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Pfizer On Reorganizing, M&A And Investing In Internal R&D

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The US market for biosimilars hasn't developed as quickly as some hoped and **Pfizer Inc.** has had first-hand experience navigating the commercial challenges. Now, as Pfizer prepares to bring a full portfolio of biosimilars to the US market, the company is reorganizing to launch those drugs from its innovative medicines unit.

Chief Operating Officer Albert Bourla offered some more details behind the decision to align the biosimilars business with its innovative brands during Pfizer's second quarter sales and earnings call July 31, pointing out that the company may soon have several biosimilars on the market.

"All of our biosimilars are either registered or about to be registered in the next 12 months, which means that they are all entering commercialization phase," Bourla said. Reorganizing the business under branded oncology and immunology will best position the biosimilars for strong launches by tapping the commercial, scientific and patient experience expertise of those business units, he said.

Pfizer also decided to realign the businesses under the innovative umbrella because, like the rest of the business, biosimilars are a "high-risk, high-reward, heavy-in-R&D investment business," he said. That says a lot about how the market for cheaper biologics is developing – or not developing – in the US.

Pfizer has launched one biosimilar in the US, *Inflectra* (infliximab-dyyb), a version of **Johnson & Johnson**'s *Remicade* (infliximab). Inflectra launched in late 2016, but has struggled to gain market share, largely because of J&J's defensive contracting strategy with payers. While J&J has taken a hit on the topline by reducing the price of Remicade, the company has been able to hold onto most of the market share. *(Also see "Payers Like Biosimilars, But Rebates Remain The Bottom Line (For Now)" - Scrip, 29 Nov, 2017.)* Inflectra generated $158m worldwide in the second quarter, growth of 68%, although it only generated $63m in the US in the quarter.

Despite the commercial challenges, Pfizer remains encouraged about the prospects for the US biosimilar market and is preparing to launch a second biosimilar in this market. *(Also see "Pfizer's Essential Health Leadership On Why US Biosimilars Will Take Off – Eventually " - Scrip, 11 Apr, 2018.)*

The US FDA recently approved *Nivestym* (filgrastim-aafi), the second biosimilar version of **Amgen Inc.**'s *Neupogen* (filgrastim) to clear the agency, along with **Sandoz International GMBH**'s *Zarxio* (filgrastim-sndz). *(Also see "Keeping Track: US FDA Approvals For Tibsovo, Kisqali And Second Neupogen Biosimilar" - Pink Sheet, 22 Jul, 2018.)* Another biosimilar, Pfizer's version of Amgen's *Epogen* (epoetin alfa) known as *Retacrit* (epoetin alfa-epbx), was approved in May, but the launch timeline is uncertain.

Pfizer also has a biosimilar of **Roche**'s *Herceptin* (trastuzumab) that was the subject of an FDA complete response letter earlier this year and the company is developing biosimilars of *Humira* (adalimumab), *Rituxan* (rituximab), *Avastin* (bevacizumab) and *Neulasta* (pegfilgrastim).

A WAY TO MAKE A BREAK

Pfizer announced its new global business structure earlier in July, which will fold biosimilars and a new hospital medicines

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

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from the editor

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The end of July was marked by the monthly meeting of the European Medicine's Agency's Committee for Medicinal Products for Human Use, which in July made a high number of drug approval recommendations before taking a month off for the summer.

Here on *Scrip* we often find ourselves speculating about the inconsistent timing of companies' press releases on CHMP decisions. The EMA releases all its meeting highlights around midday on the Friday of the week of its meeting, asking companies with drugs on its slate not to pre-announce the results. Normally companies comply, although we quite commonly see press releases earlier on the Friday morning. We even see a few companies breaking that unofficial embargo earlier in the week, too – Puma Biotechnology was a recent case in point, flagging up a positive trend vote three days before the final positive opinion for *Nerlynx* was confirmed in June.

The EMA's request poses a dilemma for listed companies, which are under obligation to share inside information with the market sooner rather than later. With CHMP meetings potentially attended by a range of people, the risk of material information that could affect a firm's stock price leaking is real in the time between the discussion of the product and the meeting highlights being posted on the EMA's website.

While it makes some sense that the EMA wants the flow of information on its meetings to be orderly, the delay between the CHMP making its decision and the news being communicated inflates insider trading risks. Is this the best way?

Scrip

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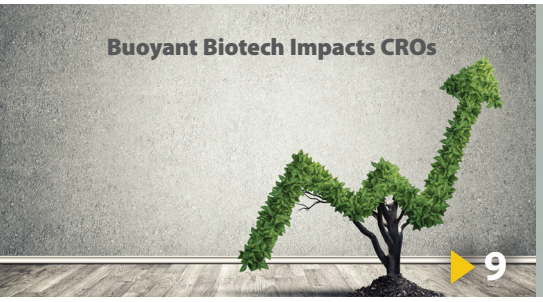

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Global First As Japan Starts iPS Cell Trial In Parkinson's
https://bit.ly/2M02NKp
Building on its national expertise in the area, Japan is starting the first clinical trial globally to assess the use of iPS-derived cells for the treatment of Parkinson's disease.

Onward Ho! Glenmark Strikes First Onco Asset Deal With China's Harbour BioMed
https://bit.ly/2MtPspY
Glenmark has sealed a licensing deal for its early stage immuno-oncology asset with China's Harbour BioMed, opening up new possibilities around collaborations between the two Asian nations. The Indian firm appears upbeat about the prospects of building further on this new linkage.

Flush With Fresh Funds, ReViral CEO Outlines RSV Trial Plans
https://bit.ly/2LZGLrc
Biotech's CEO says its lead respiratory candidate RV521 has 'caught up with rivals' in efficacy and safety.

Deal Watch: LEO Pharma Expands Market Reach Through Bayer Dermatology Deal
https://bit.ly/2Oi7BaU
LEO Pharma is buying branded topical treatments worth more than €280m in annual sales from Bayer. Also, Apricus and Sellos agree to merge, Lilly partners on translation inhibitors with Anima, and Merck leverages Sutro's technology in cancer and autoimmune partnership.

Asia Deal Watch: Daiichi Sankyo Licenses Glycotope's Gatipotuzumab ADC
https://bit.ly/2O7hojE
Daiichi Sankyo gains worldwide rights to an antibody-drug conjugate version of Glycotope's gatipotuzumab for various cancers. Also, Tasly buys China rights to Mesoblast's CV candidates and India's Cipla grows in Africa.

Finance Watch: Summer Heat Extends To Biopharma IPOs With Nine In July, 45 This Year
https://bit.ly/2njOjGD
Public Company Edition: Nine more biopharma companies launched IPOs in the US in July, bringing the 2018 total to 45 first-time offerings – three more than in all of 2017. Bluebird's $632.5m offering leads recent follow-on public offerings.

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Despite Flat Q2, Sanofi Foresees Growth In H2, Fuelled by IO And Rare Blood Units

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Shrugging off further declines in its diabetes business during the second quarter, **Sanofi**'s CEO Olivier Brandicourt used the French group's half-year update to predict a turnaround in the French group's fortunes starting with a resumption of growth in the second half, fueled not by price increases but rather by its rare blood disorder and new immunology businesses.

