang suggested Teva will have to increase its discounts from the 25%-30% it indicated, "as its competitors may be offering even greater discounts."

Oppenheimer pegged the US market for CGRP inhibitors at $15bn, assuming a 54% gross-to-net discount on the three approved products' list price, which is $6,900 per year for Aimovig, Ajovy and Emgality. Rajavelu said each of the anti-CGRP drugs could bring in $3bn-$5bn in annual peak sales.

BUILDING A MIGRAINE FRANCHISE: LILLY, ALLERGAN, AMGEN

Lilly didn't spend much of its Nov. 6 quarterly call talking about Emgality, but the company noted that the antibody also was recommended for approval in the EU during the third quarter – catching up with Aimovig and Ajovy, which were previously endorsed in Europe. In addition, Emgality is expected to be approved in Japan this year. *(Also see "Lilly Moves Into Migraine Race With CHMP Okay" - Scrip, 24 Sep, 2018.)*

Lilly Bio-Medicines President Christi Shaw said that the company intends to be a migraine market leader with Emgality and the acute migraine therapy lasmiditan – an oral drug administered on demand to stop a headache. A new drug application (NDA) for lasmiditan, which selectively targets 5-HT1F receptors expressed in the trigeminal pathway, was submitted during the third quarter. *(Also see "Phase III Lasmiditan Data Strengthens Lilly's Dual Migraine Strategy" - Scrip, 5 Aug, 2017.)*

"As we look at the marketplace, we see it continuing to grow. We like our chances in terms of being able to compete," Shaw said. "With the entire franchise we have in migraine of both preventative and acute [treatments], we think we're a leader."

Emgality will be commercialized outside of migraine as well. The antibody garnered a breakthrough therapy designation from the FDA in the third quarter for the prevention of cluster headaches, and Lilly intends to submit a supplemental biologic license (sBLA) for this indication before the end of 2018.

Teva also is developing Ajovy for cluster headache, but only for episodic cluster headaches after the drug failed in a Phase III chronic cluster headache trial. *(Also see "Teva's CGRP Inhibitor Fails In Chronic Cluster Headaches, Continues In Episodic" - Scrip, 15 Jun, 2018.)*

Amgen and Novartis have not pursued this indication for Aimovig, but like Lilly, the partners are developing a multi-drug migraine portfolio. Amgen should have Phase II results for AMG 301 before the end of 2018 in the prevention of episodic and chronic migraine headaches and intends to present the data at a medical meeting in 2019.

The company has said that AMG 301, a pituitary adenylate cyclase-activating polypeptide type I (PAC1) antibody, will be developed on its own and in combination with Aimovig.

However, Amgen Executive Vice President-Research and Development David Reese told the company's earnings call that "should we see efficacy, the question will then be, is there a distinct population of patients that may respond to PAC1 receptor inhibition as compared to CGRP inhibition? And that would be something that the development program would be intended to determine going forward."

ORAL AGENTS COMING

Allergan has been focused on oral CGRP inhibitors, and it hopes to add two to its migraine portfolio to go along with Botox, which has been approved for chronic migraine prevention (15 headaches or more per month) since 2010. Both of the CGRP inhibitors were licensed from **Merck & Co. Inc.** in 2015 to expand its portfolio in this indication. *(Also see "Allergan migraine portfolio grows with Merck CGRP antagonists" - Scrip, 8 Jul, 2015.)*

Ubrogepant, which may be the first oral CGRP inhibitor on the market, will be submitted for FDA approval in the first quarter of 2019 after Allergan reported positive Phase III results in the acute treatment of migraine headaches earlier this year. *(Also see "Allergan's Ubrogepant Succeeds In Second Acute Migraine Phase III Study" - Scrip, 27 Apr, 2018.)*

A Phase III program is just getting under way for the company's second oral CGRP inhibitor atogepant for the prevention of chronic and episodic migraines (14 headaches or less per month). The late-stage studies follow positive Phase IIb results reported this year. *(Also see "Migraine Drug Atogepant Delivers Good News When Allergan Needs It Most" - Scrip, 11 Jun, 2018.)*

Allergan Chief Commercial Officer Bill Meury said during the company's third quarter call that Botox therapeutic sales grew 12% year over year with revenue coming from all of its approved indications, which include migraine, spasticity and overactive bladder, among others. Meury said he expects the neuromodulator to peacefully co-exist with CGRP inhibitors, including Allergan's own, and anticipates that migraine will become one of the company's biggest indications via Botox plus ubrogepant and atogepant.

He noted that only about half of patients treated with CGRP inhibitors are responders and about half of Botox-treated migraine patients respond to the Allergan product, which shows that the market has room for both treatment options. "I think the outlook for 2019 and beyond is positive," Meury said.

Allergan's biggest oral CGRP inhibitor competitor, **Biohaven Pharmaceuticals Holding Co. Ltd.** will report its third quarter earnings on Nov. 13 but said when it reported second quarter financials that the company still intends to submit rimegepant for FDA approval as an acute migraine treatment in 2019. Biohaven reported positive results from two acute migraine studies earlier this year, but it now plans to initiate a Phase III trial for rimegepant in migraine prevention in the fourth quarter. *(Also see "Biohaven Posts Positive Migraine Results, But Investors Are Wary" - Scrip, 26 Mar, 2018.)*

The company also expects to report long-term Phase III safety data for rimegepant and reveal results from a Phase III acute migraine study for a fast-dissolving formulation during the fourth quarter. Biohaven licensed its lead drug candidate and the intranasal CGRP inhibitor BHV-3500 from **Bristol-Myers Squibb Co.** and said on Oct. 22 that it has initiated a Phase I study for BHV-3500, which will be developed for migraine prevention and acute treatment. *(Also see "Deal Watch: Ionis Turns To Affiliate Akcea In Amyloidosis" - Scrip, 15 Mar, 2018.)*

ALDER SEES A BIG NICHE FOR EPTINEZUMAB INFUSION

Oral CGRP inhibitors could steal significant market share when they launch in 2020 from the first three approved therapies in this class, which are all injectable, but Alder is also progressing with eptinezumab, a quarterly infusion that also may launch in 2020 after a first quarter 2019 BLA submission to the FDA.

Alder argues that eptinezumab has a rapid onset following intravenous infusion and better efficacy than injectable CGRP inhibitors, with 30% or more of patients experiencing a 75% or greater reduction in monthly migraine headaches. *(Also see "Response Rates Rule In CGRP Inhibitor Migraine Studies" - Scrip, 12 Jun, 2017.)*

The company noted in an investor presentation in September that there is a sizeable group of "procedure-oriented" neurologists, pain specialists and primary care physicians who have experience giving infused therapies for fairly common neurological indications, including migraine, multiple sclerosis and epilepsy. Each of those 3,000 doctors sees 150-200 migraine patients each month and 80% of the people they're treating are highly impacted by the disease. Those prescribers, Alder anticipates, can be addressed with an in-house commercial team of 75-125 sales representatives.

Alder's research shows that there are 5m-7m highly impacted episodic and chronic migraine patients in the US, and 52% like the idea of an infusion to prevent their headaches because of the convenience of receiving treatments only four times per year, and because they see infused medicines as working sooner and more potently than other drugs.

"We see potential for eptinezumab as an alternative treatment following failure of other CGRP ligand/receptor targeted treatments with the unique quarterly I.V. infusion profile providing additional differentiation vs [subcutaneous] competitors," BMO Capital Markets analyst Matthew Luchini said in a Nov. 5 note about Alder's third quarter update.

Morgan Stanley's Jeffrey Hung was less optimistic, saying in a Nov. 6 note: "While we acknowledge that eptinezumab may have some advantages with formulary access, being the only infused anti-CGRP, we believe Alder could face pressures on pricing and patient access like the rest of the class."

The company was encouraged by the prescription data that Amgen shared for Aimovig during its third quarter report, Alder CEO Robert Azelby noted during his company's call on Nov. 5.

Azelby said that despite available generic and branded medicines, "there is clearly a large unmet need for preventative therapy, and we believe both migraine treatment penetration and anti-CGRP class share will grow significantly over the coming years. This has been further validated by the recent anti-CGRP launches where prescription data from the first few months of launch suggesting over 100,000 patients have already been prescribed an anti-CGRP."