Olivier Brandicourt

Presenting the second-quarter performance – which saw continued declines in its troubled diabetes segment that was largely offset by its **Genzyme Corp.** rare diseases division – Brandicourt said that as the impact from the US losses of exclusivity from key drugs peaked in the second quarter, "the growth of our diversified businesses largely compensated for these headwinds. We look forward to entering a new growth phase led by our increasing focus on specialty care and our leadership positions in emerging markets and vaccines."

He was speaking to analysts after the company said its global diabetes sales slid 11.9% to €1.37bn due to lower insulin (*Lantus* and *Toujeo*) sales in the US. Its multiple sclerosis franchise also put in a disappointing performance with sales of *Aubagio* (teriflunomide) and *Lemtrada* (alemtuzumab) both missing market projections. Meanwhile its PCSK9 inhibitor *Praluent* (alirocumab) continued to ramp slowly in US, registering sales of just €60m in the second quarter, with US sales contributing €35m.

One bright spot was *Dupixent* (dupilumab), marketed with **Regeneron Pharmaceuticals Inc.** for the treatment of moderate-to-severe atopic dermatitis in adults. It generated sales of €176m in the second quarter, compared with €26m in the second quarter of 2017. Sanofi confirmed it plans to submit Dupixent to the FDA in the third quarter for an indication in adolescents with atopic dermatitis.

The company meanwhile expects great things to come from its recent purchases of hemophilia specialist **Bioverativ Inc.** and of biologics-focused company **Ablynx NV**.

Sanofi is awaiting regulatory approval for Ablynx's *Cablivi* (caplacizumab) for the treatment of acquired thrombotic thrombocytopenic purpura (aTTP), which can be fatal. Ablynx had forecast peak caplacizumab sales of €1.2bn, although Sanofi has previously said it was premature to make a prediction. The European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) in June recommended the approval of caplacizumab, while the FDA, which has granted the drug Fast Track designation, is expected to follow suit in early 2019.

REED INTRODUCTION

Brandicourt used the second quarter to introduce his new R&D chief, John Reed, who recently replaced Elias Zerhouni as new head of research and was formerly chief of research at **Roche**, the world's biggest producer of cancer drugs. Reed's appointment seems to reflect Sanofi's intention to focus more and more on research for new anticancer therapies. The American joined Sanofi on July 1 and used his first official outing as its R&D chief to extol the French group's pipeline and future therapeutic orientation.

"We have got 86 projects underway in the clinic, with 40 NMEs," he noted. "We're expecting five readouts this year [and] five additional drug approvals this year ... and another four readouts that could be registration enabling, so the pipeline is really progressing nicely," Reed told the analysts' call.

Reed said he was impressed by the breadth of therapeutic modalities that Sanofi now supports.

"Altogether, 10 different therapeutic modalities, antibodies, Nanobodies now with Ablynx, gene therapy, and with vaccines, it's really quite exciting, and it makes it exciting for our scientists. So I'm confident with that kind of toolbox with which the scientists can tackle drug targets that this will be ... attracting talent," Reed said.

US PRICING DEBATE

CEO Brandicourt said he was not surprised that the US Trump Administration was pressuring drug companies to restrain their prices. He said in fact it was overdue and that Sanofi had been an early mover in showing pricing restraint in the US and thus didn't feel the need to commit to curbing the price of its drugs there.

"We've been the first company to tie the price increase of our medicine to what we consider to be a meaningful absolute benchmark which is national health expenditure. And that is calculated by the HHS (Health and Human Services Department). As a result, we had no increase in 2017 on 56 products of our 85 prescription medicines. And overall, we had a price increase of less than 2% for a net price decrease of around 8%," Brandicourt told analysts.

"That is significantly different from what we have seen from our competitors in the recent announcement eventually not to increase prices for the rest of 2018. A company like ours has seen frankly the light coming maybe a little sooner than the others have," he said.

POTENTIAL M&A

Brandicourt said Sanofi would now bed down and integrate its two latest acquisitions – Ablynx and Bioverativ – before venturing again into the realm of M&A, but that financing room remained for added bolt-ons if they make sense.

Sanofi had previously earmarked around €20bn for use in targeted acquisitions.

"If there were any bolt-on acquisitions which were providing assets which would fit very much strategically with what we want to do, we would certainly consider them. We do have some headroom because those two deals have cost us about €13bn, so bolt-on acquisition remains possible in the next two years. But it's definitely not a short-term priority," he said.

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China Appetite For HPV Vaccine Delivers Surprise For Merck

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The appetite for human papillomavirus (HPV) vaccines in China seems insatiable, which has surprised the top executives of a US company with a decades-long presence in the country.

Merck & Co. Inc. said that the demand for its vaccine *Gardasil*, approved in China just a year ago, is much bigger than it expected. "Frankly, the uptake in China has been larger than what we would have initially anticipated, and we're still trying to ensure that we understand what the demand is there, because this is such a large opportunity," CEO Ken Frazier said during a July 28 earnings call.

The demand is such that the company is now getting ready to gear up its supplies in China. "There are so many people there that we've got to understand how much product we will need to get into that country," added the top executive.

Given the short time since the market launch, the strong demand is particularly surprising. With an approval in China in May 2017 for Gardasil and this April for *Gardasil 9* (the nine valent version), the HPV vaccines have more than delivered for Merck, which reported that overall Gardasil/Gardasil 9 sales increased 19% to $469m in the quarter, mainly driven by the strong uptake in China and favorable timing of sales in Brazil.

During the first quarter call, Merck president of Global Human Health Adam Schechter said China "represents a very good opportunity for us".

"Early in the quarter, we announced that Gardasil 9 is approved in China for use in girls and women 16 to 26 years old. We see these new regulatory actions as emblematic of an increased focus on the impact of human papillomavirus-induced diseases, especially cervical cancer," noted the president of Merck Research Labs Roger Perlmutter.

The demand for HPV vaccines is so strong in China that the market is billed by Merck (known as MSD outside North America) as an "exemplar" for Gardasil's global opportunity.

PRE-LAUNCH CAMPAIGNS DRIVE DEMAND

The demand for access to new HPV vaccines from Chinese consumers has been somewhat reflected through a booming medical tourism trade to Hong Kong and Macau. The Chinese state-run Xinhua news agency estimated that as many as two million people from mainland have flocked to the cities to receive the vaccines, which are normally administered in three shots.

The China Annual Cancer Yearbook shows that in 2015 there were estimated 98,900 newly diagnosed cervical cancer cases, with related deaths estimated at 30,500. The incidence rate of cervical cancers (which are linked to HPV infection) is steadily rising in China.

Ahead of the launch of Gardasil, Merck initiated a public awareness campaign in collaboration with local marketing partner **Chongqing Zhifei Biological Products Co. Ltd.** and health checkup group **iKang Group**. Zhifei Biological has the exclusive rights to sell Gardasil in China under a strategic agreement with Merck, and with an extensive national network managed to get the vaccine added to five provinces' procurement bidding list just five months after the launch.

Meanwhile, Merck launched an awareness campaign using online workshops and offline training, covering 20 million Chinese females and their families in 60 cities. Also, the company teamed up with Alibaba's health subsidiary AliHealth, to use one of the largest e-commerce sites in China to raise cervical cancer awareness. Other training programs targeted 5,000 grassroots physicians about HPV vaccination.