Alder also has a migraine portfolio strategy, but its next monoclonal antibody candidate for the condition is in preclinical development – the pituitary adenylate cyclase-activating polypeptide-38 (PACAP-38) inhibitor ALD1910. A first-in-human study is expected to begin in late 2019.

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Narasimhan: Novartis' Specialized Portfolio Will Lead To Bigger Breakthroughs And Greater Value

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When Vas Narasimhan stepped into the CEO shoes in February he set out a strategy to focus **Novartis AG** as a leader in transformational medicines by investing in differential technologies that will enable it to outgrow its competitors. During the company's first R&D day since the previous R&D chief took over at the top, in London on Nov. 5, he talked to journalists about the progress made towards a specialized portfolio on the back of three innovative technologies, and the challenges involved.

Novartis has made swift and decisive moves already in executing this strategy, with decisions to quit consumer healthcare with a sale to **GlaxoSmithKline PLC** of its stake in their Consumer Healthcare Joint Venture, to spin off **Alcon Inc.** *(Also see "Novartis Sees The Light And Plumps For Alcon Spin-Off " - Scrip, 29 Jun, 2018.)*, and to sell some of its Sandoz US generics business to **Aurobindo Pharma Ltd.** *(Also see "Big Statement By Aurobindo As It Seals $1bn Sandoz US Deal " - Scrip, 6 Sep, 2018.)*. This came in tandem with a two acquisitions designed to bring in novel technology platforms and deepen its innovative medicines portfolio. It announced a $2.1bn purchase of radiopharmaceutical company **Endocyte Inc.** last month, building on last year's $3.9bn acquisition of **Advanced Accelerator Applications SA** (AAA), and in April spent $8.7bn on gene therapy company **AveXis Inc.** to get its hands on a promising gene therapy technology plus a lead candidate, AVXS-101, a potential cure for infants with type 1 spinal muscular atrophy (SMA). *(Also see "Novartis Tunes Into Radiopharmaceuticals With Endocyte Buy" - Scrip, 18 Oct, 2018.) (Also see "Novartis Goes Big On Gene Therapy With $8.7bn AveXis Acquisition" - Scrip, 9 Apr, 2018.)*

Together with its established cell therapy platform that produced Kymriah, Narasimhan said, the gene therapy and radioligand technologies these acquisitions brought form the three "platforms for innovation that I believe on top of small molecules and biologicals will be enable us to get to new medicines that will have significant impact and hopefully also drive our financial performance and growth."

Narasimhan said the deals were just a start. "We have been building in-house capabilities in these three areas but I do have a belief that we need to continue to do bolt-on acquisitions in our innovative meds core," he told *Scrip*. "Historically, when we were a much more diversified company our capital needed to be spread out across many different businesses, we needed to do acquisitions in generics, or animal health or consumer health,

and now with this new focus we can go deeper into these new areas where we want to build leadership but also in invest in. I believe that over the long term, if we do that consistently and make bolt-on acquisitions and deals to complement our internal capabilities, we will build a much more valuable company over time."

Narasimhan said the stakes were high but the investments justified. "There are higher risks as you continue to focus on small molecules and biologics. I think there is a risk in not pushing into new technologies and new areas of science to find breakthrough medicines. I think in the end society will always reimburse and pay if we find these breakthrough medicines and that's going to require us to move beyond our previous playing fields. I want us to be a company that is willing to make the bets to go there. We may not always get it right but I think that gives us a better chance to be a leading, high technology innovative medicines company."

Getting in early is key to fending off rivals, he says. "My bet in these three platform areas is getting out ahead leads to a difficulty for others to follow." With CAR-T therapy Kymriah, for example, Novartis has already forged strong links with treatment centers around the world, and has built a fully scaled and licensed manufacturing network. "Our ability then to be the logical partner of choice for smaller companies with new technologies as well as to use our own discoveries gives us a big advantage because anyone else building from scratch is basically Novartis in 2015 – we have a four-year head start on them." This is no different with the radioligand technology, he added, given the supply chain logistics in handling radioactive material, which must be received by the patient before it degrades. "All the intricacies involved in that again gives us a head start."

Gene therapy will differ in that it is a much more competitive arena. "Our bet there is around the manufacturing platform and we will have scaled facility in Chicago and North Carolina, and so I think that will give an advantage. Now we have to be mindful of the next disruption, for example in cell therapy – is someone going to come up with a much shorter manufacturing process? If so, we want to be that company or partner with the company that does. Will someone solve allocart – the idea that you have off-the-shelf CAR-T? We haven't seen it yet but we definitely have to be ready for it… Again we have built up this huge expertise in house so we believe we can assess these technologies the best."

'Getting out ahead leads to a difficulty for others to follow' - Vas Narasimhan

The AAA and AveXis deals both had the added advantage of bringing with them a late-stage asset along with the technology (*Lutathera* and AVXS-101, respectively). "We got the best of both worlds. We got a platform and we got a near-term launch. That would be my preferred solution wherever possible looking externally, but I would say that we are not afraid to make [earlier] investments," he added, citing the partnership with antibody technology company, **Xencor Inc.**.

The two purchased companies are being maintained as distinct entities within Novartis, and cell therapy has also been carved out as a separate unit. That way they can each leverage Novartis resources while they build out their technologies and move towards the market with all the ensuing pricing and reimbursement difficulties. This means they can "work through all of those things that we don't have to deal with when we are dealing with *Entresto*," Narasimhan said. "It's a business model transformation when you think about it."

In terms of pricing, he said, the transformational nature of the novel treatments should speak for itself. "I think the science is pretty compelling. We are in a situation where we can cure children with pediatric ALL of cancer and with AVXS-101 we arguably have the possibility to cure children from deadly rare muscular diseases," he said. "The issue here is actually a budgetary problem – it's all at once as opposed to 10-20 years and while we are fully prepared to accept payment over time, the system's not ready."

For potential breakthroughs like AVXS-101, which has already been filed in the US, EU and Japan, he said Novartis would price well below the cost effective pricing thresholds, even though in this case it maintains that this could be as high as $4-5m a treatment. The company has started to engage with payers over possible payment structures. "I do believe over time we will get to the place when enough of these gene therapies come the system will be able to pay us over time. Over 10 years becomes a lot less of an issue because you will be spreading this out and if there is a reversion we can think about outcomes-based pricing etc. But right now that's the challenge we are in because the payment happens on one day even though we are giving a lifetime of benefit. As opposed to a chronic therapy that would give you a worse outcome for the child. More expensive system but sounds nicer from a budgetary smoothing standpoint."

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Gilead's FXR Agonist Posts Questionable Results In NASH, But Offers Hope In PSC

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Gilead Sciences Inc. unveiled Phase II data for its farnesoid X receptor (FXR) agonist GS-9674 in non-alcoholic steatohepatitis (NASH) that raise doubts for its promise in that indication compared to other candidates from the same class, but Gilead's drug fared better in a primary sclerosing cholangitis (PSC) trial, showing improvements in liver biochemistry and markers of cholestasis.

A competing NASH candidate, **Intercept Pharmaceuticals Inc.**'s obeticholic acid (OCA), showed the ability to reduce both fibrosis and steatosis in the Phase II FLINT trial, although increased lipid levels were seen in the same study. In Phase II data presented at the American Association for the Study of Liver Disease meeting Nov. 9, GS-9674 did not show a fibrosis benefit, but Gilead is building a case that its drug can reduce hepatic fat and yield other benefits in NASH patients without increasing lipid levels.

Both NASH and PSC are unmet medical needs with numerous drug candidates in clinical development pursuing a range of mechanisms of action. The NASH race – where Gilead also has the apoptosis-signaling kinase 1 (ASK-1) inhibitor selonsertib in Phase III and acetyl CoA carboxylase (ACC) inhibitor GS-0976 in Phase II – has attracted dozens of companies ranging from big pharmas to clinical-stage biotechs, while the smaller PSC indication has 10 competitors in the clinic, including nine in Phase II, according to Biomedtracker.

Gilead will continue to pursue both indications for its FXR agonist, licensed from **PheneX Pharmaceuticals AG** in 2015. Intercept has its FXR agonist OCA (marketed as *Ocaliva* for primary biliary cholangitis) in Phase III for NASH (and in Phase II for PSC), while both **Novartis AG** and **Enanta Pharmaceuticals Inc.** have FXR agonists in Phase II for NASH.