The initiatives seem to have started bearing fruit and added to China's already strong demand for the vaccines. "We're still in the beginning, frankly, at the launch in China and we're excited about that opportunity," noted Merck's Frazier.

Gardasil is not the first HPV vaccine to have received the Chinese green light, as **GlaxoSmithKline PLC** had previously sealed the sector lead with *Cervarix*, approved by the China FDA in July 2016. It has taken both online and offline approaches to marketing, including via a partnership with AliHealth.

KEYTRUDA SCORES CHINA APPROVAL

Vaccines were not the only highlight for Merck in China, where regulators approved the US firm's major PD-1 inhibitor immuno-oncology drug *Keytruda* (pembrolizumab) a day before the company's earnings call.

"Yesterday we announced that Keytruda was approved in China for the second-line treatment of unresectable or advanced melanoma, the first approval of our PD-1 therapies for melanoma in China," the company said.

Keytruda is the second PD-1 inhibitor to be approved in China after **Bristol-Myers Squibb Co.**'s *Opdivo* (nivolumab), but the first immuno-oncology therapy indicated for melanoma, a deadly form of skin cancer. The incidence of the malignancy is increasing in China by 3-5% annually, noted data from the company.

Opdivo was approved by the CFDA in June for non-small cell lung cancer, the most prevalent cancer type in China.

Globally, sales of Keytruda – despite being a relative late-comer – have now surpassed Opdivo, driven in large part by data in first-line combination use with standard chemotherapy.

Meanwhile, Merck is also expecting another oncology approval in China, for the PARP inhibitor *Lynparza* (olaparib), which the company is co-developing and will co-commercialize with **AstraZeneca PLC**. "Going forward, we expect the recent breast cancer approval in Japan and expectations for an ovarian cancer approval in China, to continue to enable strong growth," the US company said.

Other growth drivers in China may also include the diabetes treatment *Januvia* (sitagliptin), which is facing pricing pressure in the US. "We're in the middle of launching in China...where we think there is still a growth opportunity there. So what's happening is the growth outside of US is offset by the US pricing pressure," said the company in its earnings call.

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From the editors of PharmAsia News

Shire Integration Prep Progresses As Takeda Logs Solid Q1

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Integration leaders and teams from both **Takeda Pharmaceutical Co. Ltd.** and **Shire PLC** have already begun talking about the possible shape of their merged company, ahead of the Japanese company's planned acquisition of its larger target.

Following a "very fast" regulatory approval from the US Federal Trade Commission, efforts are now underway for similar clearances in other key jurisdictions, but things are still on track for a formal close to the deal in the calendar first half of 2019, Takeda executives told a first quarter results briefing.

Both firms are now working on a business combination plan across 20 different areas, and "we are starting to map what the integration would look like", president and CEO Christophe Weber said.

Things are so far moving along smoothly in the process, which is also looking at "strategically, how we could get organized in the future." But this is "in parallel of our business as usual" and will not distract from driving Takeda's existing operations, he stressed. Read the full article here

COSTS/SAVINGS

In other activity around Shire, preparations for the long-term financing of the planned $64bn deal are "progressing well", chief financial officer Costa Saroukos told the briefing, pointing to the recent agreement for a $7.5bn loan from a consortium of banks.

Takeda booked a total of JPY10.6bn ($95m) in expenses related to the acquisition in the fiscal first quarter ended June 30, mainly in financial/legal adviser and banking fees.

While this appeared to raise a few analyst eyebrows, the company said these were largely absorbed through continued cost savings under the Global Opex Initiative, including increased use of video conferencing to reduce international travel.

Following moves to divest businesses in Brazil and China over the past few months, Weber added that there was still room for further non-core asset disposals ahead of the merger.

> We are starting to map what the integration would look like

Without identifying possible candidates, he said these are likely "because of the historical [Takeda] businesses, we have many products outside of [the company's core] areas." Takeda, he added, is actively looking "at businesses which we think are underperforming or businesses that could be better managed by other companies."

The sale of non-core assets including land and securities generated an additional JPY31.9bn in cash in the quarter, as the firm looks to free up as much money as possible ahead of the Shire deal.

'SOLID' FIRST QUARTER

First quarter operating profit at JPY98.9bn was affected by sizable one-off gains from divestments in the same period last fiscal year, but excluding these, reported growth was 38% (-49% reported).

Underlying group revenues were up 6% (flat on a reported basis) to JPY449.8bn, helped by a 12% rise for the core areas of gastrointestinal, oncology, neuroscience and emerging markets. *Entyvio* (vedolizumab) for ulcerative colitis and Crohn's disease again led product sales, with growth of 34% to JPY60.1bn in the quarter.

"The momentum for this drug appears solid as Japan sales come online from July [following a recent approval for ulcerative colitis], and ahead of a potential sub-cutaneous formulation launch in 1H19," Deutsche Bank analysts said in a note.

Geographically, there was 14% overall growth in US, driven by oncology, while underlying Japan revenues were up 7% despite the general April price cut.

In China meanwhile, there was a turnaround to growth of 29% in revenues, and this market is being positioned as an "important region in the medium term, with seven new product launches planned over the next five years," Saroukos observed.

Underlying 1Q core earnings grew 40%, which the CFO described as "truly impressive" and adding to the overall "encouraging business momentum".

Commenting on what they said was a "solid 1Q", Deutsche Bank analysts said that "while the Shire deal is expected to remain the dominant driver of the share price this year, management continue to deliver on the transformation of the standalone business."

Takeda's full-year outlook remains unchanged – reported operating profit of JPY201bn (-17%) on revenues of JPY1,737bn (-2%) – and does not include the potential impact of Shire.

However, the figures do assume the US launch of one additional (therapeutically non-equivalent) competitor to multiple myeloma drug *Velcade* (bortezomib) in both intravenous and subcutaneous form in September, which is expected to cut revenues from the original product by JPY54bn.

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From the editors of PharmAsia News.

Hemlibra Effect Is Muted At Shire - For Now:
https://bit.ly/2v2l13q

Teva Braces For A Bigger Hit As Price Competition Intensifies For Copaxone

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Teva Pharmaceutical Industries Ltd.'s blockbuster *Copaxone* (glatiramer) franchise has been something of a lifeline for the company as it retrenches under new leadership amid ongoing challenges to the US generics business and mounting debt. Despite the launch of the first generic to the valuable 40 mg brand last year, Teva has been able to hold onto a roughly 85% share of the market, though it had to take a big hit on price.

Now even that slim victory is waning.

The company said during its second quarter earnings call Aug. 2 that intensifying price competition in the glatiramer market will result in more downward pressure on Copaxone in the second half of the year.

"We have been holding onto roughly 85% of the volume in the first and second quarter of this year, but we do think that it's a very high level," CEO Kare Schultz said during a same-day call. "The fact that we have two generic competitors will lead to a reduction in the volume, and then on price – it's a complicated game."

Mylan NV recently made a big price adjustment to the wholesale acquisition cost (WAC) of its generic version of the 40 mg dose, apparently after not making big inroads with the launch and after a third rival launched. Mylan's product launched in October as the first generic version of the 40 mg dose, which was a big win for that company. *(Also see "Surprise! Mylan's Copaxone Generic Sets Teva Up For A Struggle" - Scrip, 4 Oct, 2017.)* Since then, **Sandoz International GMBH** has received FDA approval of a 40 mg version called *Glatopa*, but the **Novartis AG** subsidiary has had a 20 mg dose, dosed daily, on the market for three years. *(Also see "Sandoz's Less Frequently Dosed Copaxone Generic Glatopa Hits Teva Two Months Early" - Scrip, 13 Feb, 2018.)*

Teva said it expects Copaxone to generate $600m in the US in the second half of the year, which would result in US revenues of about $1.5bn for the year. The company expects Copaxone will generate $2.1bn in 2018 globally.

Sales of Copaxone in North America – the vast majority of which come from the US – plummeted 46% to $464m in the second quarter, while globally revenues were $626m.

AUSTEDO OUTPERFORMED BY INGREZZA

The company's new specialty brand *Austedo* (deutetrabenazine), approved for chorea associated with Huntington's disease and tardive dyskinesia, generated $44m in the second quarter.

A rival drug from **Neurocrine Biosciences Inc.** called *Ingrezza* (valbenazine) – approved by the FDA for tardive dyskinesia in April 2017 just months ahead of Austedo's clearance for the same indication – appears to be out-performing. Ingrezza generated $96.9m in the second quarter, Neurocrine reported.

Teva is hopeful that a new growth driver could soon be on the market, the CGRP inhibitor fremanezumab for migraine. The drug originally had a user fee date in June, but Teva warned investors earlier this year that it wouldn't make the timeline due to a manufacturing issue at its third-party supplier **Celltrion**. *(Also see "Teva Pushes CGRP Timeline Back To End Of 2018" - Scrip, 3 May, 2018.)*

Now the company is hopeful that fremanezumab is on track for FDA approval by the revised goal date of Sept. 16. An FDA inspection of the facility has been completed.

Schultz said Teva is prepared to launch the drug immediately after approval, where it will compete against **Amgen Inc.**/Novartis' *Aimovig* (erenumab), which was approved by the FDA in May. *(Also see "Amgen's Aimovig Aims To Capture As Many Migraine Patients As Possible With $6,900 Price" - Scrip, 17 May, 2018.)* A third CGRP, **Eli Lilly & Co.**'s galcanezumab, is expected to be approved in October.

Teva played down the delay in getting to market. "I don't know that it really matters when you are second or third to market, because those products will be close," North America-Commercial Exec VP Brendan O'Grady said.

"Most of the payers right now are blocking Amgen's product, so it's difficult to get reimbursement as they are looking at this market to form," he said. "We are in conversation with payers already for 2019."

DEBT AND GENERIC HEADWINDS

Teva is in a difficult position as it looks for a way to return to growth while sales of existing products continue to slip and it is strapped with a pile of debt it is working to pay down. The company's debt was $30.1bn as of June 30. Teva has paid off $7bn in debt over the last eight quarters, the company reported. Some of that has been done by divesting non-priority assets.

The company announced a huge cost-cutting program last December that will reduce the workforce by 25%, or around 14,000 employees. *(Also see "Schultz Swings The Cleaver At Teva, Cutting 25% Of The Workforce" - Scrip, 14 Dec, 2017.)* Teva has reduced its workforce by 8,300 employees since the announcement.

The environment continues to be challenging for Teva as generic drug makers face tough headwinds across the industry, largely driven by US pricing pressure. *(Also see "Generic Manufacturers Try To Up Their Game As US Pressure Persists" - Scrip, 16 Jun, 2017.)* Industry leaders have been saying for a year that the pricing pressure is stabilizing, but challenges persist. Teva's generics sales in North America declined 29% to $947m in the second quarter, while generic product sales grew 10% in Europe to $907m.

Schultz echoed the same sentiment that some other generic industry leaders have expressed about the market. "I do think we see a reduction in price erosion, a stabilization of the pricing dynamics in the US, but it's really not had any major impact in the second quarter," he said.

Consolidated revenues were $4.7bn in the quarter, a decrease of 18% compared to the year-ago quarter. The company reported a net loss of $166m.

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Jardiance Is The Star Of Boehringer's Show, But Micardis Drag Spoils The Party

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Jardiance (empagliflozin), **Boehringer Ingelheim GMBH**'s SGLT-2 inhibitor developed in alliance with **Eli Lilly & Co.**, proved to be the star of BI's 2018 so far, increasing sales by 68% in the first half of the year, making €664m for the German major.

The family-owned company also highlighted the positive study results for Jardiance in the treatment of type 1 diabetes in addition to insulin therapy as a highlight in its H1 round up. Both trials in the EASE Phase III program, which investigated the use of empagliflozin in combination with insulin therapy in adults with type 1 diabetes, met their primary endpoint. The primary efficacy endpoint, defined as the placebo-corrected change from baseline in HbA1c after 26 weeks of treatment, was met for all investigated doses of empagliflozin (2.5, 10, and 25 mg).

The full results will be presented at the European Association for the Study of Diabetes (EASD) Annual Meeting in October, 2018 in Berlin, Germany. The two companies are now "discussing next steps and exploring regulatory options," for Jardiance, according to a press release. The drug is forecast to reach global sales of over $2bn by 2025.

The idiopathic pulmonary fibrosis drug, *Ofev* (nintedanib), also had significant growth in H1, with net sales increasing by 35% to €531m. Datamonitor Healthcare forecasts Ofev to grow dramatically with a compound annual growth rate of 11.5%, peaking in 2023 with global sales of €2.1bn before loss of exclusivity. "Ofev will succeed *Esbriet* (pirfenidone) as the market leader within idiopathic pulmonary fibrosis (IPF) on account of real-world evidence suggesting clinical trials understated its clinical profile," it says. The drug was approved in the US in 2014, with Japanese and European approval coming in 2015

BI's pharma division made net sales of €6.1bn this year so far, making up 71% of the company's total net sales. And while the business has grown "a little less strongly", according to Hubertus von Baumbach, chairman of BI's board of managing directors, than in 2017, it made net sales of €8.6bn.

The drag on growth has been largely down to the increased generic competition in Japan for the blood pressure medicines *Micardis* (telmisartan) and *Twynsta* (telmisartan/amlodipine), which BI developed in partnership with **Astellas Pharma Inc.**. Micardis 2017 sales in Japan plunged 18.7% to €1.42bn.

Micardis' patent expired in the EU in January 2012 and in the US in January 2014, with the global value of the franchise dropping by 21% from the previous year. It lost patent exclusivity in Japan in June 2017. "Very few opportunities remain for the Micardis franchise, and it is unlikely that Boehringer Ingelheim will be able to limit the expected continued decline in sales of these drugs," said Datamonitor Healthcare analyst Aine Kyle in a drug outlook.

Net sales in biopharmaceutical contract manufacturing increased to €298m, contributing about 3% of total sales.

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CONTINUED FROM COVER

business into Innovative Health, while incorporating mature products and off-patent drugs under Established Medicines and forming a new Consumer business unit.