PURSUING SAFETY EDGE IN FXR AGONISM FOR NASH

Gilead's NASH program is focused particularly on patients with advanced fibrosis, just one aspect of a multi-factorial disease also characterized by steatosis (buildup of liver fat) and inflammation. Stephen Djedjos, Gilead's executive director of clinical research, indicated that the company is focused on producing the best balance between safety and efficacy with an FXR agonist in NASH, including a lower incidence of moderate-to-severe pruritus than OCA. Without mentioning OCA by name, he noted during an interview from the meeting in San Francisco that '9674 has not shown the lipid-increasing effects that have concerned analysts in reviewing OCA's prospects.

Stephen Djedjos, Gilead's executive director of clinical research, indicated that the company is focused on producing the best balance between safety and efficacy with an FXR agonist in NASH

In a 140-patient, Phase II trial reported at AASLD that tested 100 mg and 30 mg daily doses of '9674 for 24 weeks against placebo, Gilead found that the larger dose produced a decline in hepatic fat of at least 30% from baseline in 38.9% of test subjects (p=0.011). Fourteen percent of patients receiving the smaller dose of '9674 achieved that level of hepatic fat reduction (p=0.87), compared to 12.5% in the control arm. All patients' hepatic fat levels were measured by the non-invasive magnetic resonance imaging – proton density fat fraction (MRI-PDFF) test.

The fat-reduction efficacy seen in this study does not equal the results seen in some arms of a Phase IIa study reported in April that tested '9674 monotherapy and '9674 combined with selonsertib in 12-week dosing regimens. Djedjos said the current data do not mean that the 30 mg dose of '9674 has been ruled out for further development. "I don't think we've made any decisions regarding dose yet," he said. "Again, seeing efficacy and balancing that with safety is our goal. I think it's also important to look at the durations of these studies and then how well these early markers of efficacy translate to what's likely to impact patients, which in our minds is really reductions in fibrosis."

Both doses of '9674 yielded improvements in liver chemistry tests (serum gamma-glutamyl transpeptidase (GGT)) and markers of reduced bile acid synthesis. The drug was well tolerated, Gilead added, with 14.3% of patients in the 100 mg arm reporting moderate-to-severe pruritus. For both the 30 mg and placebo arms, only 3.6% reported that side effect.

Changes in lipid profile and glycemic parameters were not different between the treatment and control arms, the company said, as the drug did not achieve a statistically significant reduction in alanine aminotransferase (ALT) enzyme levels. It also did not provide significant improvement in measures of fibrosis.

Gilead likes '9674's potential in NASH, Djedjos explained, because it is a once-daily, selective FXR agonist that has shown the ability to raise FGF-19 hormone levels better than food intake does and then reduce those levels back to normal before the next dose.

"All of those considerations were important for us when we were looking at FXR because we felt that we wanted a compound that would be effective but also safe," he said. "We felt we had to balance the concerns with FXR agonism, particularly the deleterious effects on lipids. As we know, patients with NASH have a large amount of co-morbidities; in particular, cardiovascular disease is a major concern for those patients. Our development strategy has really been that agents for NASH have to have at least a neutral if not a beneficial cardiovascular profile."

"By having a relatively limited transit time through the liver and metabolism, we were still able to get efficacy as measured

CONTINUED ON PAGE 14

ACT NOW – Cancer Trials At The Leading Edge

Adoptive Cellular Transfer (ACT): Novel Cancer Trials Demand That Participating Sites Act Differently

By Martin Lachs Ph.D (VP Project Management, Oncology & Haematology), **Olivier Saulin** (Senior Project Manager, ICON France) **and Chris Learn Ph.D, PMP** (Program Manager, Oncology Haematology)

In the past five years the evolution of adoptive cellular transfer (ACT) for the treatment of lymphoma, leukaemia and myeloma patients has grown exponentially as the efficacy and specificity of these treatments offer curative promise , creating new hope for patients. With European Medicines Agency (EMA) and US Food and Drug Administration (FDA) approvals of *Kymriah* (tisagenlecleucel) and *Yescarta* (axicabtagene ciloleucel) autologous CAR T therapies, ACT is moving towards the frontline setting, expanding the clinician's armamentarium of cellular cancer treatments. High cost remains a concern but the explosion of commercial companies exploring allogeneic, polycistronic, switchable constructs and novel local manufacturing approaches is likely to reduce future costs, whether through competitive pressure and/or technological advances. Access to ACT therapies will broaden globally, engaging smaller community settings. The successful development of cell therapies is dependent on the growing number of academic medical or hospital centres which are able and willing to participate in clinical trials. Until now, the expertise has resided in larger specialised haematology centres in the US, Europe and China. However, with more technologies come more trials, and solid tumour interests are increasingly penetrating the field.

As more pharma and biotech companies bring their ACT platforms to the clinic, there is a need for the assistance of clinical research organisations (CROs) to support the conduct of clinical trials. Valued for their relationships with trial centres, CROs have been thrust into the forefront of operationalising ACT studies. So what can sites expect and commit to when participating in ACT trials? Based on our CRO experience, there are four areas of focus: Regulatory, Logistical, Patient Safety and Data Management.

Regulatory knowledge is paramount. ACT studies are classified in the genetically modified organism (GMO) category, which has bespoke requirements. In many countries, applications must be submitted to specialised local and/or national agencies. Additional time for the regulatory set-up period should be anticipated and it is essential to have a team on hand that is familiar with navigating GMO regulations, as these regulations are constantly evolving. For example, the US National Institutes of Health (NIH) is reevaluating gene therapy oversight to eliminate duplicate reporting. In large academic centres, regulatory expert groups are well established. However, as competition for ACT studies grows, and established centres of excellence experience resource constraints within their own regulatory groups, there will be an evolving drive and opportunity for community hospitals to engage in ACT clinical development. These institutions will need to equip themselves with regulatory expertise. Another perspective is that even in the centres where ACT is established, it has been focused in the haematology-oncology divisions. With the advent of new therapeutic targets against sarcomas and other solid tumours,

oncology departments will need to familiarise themselves with information that may already be resident elsewhere within their own hospitals.

The intensive and demanding logistics of conducting ACT trials necessitates a high degree of organisation within institutions and sophisticated inter-departmental cooperation. Apheresis is a core component of autologous ACT requiring the engagement of transplant units at the centre of the process, including lymphodepletion and infusion of cells. Apheresis unit/materials and transplant unit audits are mandatory practices in an ACT clinical trial. Each commercial sponsor is likely to have its own audit requirements. So transplant units working on multiple studies for different pharmaceutical companies should be prepared to entertain many audits. Standardisation or universal accreditation of ACT studies remains an aspiration. Sites that have revised their infrastructure to meet demands of ACT have been the most successful in conducting studies. For emerging allogeneic approaches, apheresis is not part of the treatment paradigm but transplant units remain pivotal with their role in lymphodepletion and T-cell infusion. In autologous approaches, the chain of identity which ensures a patient receives their own cells post-modification requires careful coordination through form filling and registration. This is no small feat of resource management. Patient scheduling is also a sensitive matter as with autologous therapies, there are manufacturing scale capacity and limitations at facilities where cells are modified via viral vectors, plasmids, transposons, etc. Managing site and patient expectations is a key factor as well as scheduling the patient treatment pathway across the various clinical care teams. Larger academic institutions have established specialised ACT units that specialise in cellular therapy studies.

The positive results with ACT come with concomitant safety risks that require skilled patient management. Sites require robust standard operating procedures (SOPs) specific to ACT-related adverse events. During the acute infusion phase, the inpatient setting provides good access to health care experts in the supervision of the greatest potential risks such as cytokine release syndrome, neurotoxicity or graft versus host disease (GVHD; allogeneic approaches). However, once the patient is discharged, a dedicated line of communication for them is recommended, as well as immediate proximity to skilled urgent care.

Managing site and patient expectations is a key factor as well as scheduling the patient treatment pathway across the various clinical care teams.