During the second quarter call, CEO Ian Read said the decision to reorganize was driven by Pfizer's confidence in the pipeline and the need to structure the business around growth drivers. The timing was right following the completion of US tax reform and with the company having reached a decision in 2016 not to split up its business groups. Pfizer is in the process of reviewing strategic options for the consumer business, including a potential sale or spin out of the business, and plans to make a decision by the end of the year.

The new structure, Read said, continues to simplify the business organization and should not prevent the company from separating the company in the future if factors change.

"It allows us to continue to evaluate our business segments to see if they're worth more inside Pfizer than outside of Pfizer, so we will continue to do that," Read said. "We have always been focused on shareholder return, not the size of the company, and so rest assured that we will, as these businesses continue to develop, look at opportunities to maximize their value."

Pfizer appears to doubling down on internal R&D as the path to growth versus big M&A. The company said it will increase R&D spending in the second half of the year to invest behind late-stage pipeline assets. The company increased R&D spending guidance for the year to $7.7bn-$8.1bn from a previous target of $7.4bn-$7.9bn.

Read said Pfizer doesn't need a big transformative deal now. "I think our leadership team is united on this view," he said. "We'd be far better off focusing on developing our pipeline, investing in our pipeline, bringing these products to market, growing these products, than undertaking a large deal," he said. Pfizer is continuing to evaluate opportunities, he said, but with more of a focus on single-product transactions involving assets in late Phase II or early Phase III with an eye on a five-year horizon to market.

Some of the near-term pipeline catalysts include tafamidis for transthyretin cardiomyopathy (TTR-CM), which Pfizer will present Phase III data on in August; the NGF inhibitor tanezumab, partnered with **Eli Lilly & Co.**, for pain; and the PARP inhibitor talazoparib, pending at FDA with action expected in December. One area Read mentioned the company would be interested in investing in further is gene therapy. The company already has three gene therapies in clinical development, including products for Duchenne muscular dystrophy and hemophilia.

"We are committed to gene therapy. We would look to tuck-ins if they were available," Read said. "We certainly are not going to buy gene therapy that we think is way overpriced, but we will buy gene therapy that we think has value." Despite an encouraging second quarter performance, with revenues up 4% to $13.47bn, some analysts are concerned about Pfizer's longer-term growth outlook absent big M&A.

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Buoyant Biotech Funding Environment Directly Impacts CRO Q2s

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The first half of 2018 has been so successful for biotech venture capital fund raising that it looks on track to beat the total figure for 2017 by Q3. $9.67bn was raised in venture capital during the first half, and while this is excellent news for drug developers, it also has a positive knock-on effect on the industry's services providers, as was evidenced in the main players' Q2 results. *(Also see "Finance Watch: 2018 Biopharma VC Investment Could Beat 2017 One Quarter Ahead Of Schedule" - Scrip, 16 Jul, 2018.)*

Each company within the CRO peer set has, so far, published favourable results, with companies that service the smaller biotechs showing noticeable improvements. **Medpace Inc.**, for example, a CRO that is traditionally linked with smaller pharma and biotech, has impressed analysts with its strong bookings, up by 48%, earnings per share (EPS) growth of nearly 70%, and new business of $155m.

In a conversation with *Scrip*, John Kreger, analyst at William Blair, explained that biotech companies "historically increase their R&D spending budgets at a faster clip than larger clients and they tend to outsource a much higher portion of the work. So abundant capital flowing into biotech has a direct impact on CROs, fueling higher levels of awards, which eventually translates into higher levels of revenues and earnings." This trend is set to continue for the rest of the year, setting up 2019 for improved organic revenue growth.

Indeed, organic growth is something that reflects in **ICON PLC**'s results. It recorded net business wins in the quarter of $600m, which is a new record for the company, and saw the first organic growth in a year, albeit at a modest 2%. ICON is a preferred provider of clinical research services to **Pfizer Inc.**. *(Also see "Pfizer selects ICON and Parexel as preferred partners" - Scrip, 26 May, 2011.)* This business accounted for 13.5% of revenues in Q2 for the CRO, and 10% of its backlog.

While a new wave of biotech clients is good news for the contract services players, it could also mean a stronger negotiating stance when arranging new agreements with the pharma industry. "CRO fundamentals are healthy and getting healthier," explains Jefferies analyst David Windley. "Demand is high, and revenue growth is actually re-accelerating. That means the fight to get the right team for a biopharma's important Phase III compound will get tougher. The pricing environment is likely to harden."

Biotech funding is up on average by more than 50% compared to the second quarter of 2017, and while this bodes well for the CRO industry moving forward through the rest of the year, especially those with smaller companies in their client base, such as Medpace, or a mixed client base such as ICON, what of the larger players that traditionally do not work with smaller biopharma clients, such as **IQVIA** and **Covance Inc.**?

Biotech funding aside, the "unrelenting pressure" on large and small biopharma alike to become more efficient shows no sign of decreasing, and this continues to have an impact on CROs, whatever their size. "This structural imperative has been in place since the 1990s and we see no reason why it won't be in place a decade from now," says Kreger. "Increasingly, biopharma companies are asking themselves, 'is this function a core skill?' If not, they are outsourcing it."

IQVIA (the merged **Quintiles Transnational Holdings Inc.** and IMS) showed steady progress in Q2, with a 9% increase in revenues and the strongest bookings quarter in the company's history. Ari Bousbib, the company's CEO, said that the company's "significant strategic investments" in innovation over the past 18 months were beginning to "build operating momentum." As such, the company has raised its profit and revenue guidance for the next quarter, expecting between $2.55bn and $2.6bn, and adjusted EBITDA between $540m and $560m.

Laboratory Corp. of America Holdings made a 13% rise in its earnings in Q2, of $2.9bn. The drug development arm of its business, Covance, made a staggering 30% increase in revenues, of $1.05bn. The increase was primarily due to acquisitions (LabCorp bought **Chiltern International Ltd.** for $1.7bn in July 2017) as well as organic growth and the benefit from foreign currency translation of approximately 180 basis points. Indeed, stronger dollar environments like the ones experienced since April are good for the CRO market, because it deflates non-US expenses and help margins.

Syneos (INC Research and inVentiv's rebranded entity) and **PRA Health Sciences Inc.** will be publishing results in the next two days. The industry can expect "respectable bookings and underlying stable pricing", according to Kreger. It will be interesting to see if the **Takeda**/**Shire** merger is doing anything to alter the flow of activity into PRA, as it is the preferred provider for clinical development for Takeda. It also set up a new joint venture with the Japanese major in February as part of the pharma's company's R&D overhaul. *(Also see "Takeda Extends PRA Alliance To Japan With New JV" - Scrip, 15 Feb, 2017.)*

Jefferies analyst Windley believes the industry will see "more of the same" positive results from these two companies, with strong bookings, revenue growth, and outlook, expected. "We have found that the bulk of CRO performance is correlated," confirms Kreger. "If the tide is rising then the whole group should do well. If the tide is falling, then the whole group will probably struggle.

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Almirall Inks 'Transformational Deal' Buying Allergan's US Derma Portfolio

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Calling it a 'transformational deal' that will expand its presence in the all-important US market, Spain's **Almirall SA** has bought **Allergan PLC**'s US dermatology portfolio in a transaction worth up to $650m.

The purchase, which is expected to close in the fourth quarter, includes an upfront cash payment of $550m and a potential earn-out of up to $100m payable in 2022 based on the performance of the portfolio.

ADDED DERMA DRUGS

It's a major step in Almirall CEO Peter Guenter's program to revamp the group, and brings it the brands *Aczone* (dapsone), *Tazorac* (tazarotene) and *Azelex* (azelaic acid) for the treatment of acne, and *Cordran Tape* (fludroxycortide) for dermatoses.

It also includes *Seysara* (sarecycline), a new, first-in-class tetracycline-derived antibiotic with anti-inflammatory properties for the treatment of moderate to severe acne vulgaris in patients nine years of age and older. FDA approval of Seysara is likely in the fourth quarter of this year. Almirall expects peak sales of Seysara of $150-200m.

BOLT-ON ACQUISITION

The move, announced Aug. 3, is consistent with CEO Guenter's stated hunt for bolt-on acquisitions. *(Also see "Almirall To Put More Skin In The Game With Derma Buys " - Scrip, 14 May, 2018.)*

"This is a transformational deal for Almirall," CEO Guenter said in a statement. "It is perfectly complementary to our existing platform and will be immediately accretive to our earnings, the former Sanofi executive said, adding that the acquisition consolidates and reinforces Almirall's presence in the US.

The group's global and US leadership team now "is comprised of several former Allergan senior executives with a deep knowledge of the acquired product portfolio," he noted.

Buying Allergan's US dermatology portfolio will expand the Spanish group's platform in the world's largest dermatology market and expand its capabilities there and provide critical mass to launch its candidate KX2-391, which Almirall's CEO says has the potential to become the new standard of care in actinic keratosis, a pre-cancerous skin condition resulting in patches of thick, scaly, or crusty skin. It forecasts that annual peak sales of the product will exceed €250m.

> 'This is a transformational deal for Almirall. It is perfectly complementary to our existing platform and will be immediately accretive to our earnings'

KX2-391 recently showed positive top-line results in two Phase III trials, meeting their primary endpoints of complete clearance of actinic keratosis lesions at day 57.

Almirall and US-based **Athenex Inc.** entered into a strategic partnership in December 2017 to develop and commercialize KX2-391 in the US and Europe, under which Athenex will receive an upfront fee, development and sales milestones, and royalty payments.

Actinic keratosis is the most common precancerous condition in dermatology. It affects more than 55 million Americans. Guenter has said that many patients with AK remain undiagnosed or untreated. He describes KX2-391is a potential game changer in the treatment of this disease.

SKILARENCE AND TILDRAKIZUMAB

Meanwhile analysts say Almirall's oral psoriasis treatment *Skilarence* (dimethyl fumarate) has had an encouraging launch in the European market, racking up sales of €8m in the first half of this year. Almirall projects peak Skilarence sales of €50m.

The Barcelona-based group is now preparing for a European launch for anti-IL23 antibody tildrakizumab, which it has licensed from **Sun Pharmaceutical Industries Ltd.** The latter got approval from the FDA in March for the drug, which binds to the p19 subunit of interleukin-23 and is branded as *Ilumya*.

In late July, Almirall received a positive opinion from the the European Medicines Agency (EMA)'s drug evaluation committee, the CHMP, for tildrakizumab for the treatment of patients with moderate-to-severe chronic plaque psoriasis, making approval in the EU likely sometime in the fourth quarter. Almirall projects peak sales of the drug in Europe of €200m.

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Regeneron And Bluebird Team Up In Cell Therapy 'Joint Venture'-Style Deal

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Regeneron Pharmaceuticals Inc. and **bluebird bio Inc.** are teaming up in a cell therapy collaboration, and they hope together to overcome some of the safety and efficacy challenges that have faced the first generation of chimeric antigen receptor T-cell (CAR-T) therapies.

The two companies announced a deal Aug. 6 to collaborate on the discovery and development of antibodies and T-cell receptors directed against tumor-specific proteins and peptides. Under the arrangement, Regeneron has agreed to make a $100m equity investment in bluebird, at a substantial 59% premium to the $150 closing price on Aug. 3. The $37m premium will be credited against Regeneron's initial 50% funding obligation for collaboration research, after which the partners will fund research equally.

"This is a partnership of equals. We are going to be sharing the costs equally, sharing the labor," Regeneron's Head of Business Development Nouhad Husseini said in an interview. "It will be like a small little company working in this CAR-T field in a joint venture type of fashion."

Regeneron will have the right to opt-in to a co-development and co-commercialization arrangement for certain targets at the IND filing stage, with a 50/50 cost and profit sharing. If Regeneron does not opt-in, the company is eligible to receive milestone payments and royalties from bluebird on any resulting products. The partners have selected six initial targets and may select additional targets over the five-year collaboration term. As this is an early drug discovery collaboration, the partners expect it could take a couple of years for any drugs to reach the clinic.

The companies hope that by combining bluebird's cell therapy experience with Regeneron's *VelociSuite* technologies for creating antibodies and T-cell receptors that they will be able to overcome some of the initial challenges cell therapies have faced. Regeneron brings expertise in target discovery, where it expects to identify drug targets that are uniquely expressed on the tumor and not on healthy tissue, both intracellular and extracellular.

"This is what got us excited and we said, we need to go out there and make a deal happen," Husseini told *Scrip*. Bluebird, meanwhile, brings an expertise in cell therapy, manufacturing and approaches to overcoming tumor defense mechanisms, he said.

"The hope is if we can solve both of those problems together, we can unlock a whole array of additional tumors," Husseini added. "We hope that together, Regeneron and bluebird, can really be leaders in this field."

Despite the first wave of initial breakthroughs in the field by companies like **Novartis AG**, **Kite Pharma Inc.** (now **Gilead Sciences Inc.**) and **Juno Therapeutics Inc.** (now **Celgene Corp.**), Regeneron said the field remains nascent, with a big opportunity for new innovation.

The partnership builds on Regeneron's budding immuno-oncology portfolio. The company's first oncology launch is expected later this year in the US. Its PD-1 antibody cemiplumab, partnered with **Sanofi**, is pending at the US FDA for approval for metastatic cutaneous squamous cell carcinoma (CSCC) with a Oct. 28 user fee date. The companies are also studying cemiplumab in a Phase III trial in non-small cell lung cancer (NSCLC).

Bluebird is also an emerging player in immuno-oncology. The company's second-generation CAR-T therapy bb2121, targeting B-cell maturation antigen (BCMA), is partnered with Celgene and getting some attention on the basis of early data in patients with relapsed/refractory multiple myeloma. The CAR-T therapy has shown encouraging safety and efficacy, including progression-free survival, in patients with multiple myeloma, with positive data presented at the American Society of Hematology meeting last December and the American Society of Clinical Oncology meeting in June.

Celgene was originally partnered on a broader CAR-T alliance with bluebird but backed out of the arrangement in 2015 when it signed a sweeping alliance with Juno Therapeutics; it later acquired the company outright.

Regeneron said the deal is one of several investments the company is making to become an important oncology player. "I think immuno-oncology will be a place that Regeneron will invest heavily in going forward," Husseini said.

The deal with bluebird is part of a strategy Regeneron "thought about for a long time" to invest in CAR-T.