ACT studies generate large amounts of data over a short period of the treatment cycle including laboratory, other safety data, prior treatments and concomitant medications – these patients have multiple lines of prior therapy. As such, robust, validated electronic medical record systems are required. Data quality and currency become a challenge with the large volumes of data, estimated to be up to 10 times that observed in other oncology studies. The site's data coordinators must have sufficient time to enter data expeditiously as sponsor companies and regulators are constantly looking for updated safety information. Considering the numerous and still evolving risks of ACT therapies, the importance of data currency cannot be understated.

ACT will continue to make significant inroads into both haematological and solid malignancies with increasingly sophisticated and diverse cell constructs. Whilst the good news is that this is providing increased access for patients to treatments across a broader swath of health care facilities, there is also increased competition for study site resources. Being prepared with regulatory intelligence, scalable logistics, resource commitments, as well as dedicated patient safety and data management teams will present challenges that surpass those of other oncology clinical trials. This is life at the leading edge.

About ICON

ICON plc is a global provider of outsourced development solutions and services to the pharmaceutical, biotechnology and medical device industries. The company specialises in the strategic development, management and analysis of programmes that support clinical development. With headquarters in Dublin, Ireland, ICON currently operates from 93 locations in 38 countries and has approximately 13,650 employees. Further information is available at ICONplc.com.

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CONTINUED FROM PAGE 11

by reductions in steatosis or liver biochemistry, and I think we were able to balance that with the safety without seeing those lipid effects," Djedjos added.

In clinical trials, Intercept's OCA has yielded increased levels of low-density lipoprotein (LDL) or "bad" cholesterol, which some analysts fear may offset its other benefits in addressing NASH symptoms. *(Also see "Intercept's NASH Phase III Enrolling Slowly; Gilead Could Gain Ground" - Scrip, 13 Jan, 2017.)*

A Biomedtracker analysis called the data "mixed results that fail to confirm the encouraging results seen in a smaller Phase IIa study." In a 12-week, five-arm, 70-patient study released in April, a 20 mg dose of '9674 yielded a 30% or greater reduction in hepatic in seven patients in a 10-patient cohort. A 20-patient cohort receiving 20 mg of '9674 along with 18 mg of selonsertib saw 50% of patients achieve the 30% or greater fat-reduction mark.

Biomedtracker pointed out that the 100 mg dose met statistical significance for liver fat reduction in the larger Phase II trial, but disappointed on other measures. "Although comparisons to Ocaliva are difficult due to the different methodologies used in the two trials, we note that Ocaliva demonstrated significant improvement on both steatosis and fibrosis measures, suggesting that it is a more effective FXR agonist," the analysis stated. "While GS-9674 appears to be less efficacious than Ocaliva, it was also associated with less placebo-adjusted pruritus (10.7% versus 17%) and while there were increases in cholesterol compared to placebo, with GS-9674 they are not statistically significant."

NASH COMBO STUDY FULLY ENROLLED

Gilead also reported that the Phase II ATLAS study investigating combination treatment with its three clinical candidates for NASH with advanced fibrosis (F3-F4) has completed enrollment ahead of schedule. The Phase II study will include seven arms, testing each of the three candidates as monotherapy and each of the three two-drug combinations with those compounds, as well as a placebo arm. The data from that study will inform Gilead's decisions on which combination regimens look most promising in NASH, Djedjos said.

The firm also is presenting data from its NASH studies demonstrating non-invasive methods of NASH diagnosis and prognosis, for which the current standard is liver biopsy. In its Phase III STELLAR program for selonsertib, Gilead says tests like Fibrosis-4 (FIB-4) index, Enhanced Liver Fibrosis (ELF) and the *FibroScan* (FS) liver-stiffness test showed the ability to differentiate advanced fibrosis comparable to liver biopsy.

"When used sequentially, FIB-4, followed by either FS or the ELF test, accurately identified advanced fibrosis in 76%-81% of patients, while reducing the frequency of indeterminate results to as low as 13%," the company said.

PSC MAY MOVE INTO PHASE III

In PSC, a 52-patient, 12-week study in non-cirrhotic patients also tested 100 mg (n=22) and 30 mg (n=20) doses of '9674 versus placebo (n=10). Patients receiving the 100 mg dose demonstrated statistically significant improvements across several liver biochemistry tests, Gilead reported. These included median reductions of: 20.5% in serum alkaline phosphatase (ALP), compared to 3.4% for placebo; a 30.3% in GGT, compared to 1.1% for placebo; 49.4% in ALT, compared to 12.9% for placebo; and 42.3% in aspartate aminotransferase (AST), compared to 10.8% for placebo.

The drug was well tolerated, with a 13.6% incidence of grade 2 or 3 pruritus at the 100 mg dose and a 20% incidence at the 30 mg dose, while the incidence rate was 40% in the placebo group. No elevation of serum lipids was seen, Gilead said.

The company is working with regulators to determine next steps for '9674 in PSC, including the possibility of advancing it to Phase III, Djedjos said.

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China Set To Become Global Drug Innovation Center

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There was bullish optimism on recent trends in China from scientists and business leaders at this year's FT pharma conference. They noted that the huge country has started embracing digital healthcare ideas faster than many countries and regulatory approvals are becoming much quicker – trends that offer opportunities for global pharma companies operating there and that will also see the export of high-quality home-made Chinese medicines globally in the not-to-distant future.

Attendees of this year's FT Global Pharmaceutical and Biotechnology Conference in London took part in an interactive panel discussion on China and heard views from a panel of speakers about what China's rising investment in life sciences, recent regulatory initiatives and increasingly educated indigenous army of researchers will mean for Chinese ambitions to take an eventual lead in key emerging therapeutic areas and innovation, including genomics, gene editing and gene therapies.

Speakers on the panel applauded recent moves by the Chinese industry regulator paving the way for faster drug approvals and greater access for patients to advanced therapies, and said the trend looked set to continue.

Meanwhile China is embracing digital at a faster pace than most other countries, and lacks the burden of legacy primary health care systems which should help it to focus on creating innovative new treatment and service models.

ASTRAZENECA VIEW: 'CHINA A MEDICAL INNOVATION LEADER' BY 2025

Mark Mallon, **AstraZeneca PLC**'s head of global product and portfolio strategy, set the tone, saying that China by 2025 at the latest will be a leader in medical innovation, and would be exporting home-made medicines to global markets by then.

"We believe China will be a leader in innovation, firstly because the government there is really committed to improving healthcare for its citizens and part of that is ground-breaking innovative medicines and partly it's about leveraging digital technology to improve efficacy and effectiveness of the healthcare systems. They also want

Regulatory easing, rising investment and R&D innovation set to generate Chinese drug breakthroughs

to have that capability themselves. And they have the resources and scale to become a driver of innovation."

Positive changes to regulatory processes in China include the accelerated review and approval process for clinical trials, for which the standard timeline is 60 working days provided the applicant can meet the review requirements.

In 2017, China joined the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH), an organization that brings regulators and the industry together to discuss and set such rules for drug registration and use. It also became one of the members of ICH Management Committee (MC). The adoption of ICH has enabled more scientific and transparent communication on drug development for products.

AstraZeneca said reforms had allowed it to optimize the evaluation and approval process for drug registration, to get cancer drugs *Tagrisso* (osimertinib) and *Lynparza* (olaparib) approved in less than nine months.

Tagrisso won the go-ahead there within 7.5 months in 2017 as a second-line treatment for EGFR T790M mutation-positive metastatic non-small cell lung cancer, an indication for which it already had approval in the US and Europe. Its NDA of Lynparza in BRCA-mutated ovarian cancer was approved within 8.5 months in 2018.

China's acceptance of overseas clinical trial data for regulatory review has meanwhile been leveraged by AstraZeneca for several applicable products.

"This uptick in reimbursement and access all adds up to great news for patients in China and big opportunities for local companies and global companies operating there, and ultimately it's going to lead to great news for patients around the world because China can be a big source of innovative medicines in the not-too-distant future," Mallon said.

CHI-MED VIEW: 'IT'S JUST THE BEGINNING'

Christian Hogg, CEO of **Hutchison China Meditech Ltd.**, known also as Chi-Med, said: "Ten or 15 years ago people would look at China with a raised eyebrow [when talking about prospects for medical innovation there], but that's certainly not the case now."

In September, Chi-Med won approval from the National Medical Products Administration of China for *Elunate* (fruquintinib) in colorectal cancer. The London-listed company is collaborating with **Eli Lilly & Co.** on the closely watched "made in China" medicine, the first China-discovered and developed mainstream cancer drug to win unconditional approval following a randomized clinical trial.

"It's taken 20 years for Chinese innovation to build up to the stage that it's at now where everyone is noticing the fact worldwide and realizing that drug candidates can actually be created in China for the global market," Hogg said, adding: "It's just the beginning."

MSD VIEW: 'UNPRECEDENTED CHANGE' IN CHINA

Alan Morrison, who runs the international regulatory affairs for **Merck & Co. Inc.**'s **Merck Sharpe & Dohme**, said he agreed with other panelists' assessments.

MSD first began operating in China in 1994; it now has three sites in China – an R&D site, commercialization center and a packaging hub in the country, and employs just over 5,000 people there. China represents the second-largest country operationally outside the US for MSD.

"It's clearly a time of unprecedented change and opportunity" in China's drug innovation and regulatory landscape, he told the conference.

> China is embracing digital at a faster pace than most other countries, and lacks the burden of legacy primary health care systems

LEGEND BIOTECH CEO NOTES CHINA GROWING ACADEMIC PROWESS

Legend Biotech Corp. CEO Yuan Xu said that the huge rise in medical research graduates in China will increasingly generate innovation within the Chinese life sciences sector.

She told the conference that China's higher education Science, Technology, Engineering, and Math (STEM) research environment will play a key role in influencing whether China is successful in transitioning from a manufacturing-based economy to an innovation-driven, knowledge-based economy.

"The total number of STEM graduates from China today is more than those in all western countries combined, giving a very good workforce for future innovation.We will be able to hire very highly trained college graduates and researchers there."

She noted China's long history of making antibiotics, a process involving fermentation.

"This is the foundation for biosimilars and biologics and gene- and cell-therapy and China also has a long history in making vaccines which is also very similar technology to biologics and gene- and cell-therapy."

She said government financial largesse was meanwhile flowing more and more into innovative activities and IT technology, and that would feed through more and more to high-quality medicines and healthcare.

"The statistics now show that VC funding in China is on a par with that in the US and half of those VC investments are from China-based investors. All these factors are helping China position itself and then accelerate into a leadership role for medical innovation," she concluded.

Published online 7 November 2018

Better Together: New Deal Adds Weight To China Biosimilar/Biobetter Swap

BRIAN YANG & JUNG WON SHIN

In a move indicative of broader trends, **Abclon Inc.** of South Korea has licensed out global sales rights to its novel HER2-targeting therapeutic monoclonal antibody AC101 to **Shanghai Henlius Biotech**, which with a valuation of close to $3bn is one of China's largest biotech unicorns.

Henlius, part of **Fosun International Ltd.**, is at the forefront of the country's biosimilars development, but the latest deal signals a strategic departure from this sector and more towards innovative biologics, for which rapid growth is expected in China driven by reimbursement expansion and pricing negotiations.

Henlius exercised an option to acquire global rights to AC101 given to the company when it first reached a licensing agreement with Abclon in October 2016 for the investigational product's Greater China rights only.

As a result of the new agreement, the total licensing deal size for AC101 (including that in 2016), has reached $56.5m plus sales royalties; Abclon will receive $10m upfront as part of the latest deal.

Developed using Abclon's proprietary NEST (Novel Epitope Screening Technology) platform, AC101 is being developed for HER2-positive breast and gastric cancer, in which HER2 is highly expressed in about 25% of patients. Preclinical studies have shown the efficacy of a combination of AC101 and trastuzumab (originally **Roche**'s *Herceptin*) to be superior to trastuzumab or pertuzumab (Roche's *Perjeta*), as well as to a combination of trastuzumab and pertuzumab, in the two indications.

BIOSIMILAR WINDOW CLOSING?

In a September interview with *Scrip*, Henlius CEO Scott Liu said that the window for biosimilars in China was closing for newcomers, but that innovation opportunities for novel biologics were still wide open, especially for immuno-oncology and combination therapies.

When asked about the Abclon deal by *Scrip*, Henlius spokesperson Nancy Yan Wang noted the expansion of the two companies' original deal, and that the Shanghai-based firm – whose motto is "Affordable Innovation" – had been focusing more on innovative biologics in the time since this was reached.

Shanghai Henlius is now proceeding with clinical trials of six antibody biosimilars and seven novel antibody drugs. Among these, HLX01 (rituximab biosimilar) is pending regulatory approval in China, and four others including HLX02 (trastuzumab biosimilar) are undergoing Phase III clinical trials.

NEW DRUG FRENZY

China's ongoing policy reforms to encourage innovation, including favorable pricing for new drugs over generics, the granting of priority reviews and rare disease designations, and increasing public demand for access to new cancer treatments, are all serving to draw more biotechs to invest in innovative products rather than biosimilars.

Innovent Biologics Inc., which recently raised $421m in a successful IPO in Hong Kong, started off developing biosimilars but quickly ventured into move innovative therapies in the immuno-oncology field, developing its own anti-PD-1 antibody. Other Chinese firms developing biosimilars have also been building out their new drug portfolios, for fear that biosimilars will command relatively low pricing power and face limited uptake given the generally poor market penetration of biologics in China. This has been attributed to various factors including their lack of reimbursement and relatively higher prices over conventional drugs.

Against the background of the government-supported push for more innovative new drugs to be brought to market, Henlius has been developing several novel products, including the PD-1 inhibitor HLX-10, the anti-PD-L1 antibody HLX-20, and a combination of its PD-L1 inhibitor with biosimilar bevacizumab.

ABCLON SEEKING FURTHER DEALS

For its part, Abclon is developing novel antibody-based therapeutics using next-generation proprietary platform technologies such as NEST, AffiMab and CAR-T, and is also seeking licensing deals for its other pipeline assets. These include AM202, a bi-specific antibody targeting both tumor necrosis factor alpha and interleukin-6.

"Shanghai Henlius Biotech is the leader of antibody drugs in China," CEO Jong-Seo Lee said in a statement. "We believe it is the best partner for development and commercialization of AC101."

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From the editors of PharmAsia News.

Scrip Awards Finalists 2018

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WuXi AppTec's Biotech Company of the Year Award

The biotech industry's entrepreneurial spirit and cutting-edge science are vital to the life sciences industry. This award honors outstanding achievement by biotech companies over the qualifying 12 months.

Genmab

Over the last year, Genmab continued to advance its product pipeline and maintain solid financials. Sales of its first-in-class CD38 antibody Darzalex by partner Janssen Biotech in 2017 reached blockbuster status. Genmab also reported positive data for its tisotumab vedotin program in cervical cancer and doubled its proprietary pipeline with two new programs.

AveXis

Gene therapy company AveXis has 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 testament to its cutting-edge, transformative science.

F-star

F-star made significant progress over the year both in advancing its pipeline of first-in-class bispecific antibodies and enriching its collaborations. It announced a collaboration with Merck KGaA for the generation of five bispecifics in immuno-oncology, and took its lead compound FS118 into the clinic for advanced malignancies that have progressed while on PD-1/PD-L1 therapy.

Neurocrine Biosciences

This past year has been the most successful to date for Neurocrine. It launched its first FDA-approved product, Ingrezza, the first and only drug for patients with tardive dyskinesia. Ingrezza reached net sales of $116.6m for the year. Total revenue for 2017 was $161m with a second product, elagolix, gaining FDA approval in July.

Bicycle Therapeutics

The past year saw Bicycle Therapeutics take its first-ever Bicycle product into the clinic with the launch of a Phase I/IIa study of lead drug candidate BT1718. Following its £45m Series B financing last June, the clinical-stage company signed and extended collaborative alliances and continued to advance its portfolio of cancer therapeutics, including Bicycle Toxin Conjugates.

Diurnal Group

During the year, Diurnal delivered a key milestone, the EU approval of its first product, Alkindi, for adrenal insufficiency in infants, children and adolescents and subsequently launched it in Germany. This places Diurnal as one of a select few UK biotechnology companies that have successfully taken a product from concept through to commercialization.