"It is a very different space than doing antibodies, and being in the cell therapy field requires a very different expertise, a different infrastructure," Husseini said. "We made that decision awhile back, that if we were going to enter this space than we wanted to this with a partner."

He pointed to a deal two years ago that marked Regeneron's entry into the field, a licensing agreement with off-the-shelf cell therapies developer **Adicet Bio** for $25m upfront.

The company has signed several other small deals throughout 2017 in IO, including one with **Inovio Pharmaceuticals Inc.** to study Regeneron/Sanofi's checkpoint inhibitor in combination with Inovio's T-cell activating immunotherapy, and a deal with **ISA Pharmaceuticals BV** to study it in combination with ISA's immunotherapy targeting human papillomavirus type 16.

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Ironwood Pulls Plug On Struggling Gout Drug Zurampic

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Ironwood Pharmaceuticals Inc. is terminating an agreement with **AstraZeneca PLC** for US rights to the gout drug lesinurad, approved alone as *Zurampic* and part of the combination product *Duzallo*, as will be focusing on its gastrointestinal primary care franchise as well as other pipeline assets.

News of termination of the deal for lesinurad, which is a first-in-class URAT1 transporter, came on Aug. 6 as part of Ironwood's second-quarter earnings announcement.

Ironwood had paid AstraZeneca $100m upfront plus milestones and royalties for US rights to the drug in April 2016, following Zurampic's approval by the US FDA in December 2015 and launch in October 2016. The fixed-dose combination Duzallo, which combines a 200 mg dose of lesinurad with a 200 mg or 300 mg dose of the generic xanthine oxidase inhibitor allopurinol, was approved by the FDA in August 2017 and launched in October that year.

Aachen, Germany-based **Grunenthal GMBH** licensed rights to lesinurad in Europe and Latin America in 2016.

Second-quarter sales for Duvallo and Zurampic were reported in the Ironwood's "other" revenue category, which amounted to only $3m. Ironwood plans to cut its workforce by 125 employees, mainly sales reps, having previously dropped 60 employees. The full year cost of restructuring will be in the range of from $18m to $21m, including costs associated with workforce reductions.

The company expects to see a $75m to $100m reduction in full-year operating expenses, mostly selling general & administrative (SG&A) expenses, beginning in 2019. In the second quarter, Ironwood wrote down about $2m related to the lesinurad inventory and purchase commitments. It also expects to record an intangible asset impairment of $150m and a gain on fair value remeasurement of contingent consideration of $30m in its third quarter financial statements, Chief Financial Officer Gina Consylman said during the company's earnings call.

Lesinurad was originally developed by **Ardea Biosciences Inc.**, which was acquired in 2012 by AstraZeneca for $1.26bn. The drug initially looked very promising, before a renal safety signal reared its ugly head.

For safety reasons, a lower dose than planned – 200 mg – was ultimately approved by the FDA for use with allopurinol or **Takeda Pharmaceutical Co. Ltd.**'s xanthine oxidase inhibitor *Uloric* (febuxostat). Labeling included a boxed warning for renal failure, which notes that this is more of a risk when Zurampic is given as a monotherapy.

The company viewed Zurampic as a market primer for the Duzallo combination product, which it expected would allow a full launch in gout. However, during its Aug. 6 earnings call, Chief Commercial Officer Thomas McCourt noted that uptake was "quite a bit slower than we expected."

Struggling to understand why the launch was so slow, Ironwood invested in promotional activities with consumers and physicians in test markets. As the company pushed the product hard, it saw some promotional response but it wasn't enough to make the company confident to continue to invest, the exec said.

CEO Peter Hecht said that the "decision to terminate was not taken lightly but we are confident it is the right decision and that it enables us to allocate capital to the highest return opportunities and to drive growth."

McCourt indicated it's in the best interest of the business to terminate the agreement on lesinurad and focus on creating high value through its GI portfolio opportunities.

LINZESS SALES RISE WITH DTC

In an Aug. 6 note, Wedbush Securities analyst David Nierengarten said that Ironwood's decision to back out of the licensing agreement delays time to cash flow positivity due to restructuring costs, but improves the long-term outlook because the gout program has been a "cash drain" on the company.

"The charges will push off start of profitability (from an operational perspective) to 1Q19 from 4Q18 in our view," Nierengarten said.

During the quarter, the company reported revenues were up by 25% compared with the same period in 2017 to $81m, primarily driven by performance of the constipation-predominant irritable bowel syndrome (IBS-C) drug *Linzess* (linaclotide), which launched in 2012 and is partnered with **Allergan PLC**.

Sales of Linzess were up by 14% year-over-year to $192m; profits are split equally with Allergan.

Growth was driven by a direct-to-consumer campaign in the second quarter, McCourt explained.

Ironwood reported that more than 2 million unique patients have filled about 11 million prescriptions of Linzess since the drug launched at the end of 2012. The company still sees itself as still being in growth mode and will – in partnership with Allergan –continue to invest in the market.

"Keep in mind, we've treated little over 2 million patients, but there's another 30 million Americans out there that are continuing to suffer, and we're looking at other ways in which we can activate patients and motivate physicians to treat patients more broadly," McCourt said.

That includes a Phase IIIb trial studying the effect of linaclotide on bothersome abdominal symptoms including bloating, discomfort and pain associated with IBS-C. If this is successful, it will create "an opportunity to deliver a more impactful promotional message that will activate more patients to demand Linzess and provide physicians with an even more compelling reason to prescribe Linzess for their patients," McCourt said.

The company is also developing a delayed-release formulation of Linzess that has the potential to be a non-opioid pain-relieving agent for millions of patients suffering from all forms of IBS, the exec said.

"We recently reached agreement with the FDA regarding trial design and endpoints and are now in the process of finalizing the Phase IIb protocol," McCourt said.

New GI pipeline assets are also progressing. A pivotal Phase III program of the company's gastric retentive bile acid sequestrant IW-3718 recently started in persistent gastroesophageal reflux disease (GERD). The primary endpoint will be related to reduction in heartburn severity and the drug will be tested on top of standard of care proton pump inhibitors (PPIs).

Ironwood intends to target the estimated 10 million US patients with persistent GERD who continue to experience heartburn and regurgitation despite treatment with PPIs. Given limited treatment options, the drug represents a huge opportunity commercially, McCourt said.

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Laquinimod Disappoints Again, This Time In Huntington's Disease

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Active Biotech AB/Teva Pharmaceutical Industries Ltd.'s oral immunomodulator, laquinimod, has failed to show efficacy in another potential indication, Huntington's disease, with the mainly negative top-line results from the Phase II LEGATO-HD study adding to last year's disappointment in multiple sclerosis.

Active Biotech's share price declined by 35% in early trading on July 31, the day the Lund, Sweden-based biotech company announced that the results of the LEGATO-HD in Huntington's disease (HD) did not meet the study's primary endpoint of change from baseline in the Unified Huntington's Disease Rating Scale, Total Motor Score (UHDRS-TMS) after 12 months of treatment.