To find out more about attending the Scrip Awards, visit www.scripawards.com

Business Development Team of the Year (Sponsored by Skipta)

This Award will honor the achievements of business development teams whether they are from a pharma or biotech company or a cross-company team responsible for a specific deal or collaborative project.

AstraZeneca and Avillion partnership team

This team forged a partnership between Pearl Therapeutics, a wholly owned subsidiary of AstraZeneca, and Avillion to co-develop the respiratory product PT027 for asthma in the US. What is unique about this partnership is that the respective contributions from each party and the agreed allocation of risk enabled an IFRS-compliant deal structure.

Bicycle Therapeutics' business development team

Bicycle's business development team is uniquely nimble for a company its size as it straddles two continents. Its key achievements over the past 12 months include a research collaboration with Bioverativ, and expanding existing alliances with AstraZeneca and Thrombogenics. It also started clinical development of its lead candidate BT1718 under its alliance with Cancer Research UK.

CinnaGen's business development team

CinnaGen's business development team vision is to play an impactful role on CinnaGen's road to become a global biopharmaceutical player and increase access to high quality biologic medicines across the globe. The team has been engaged in various business activities, from M&A to technology transfer, licensing, finish product export, strategic partnership and alliance management.

Evotec's business development team

This team led Evotec into a major strategic collaboration with Sanofi to establish a new open innovation platform near Lyon to accelerate infectious disease research and development. This ground-breaking initiative to tackle infectious diseases has provided Evotec with the largest translational platform of any company in the infectious disease space.

F-star's business development team

This team's key achievements over the past 12 months include the creation of its fourth asset centric vehicle, F-star Delta in partnership with Merck KGaA, and the sale, only 20 months after creation, of F-star Gamma to Denali Therapeutics for an upfront payment of $24m with contingent additional milestones up to $447m.

Rentschler Biopharma/Leukocare alliance business development team

The aligned business development teams of Rentschler Biopharma, Rentschler Fill Solutions and Leukocare offer drug substance development and production, fill and finish services, plus formulation development. This enables best-in-class formulation development, considered at every step of the biopharmaceutical development and manufacturing process "from gene to vial", a unique offering in the biomanufacturing space.

Yuhan Strikes Long-Awaited Lung Cancer Deal Through Huge Janssen Alliance

JUNG WON SHIN jungwon.shin@informa.com

Yuhan Corp. has reached a license and co-development agreement with **Janssen Biotech Inc.** for the South Korean company's novel third-generation EGFR tyrosine kinase inhibitor (TKI) lazertinib, in a massive deal worth as much as $1.25bn in total plus double-digit sales royalties to Yuhan along with the drug's originators.

The move marks another long-awaited mega licensing alliance between South Korean and global pharma firms, and adds to the increasing international recognition of the Korean pharma industry's rising innovative R&D strength.

It comes after a more than two-year absence in large out-licensing agreements by Korean pharma companies, since **Hanmi Pharmaceutical Co. Ltd.**'s tie-up with **Roche** in 2016 for the pan-RAF inhibitor HM95573, and is being seen as good news for Yuhan - which had been seeking a global partner for the compound – and the wider Korean pharma industry.

Reflecting longer term upside from the deal, shares of Yuhan surged by their daily limit of 30% in Seoul to close at KRW231,000 ($205) on Nov. 5.

DEAL STRUCTURE

Under the agreement, Yuhan will receive $50m upfront and milestone payments of up to $1.205bn, plus double-digit sales royalties after commercialization of the drug.

In return, Janssen gains exclusive worldwide rights, excluding South Korea, to develop, manufacture and commercialize lazertinib, with Yuhan retaining development and commercialization rights at home, Yuhan said in a statement.

Korean biotech **Oscotec Inc.** and its US subsidiary **Genosco** will also be major beneficiaries, receiving 40% of the proceeds of the new license agreement, including royalties, given that Yuhan originally licensed in the compound from the companies in 2015. Development has also been supported by the Korea Drug Development Fund.

Janssen and Yuhan now plan to jointly proceed with global clinical trials of lazertinib beginning in 2019, both as a monotherapy and combination therapy for non-small cell lung cancer (NSCLC). Janssen will lead the global clinical trial programs, while Yuhan will conduct the studies in South Korea.

Lazertinib (YH25448/GNS-1480), an oral, potent, highly mutant-selective and irreversible third-generation EGFR-TKI, is able to penetrate the blood-brain barrier (BBB). It specifically targets the activating EGFR mutations Del19 and L858R, as well as the T790M mutation, while sparing wild type; various EGFR mutations are present in about 10-15% of NSCLCs.

The molecule is already being evaluated by Yuhan in a Phase I/II trial as both a first- and second-line therapy in advanced NSCLC, and the hope is to develop it into the best-in-class third-generation EGFR-TKI for patients with advanced T790M mutant NSCLC including brain metastasis.

ASCO DATA

At this year's American Society of Clinical Oncology (ASCO) annual meeting, Genosco announced data from the Phase I/II open label, dose-escalation study in advanced EGFR-TKI-resistant NSCLC with or without CNS metastasis, which concluded that lazertinib was well-tolerated with low rates of Grade 3 or higher adverse events, and exhibited robust activity in patients with NSCLC with acquired resistance to EGFR-TKIs, with or without brain metastasis.

"These data are impressive and underscore the potential of lazertinib to be the best-in-class third-generation EGFR-TKI for patients with advanced EGFR T790M mutant NSCLC, including brain metastasis. And importantly, the treatment was well-tolerated with no dose-limiting toxic effects," said the study's principal investigator Dr Byoung Chul Cho at the time.

"Results indicate that lazertinib compares favorably with results from a similar Phase I/II [AURA1] clinical trial of osimertinib, a currently marketed 3rd generation EGFR-TKI."

A total of 118 patients (38 in the dose-escalation cohort and 80 in the expansion cohort) with EGFRm advanced NSCLC with acquired resistance to EGFR-TKIs with or without brain metastasis were enrolled in the lazertinib Phase I/II study as of April 20, 2018.

No dose-limiting toxicities were observed up to 320mg and there were no dose-dependent increases in treatment-emergent adverse events. Of the evaluable patients (n=110) with a confirmed response at the date of data cutoff, lazertinib demonstrated promising anti-tumor efficacy signals with a confirmed objective response rate (ORR) of 61% across all dose levels.

Of note, the confirmed ORR in patients with T790M+ was 86% at the lazertinib 240mg dose level and in patients with brain metastasis, the intracranial ORR was 55% across all dose levels

'PROMISING COMPLEMENT' TO JANSSEN PORTFOLIO

For Janssen, the new deal marks a continuing beefing-up of its pipeline in oncology, which is becoming an increasingly important priority therapeutic area for **Johnson & Johnson** along with its more established immunology business, still seen as its top franchise globally.

"As a third-generation epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) for patients with EGFR mutations, lazertinib is a promising complement to the Janssen Oncology portfolio. We look forward to studying the potential of this novel agent in both combination and monotherapy approaches as we continue to advance the development of targeted therapies for patients with non-small cell lung cancer," Johnson & Johnson told *Scrip* in a statement.

According to its website, lung cancer appears to be an area of focus for Janssen. The company is already advancing JNJ-61186372 through clinical development, encouraged by early data from a Phase I trial in advanced NSCLC with the bispecific antibody, which targets EGFR and cMET.

"Further, Janssen continues to progress a pipeline of novel early assets and therapeutic approaches as we are committed to developing innovative treatments that may

CONTINUED ON PAGE 20

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CONTINUED FROM PAGE 18

improve and prolong the lives of people diagnosed with lung cancer, the leading cause of cancer mortality in the world," added J&J in the statement.

FACING UP TO TAGRISSO

In terms of the competitive landscape in EGFR mutation-positive NSCLC, the overall segment is fairly crowded, with five EGFR-targeted TKIs now approved across the major markets. A number of generic competitors are also on the way, Hardik Patel, Therapeutic Area Director, Oncology, at Informa's Datamonitor Healthcare told *Scrip*.

"However, in terms of EGFR-positive patients who also have the T790M mutation, there is really only one product available for these patients, which is *Tagrisso* [**AstraZeneca PLC**'s osimertinib, as referenced in the ASCO results]. It's estimated that about half of EGFR-positive patients will have the T790M mutation, so there is still an opportunity to gain market share within this segment," Patel commented.

"But Tagrisso is a very effective drug, and it has been approved for EGFR T790M mutation-positive patients since 2015, so lazertinib will need to demonstrate strong clinical efficacy in order to successfully compete with Tagrisso," given it is a relative latecomer, he added.

Tagrisso is also being moved into the first-line setting in major markets, most recently in Japan.

While only around 10-15% of NSCLC patients in the US and Europe have EGFRm NSCLC, this proportion rises to 30-40% in Asia, and the secondary EGFR T790M resistance mutation – against which osimertinib is also active – causes resistance to standard EGFR inhibitors in around two-thirds of these.

Such patients are particularly sensitive to treatment with EGFR-TKIs, which act to block the cell signalling pathways that drive tumor growth. About 25% of patients with EGFRm NSCLC also have brain metastases at diagnosis (increasing to approximately 40% within two years of diagnosis).

Helped by the latest deal, Yuhan should be able to speed up its R&D efforts in key therapeutic areas, including oncology and immuno-oncology. At present, six of the firm's 11 strategic investment projects in new drug development are in oncology, including four in immuno-oncology.

At a recent meeting in Seoul, Moo Young Song, a research scientist at Yuhan, cited the lazertinib lung cancer program as a successful example of external open innovation. *(Also see "Korean Pharma Finds Own Way To Collaborative And Open Innovation" - Scrip, 2 Oct, 2018.)*

"For us, early stage partnership is the key," he said at the time. "We bring in early-stage compounds from bioventures and add value using our know-how and then license them out to third parties."

Lazertinib was seen as Yuhan's leading novel oncology drug asset with potential to be licensed out to a global pharma partner, and expectations had been increasing since the positive clinical trial results were unveiled at international conferences including ASCO.

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From the editors of PharmAsia News.

AstraZeneca Q3 Sales Rise 'Is Milestone', CEO Soriot 'Not Leaving'

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Marking a crucial milestone in its turnaround plans, **AstraZeneca PLC** in the third quarter saw product sales growth for the first time since 2014, a trend the group's CEO Pascal Soriot said will only strengthen, backed by new product launches and helped by the absence of fresh patent expiries of aging blockbusters.

After nine consecutive quarters of sales decline, the UK pharma was able to post sales growth of 9% in the latest quarter measured in constant currencies, beating market forecasts and fueled by strong drug launches and buoyant growth in key emerging markets.

Newly marketed therapies such as the PARP inhibitor *Lynparza* (olaparib), second-generation EGFR inhibitor *Tagrisso* (osimertinib) and checkpoint inhibitor *Imfinzi* (durvalumab) in cancer treatment as well as SGLT2 inhibitor *Farxiga* (dapagliflozin) for diabetes and *Fasenra* (benralizumab) for severe asthma continued to sell well in the third quarter and show great promise, the CEO said.

"Today marks an important milestone for the future of AstraZeneca, with the performance in the quarter and year to date showing what we expect will be the start of a period of sustained growth for years to come," Soriot told journalists when presenting the quarterly update.

"We have had a very hard time over the past four years with very large patent expiries; The good news is those are now behind us and we don't have any substantial patent expiries for another six years or more, so we have a very good period of time where we can focus on launching products and growing," he said, adding that AstraZeneca would continue to replenish its early-stage pipeline.

GUIDANCE MAINTAINED

The company said it therefore remained on track to deliver its full-year 2018 guidance of product sales growing by a low single-digit percentage and core EPS of $3.30 to $3.50.

Soriot also said AstraZeneca's growth rate should be strong enough to achieve its 2023 annual sales target, first projected in 2014 when the then-ailing group was fighting off an unwanted takeover from **Pfizer Inc.**. The $45bn target set then reflected the exchange rate of the day; Soriot has noted that the dollar has since strengthened so that $45bn goal is now around $40bn based on current currency exchange rates.

"We are on track to get to this goal of $40bn or so," the CEO told journalists at the group's latest quarterly update.

He noted the sales target for 2023 which was set in 2014 was based on performance predictions. "As always in our business, some projects made then didn't work, and others worked better than expected," he commented.

CONTINUED ON PAGE 23

Genentech's Immunology/Infectious Disease Deal Maker On Following The Science

JO SHORTHOUSE joanne.shorthouse@informa.com

Don O'Sullivan, Head of Genentech Immunology & Infectious Disease Business Development

When reflecting on the licensing deals inked this year by biotech behemoth **Genentech Inc.**, two really stand out: the June deal with microbiome company **Microbiotica Ltd.** to discover, develop and commercialize treatments for inflammatory bowel disease (IBD), *(Also see "Genentech Mines The Microbiome Again With IBD Deal" - Scrip, 7 Jun, 2018.)* and the collaboration signed with Germany's **Affimed NV** to develop and commercialize novel natural killer (NK) cell engager-based immunotherapeutics to treat multiple cancers. *(Also see "Roche Pact Is Affirmation Of Affimed Technology " - Scrip, 28 Aug, 2018.)*

Both these deals bring cutting edge science to **Roche**'s biotech arm, says Don O'Sullivan, the company's head of Immunology and Infectious Disease business development, and the man behind Genentech's move into the science and potential of the microbiome. It may not be Genentech's first foray into the world of the microbiome, *(Also see "Deal Watch: Genentech Gets Down In The Dirt With Lodo Therapeutics" - Scrip, 11 May, 2018.)* but it certainly marks a line in the sand; the biotech is serious about the potential this field of science brings to medicine.

"That was a real significant move for us; we are following the science. We've been watching that space for a while, and waited to find a company that came to us with a true depth of science and innovation," O'Sullivan explained to *Scrip*.

The deal centers on IBD, Crohn's disease and ulcerative colitis. The companies are analyzing samples from clinical trials for etrolizumab, Genentech's humanized IgG1 MAb which targets the beta 7 integrin subunit, and IL22-Fc a recombinant human protein with potential application across multiple inflammatory and metabolic diseases. From these samples the team identifies bacterial signatures which could identify response to drugs, non-responders, novel targets and novel therapeutics.

Genentech had been monitoring the microbiome space closely for "at least four years" before a deal was struck. Largely a field of observational studies, it was only when Microbiotica and its co-founder and chief scientific officer Trevor Lawley brought "rigorous science" to Genentech's table that a scientific meeting of minds between the two companies could be arranged.

"You can tell, within an hour of our scientists talking to their scientists, whether there's going to be a deal, without doubt. There was deep scientific respect, and rigor that both teams bring to the table and frankly, the scientists were nagging us to get the deal done as quickly as possible," recalls O'Sullivan.

And this marker of intent is clear on other deals that Genentech has struck this year, the $95m deal with Affimed, for example and the collaboration announced in April between Roche's biotech arm and the Seattle-based **Kineta Inc.** on a non-opioid pain therapy that is touted to be "disease modifying".

"There has to be that connection with the scientists at first, otherwise there's going to be no deal," says British-born O'Sullivan.

When asked about his devotion to finding new medicines, O'Sullivan answers simply: "It's my life." He has worked at the San Francisco-based company for over eight years, and before that was in corporate development at **Genzyme Corp.**. He has a PhD from Cambridge University in Molecular Biology, and an MBA in Healthcare and Finance from The Wharton School.

O'Sullivan was also the dealmaker behind arguably Genentech's most exciting new discovery, the 'unexpected antibiotic'. This "small deal" done with a San Diego-based company, **RQx**, in 2013 may potentially bring the first new class of Gram-negative antibacterials since 1968. In September, the paper *Optimized arylomycins are a new class of Gram-negative antibiotics* appeared in *Nature*. "Antibacterial drug discovery is not easy and it's a reflection of the high degree of science and rigor that goes into the program," he says.

"Partnering is always going to be key," says O'Sullivan, when asked about how the future of new medicines will be developed in infectious disease and immunology. "With a lot of the funding that has been available recently, it's good to see that there is a lot of new exciting companies being formed and having the money to do the killer experiments. We feel excited about the space."

Meeting with *Scrip* at the BIO-Europe conference, O'Sullivan is of course primarily attending to meet with infectious diseases companies, to sniff out the latest scientific potential. "We meet with a lot of these companies, we give them counsel as to what data we need to see to sign a deal," he explains. "They go away, do their work and come back and then when we meet them the next year, it's just great to see that improvement. There is significant advancement in the antibacterial space at the moment."

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

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

Selected clinical trial developments for the week 2–8 November 2018

LEAD COMPANY/PARTNER	COMPOUND	INDICATION	COMMENTS
PHASE III SUSPENDED			
Clearside Biomedical, Inc.	*Xipere* (triamcinolone acetonide)	Retinal Vein Occlusion	SAPPHIRE (*w/Eylea*); Missed Primary Endpoint
PHASE III RESULTS PUBLISHED			
AstraZeneca PLC	*Fasenra* (benralizumab)	Asthma	BORA; *The Lancet Respiratory Medicine*, Nov. 7, 2018
Roche Holding AG	*Perjeta* (pertuzumab)	Breast Cancer	TRAIN-2; *The Lancet Oncology*, Nov. 6, 2018
Sanofi/Regeneron Inc.	*Praluent* (alirocumab)	Dyslipidemia	ODYSSEY Outcomes; *NEJM*, Nov. 7, 2018
Merck & Co., Inc.	*Vytorin* (ezetimibe)	Dyslipidemia	IMPROVE-IT; *The Lancet Diabetes & Endocrinology*, Nov. 2, 2018
PHASE III INTERIM/TOP-LINE RESULTS			
AVEO Pharmaceuticals, Inc.	*Fotivda* (tivozanib)	Renal Cell Cancer (RCC)	TIVO-3; Positive Results
Eli Lilly & Company	*Trulicity* (dulaglutide)	Diabetes Type 2	REWIND; Reduced CV Events
Mallinckrodt plc	VTS-270	Niemann-Pick Disease	Mixed Results
Ampio Pharmaceuticals, Inc.	*Ampion* (albumin fraction)	Osteoarthritis and Osteoarthritis Pain	AP-003-C OLE; Reduced Pain
Foamix Pharmaceuticals Ltd.	FMX103 (minocycline) foam	Rosacea	FX2016-11 and FX2016-12; Met Primary Endpoints
Endo International plc	*Xiaflex* (collagenase clostridium histolyticum)	Cellulite	RELEASE-1, -2; Improved Appearance
UPDATED PHASE III RESULTS			
BioMarin Pharmaceutical Inc.	*Brineura* (cerliponase alfa)	Neuronal Ceroid Lipofuscinosis	Stable Disease In Extension Study
BioMarin Pharmaceutical Inc.	*Palynziq* (pegvaliase-pqpz)	Phenylketonuria	PRISM-1; Durable Responses
BeyondSpring Pharmaceuticals	*Plinabulin*	Neutropenia/Leukopenia	Protective-1; Positive Results
Presidio Pharmaceuticals/Ascletis	ravidasvir	Hepatitis C	Durable Responses In Combination Therapy
PHASE II SUSPENDED			
Juventas Therapeutics, Inc.	JVS-100	Peripheral Arterial Disease	STOP-PAD; Wound Healing Not Improved
PHASE II INTERIM TOP_LINE RESULTS			
Concentric Analgesics, Inc.	CA-008	Post-surgical Pain	Dose-Ranging Bunionectomy Study
GenKyoTex S.A.	GKT831	Primary Biliary Cholangitis and Hepatic Fibrosis	GSN000300; Met Primary And Secondary Endpoints
Mirum Pharmaceuticals Inc./ Shire plc	maralixibat	Alagille Syndrome	ICONIC; Reduced Bile Acids And Pruritus
Entera Bio, Ltd.	Oral PTH (1-34)	Hypoparathyroidism	Positive Results
OncoSec Medical Inc.	TAVO (tavokinogene telseplasmid/IL-12)	Melanoma	PISCES/KEYNOTE-695; Early Signals Of Reversing Resistance

Source: Biomedtracker | Informa, 2018

CONTINUED FROM PAGE 20

An example of something that worked much better than the company had expected was cancer medicine Tagrisso.

"At the time [that we set the target] we had competition from other rivals and we didn't know that [Tagrisso] was crossing the blood-brain barrier and had an effect on brain metastasis … so our forecast for Tagrisso back then was quite low. Now we're talking about a product with peak sales of potentially $4bn," he said.

SORIOT SAYS HE'S STAYING

The French CEO – who took the helm at AstraZeneca in 2012 – said the positive excitement of turning the troubled company around continued to keep him happy.

"I'm enjoying what I'm doing. I'm enjoying working with the team here. We still have a lot of work to do together. And there are a lot of exciting things that are happening. So I have no plan to move on," the CEO said, a message that investors will doubtless welcome along with news of the company's return to sales growth.

TO OVERSEE 'PHASED' RECOVERY PLAN

Soriot said the turnaround strategy for AstraZeneca had always focused on rebuilding the pipeline.

"We've done that and we continue to do so. Phase two of the plan – which is where we are now – is to get new products approved and to turn them into blockbusters, and that's what our commercial teams are very busy doing now.

"Phase three, which will start soon, is to turn this top-line growth into profits and let the top-line growth drop to the bottom line. So clearly over the next few years we expect our operating margin to grow and our EPS to strengthen." He said the company would continue to spin-out or license out assets that weren't deemed to be 'core' therapeutic activities for the group, those being oncology, respiratory, cardiovascular, renal and metabolism.

"Essentially we prefer a strategy of 'purification' of our portfolio and re-investing a lot of that money into building our own pipeline and launching our products so we'll end up with a much leaner, more focused, much faster growing company when we swing out of this period of decline."

AND NO BIG M&A

Large acquisitions would not be part of the company's strategy going forward.

"Our focus is not on large acquisitions; it is on continuing to build our pipeline. We want to move the next wave of products into late stage development. We already have products in that stage and we want to move more products into that stage."

"And we want to complement that with licensing. Our deal with Innate is a good example of this," Soriot said, referring to the recently agreed collaboration under which the UK-based big pharma will gain rights or access to several promising immuno-oncology candidates from **Innate Pharma SA** while the French biotech receives a license to AstraZeneca's rare oncology disease product, *Lumoxiti* (moxetumomab pasudotox-tdfk) to further its own US and EU commercial ambitions. *(Also see "Innate Pharma's Expanded IO AstraZeneca Deal Jump-Starts US Ambitions" - Scrip, 23 Oct, 2018.)*

Published online 8 November 2018

APPOINTMENTS

Executive	To Company	New Role	From Company	Previous Role	Effective Date
Norton Oliveira	Alnylam Pharmaceuticals Inc	Senior Vice President and Head, Latin America	Gilead Sciences	Vice President, Latin America and Caribbean	7-Nov-18
Phil Jeffrey	Bicycle Therapeutics Ltd	Senior Vice President, Preclinical Development	Pfizer Inc	Head, Translational Sciences	1-Nov-18
Axel Mescheder	Cristal Therapeutics	Chief Executive Officer and Chief Medical Officer	Lanthio Pharma	Chief Medical and Development Officer	2-Nov-18
Jason T. Gammack	Inscripta	Chief Commercial Officer	QIAGEN	Vice President, Life Science Business Area	1-Nov-18
Kim Sablich	Myovant Sciences Ltd	Chief Commercial Officer	GlaxoSmithKline plc	Vice President, Primary Care Marketing, US	7-Nov-18
Natascha Schill Schulze	Neurimmune Holdings AG	Vice President, Project and Alliance Management	Biogen Switzerland AG	Managing Director	1-Nov-18
Richard Woodman	Onconova Therapeutics Inc	Chief Medical Officer and Senior Vice President, Research and Development	Novartis Oncology	Senior Vice President, Head, US Oncology Clinical Development and Medical Affairs	7-Nov-18

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

Source: Medtrack | Informa, 2018

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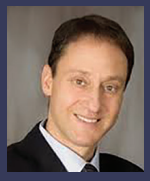
Jessica Morris, Co-founder, **OurBrainBank**, SVP and Partner at **FleishmanHillard**, *USA*



Professor Kenneth Getz, Director and Associate Professor at **CSDD**, **Tufts University School of Medicine**, *USA*

Inma Martinez, Venture Partner, Data Sciences & Product Innovation at **Deep Science Ventures**, *UK*

Daniel Prieto-Alhambra, Associate Professor & NIHR Clinician Scientist at **Oxford University**, *UK*

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