There might be a glimmer of hope - the study's secondary endpoint, reduction of brain atrophy (measured by caudate volume), was met. But with the LEGATO-HD results adding to previous negative Phase III results in the CONCERTO study in multiple sclerosis, there appears to be only a limited future potential for a candidate drug that at one time Teva hoped would replace its aging bestseller, *Copaxone* (glatiramer acetate) in multiple sclerosis. Teva has discontinued development of laquinimod for MS, but has continued evaluating it in Huntington's disease.

In December 2017, Active Biotech and Teva reported that laquinimod had missed its primary endpoint in the ARPEGGIO study in patients with primary progressive multiple sclerosis. The primary endpoint of brain atrophy, defined by percent brain volume change (PBVC) from baseline to week 48, was not met after daily oral doses with 0.6 mg of laquinimod. The secondary endpoint of time to confirmed disability progression was also not met. There was, however, a reduction in new T2 lesions observed in patients treated with laquinimod 0.6 mg. *(Also see "Pipeline Watch: Phase III Studies of CSL112 And RT-100 Imminent" - Scrip, 8 Dec, 2017.)*

Earlier, in May 2017, Active Biotech and Teva reported that laquinimod had missed its primary endpoints in the Phase III CONCERTO study in relapsing remitting multiple sclerosis. The failure followed two previous Phase III studies in MS, ALLEGRO and BRAVO, that had shown positive results.

> There appears to be only a limited future potential for a candidate drug that at one time Teva hoped would replace its aging bestseller, *Copaxone*

OTHER THERAPIES MOVE FORWARD

Active Biotech did not give further details about the results of LEGATO-HD or its future plans for the product, saying only that the LEGATO-HD results would be fully analyzed and the results presented at future medical meetings.

Still the news will likely push other candidate Huntington's therapies into the spotlight. For example, earlier this year, **Roche** and its partner **Ionis Pharmaceuticals Inc.** reported that an antisense product, IONIS-HTTRx, reduced levels of the disease causing mutant huntingtin protein in a Phase I/II study. *(Also see "Ionis/Roche's Huntington's Drug 'Next Spinraza'?" - Scrip, 5 Mar, 2018.)*

In a 2017 "Market Spotlight" report on Huntington's disease, Datamonitor Healthcare analysts noted that other potential Huntington's disease therapies in Phase II studies include WVE-120101 from **Wave Life Sciences Ltd.**; a monoclonal antibody targeting semaphorin, VX15, from **Vaccinex Inc.**; and a vasopressin-targeted molecule, SRX246, from **Azevan Pharmaceuticals Inc.**

The laquinimod news is a setback for Active Biotech, that at the end of 2017 warned it would need extra funding, although an over-subscribed rights issue in April 2018 raised approximately SEK46.9m ($5.4m) after issue expenses.

The biotech has other compounds in clinical studies in neurodegeneration, including paquinimod, which is at the end of Phase I in systemic sclerosis, and tasquinimod, which is at the start of Phase I for multiple myeloma. *Anyara*, a tumor targeting immunotherapy, was planned to be evaluated in combination with a PD-1 checkpoint inhibitor, in a Phase I study in patients with advanced cancer, in its collaboration with **NeoTX Therapeutics Ltd.**.

LEGATO DETAILS

In the LEGATO-HD study, 352 patients with Huntington's disease were randomized to either 0.5 mg or 1.0 mg doses of laquinimod, or placebo, for 12 months. At baseline, there were similar numbers of men and women in the study with a mean age of 43.9 years, mean UHDRS-TMS score of 24.4, and mean UHDRS-Total Functional Capacity (TFC) score of 11.1. 287 patients completed the study and 65 terminated early, including 30 patients who had been treated with a 1.5 mg dose before that dose was terminated in January 2016 because of cardiovascular concerns that arose in a multiple sclerosis clinical study.

The primary endpoint evaluated in LEGATO-HD was the change from baseline at month 12 in UHDRS-TMS for the 1.0 mg dose, compared with placebo. The secondary endpoint measured the percent caudate atrophy (the percent change in caudate volume) from baseline to month 12 compared with that seen with placebo. Other endpoints included changes in measures of motor function, cognitive function, and functional capacity.

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PCSK9 Pick-Me-Up: New Cholesterol Guidelines May Mean Lower LDL Targets

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The lower the cholesterol the better, according to a new meta-analysis of outcomes trials in *JAMA Cardiology* – but it remains to be seen whether this mantra will be adopted in updated practice guidelines set for release in November.

New guidelines on cholesterol levels from the American Heart Association (AHA) and the American College of Cardiology (ACC) are slated to be presented on Nov. 10 at the AHA annual meeting. They were last updated in 2013, two years prior to the approval of the PCSK9 inhibitors – **Amgen Inc.**'s *Repatha* (evolocumab) and **Sanofi/Regeneron Pharmaceuticals Inc.**'s *Praluent* (alirocumab).

A change in guidelines to reflect lower targets would be a huge positive for the PCSK9 inhibitors, which have struggled with reimbursement hurdles and sluggish launches.

Traditionally, cardiologists aimed to get high-risk patients who have had a prior event (secondary prevention) to an LDL cholesterol target of 70 mg/dL. However, the 2013 version of the guidelines moved away from LDL targets in favor of risk reduction based on age and other factors, and emphasized drugs with proven cardiovascular outcomes benefits – notably the time-tested statins.

But clinicians generally are more comfortable with numerical targets and the 70 mg/dL goal reappeared in interim consensus guideline documents published after 2013, Marc Sabatine, chairman of the Thrombolysis in Myocardial Infarction (TIMI) Study Group at Brigham and Women's Hospital and Harvard Medical School in Boston, explained in an interview.

PCSK9 inhibitors have a robust effect on cholesterol and in the last few years, proof of a cardiovascular outcomes benefit came in the FOURIER and ODYSSEY outcomes studies of Repatha and Praluent, respectively, both in high-risk patients already being aggressively managed with standard-of-care cholesterol drugs.

Repatha got a labeling claim for a cardiovascular outcomes benefit at the end of 2017 and the ODYSSEY data are under review in the US and Europe.

PROS OF ULTRA-LOW LDL-C

A meta-analysis by Sabatine and colleagues published on Aug. 1 in JAMA Cardiology supports not only a return to LDL targets, but a call to go far lower than 70 mg/dL in high-risk patients. Previous outcomes research by the Cholesterol Treatment Trialists Collaboration (CTTC) showed that treatment with statins, in patients who had a baseline LDL of levels of about 3.4 mmol/L (131.5 mg/dL), was associated with a 22% reduction in major vascular events per 1-mmol/L (38.7 mg/dL) lowering of LDL-C.

Sabatine and colleagues wanted to determine the magnitude of LDL-C lowering in high-risk patients who already had low LDL-C, like the ones studied in trials of non-statins. They examined results from the FOURIER trial of Amgen's Repatha, IMPROVE-IT of **Merck & Co. Inc.**'s *Zetia* (ezetimibe), which is now known to target the Niemann-Pick C1-Like 1 transporter, and REVEAL of Merck's cholesteryl ester transfer protein (CETP) inhibitor anacetrapib.

The researchers excluded Sanofi/Regeneron's ODYSSEY outcomes study of Praluent, because the lowest reported starting LDL-C subgroup was only less than 2.1 mmol/L (80 mg/dL).

For the study, researchers examined risk reduction gained for each increment of LDL-C lowering, measured as 1-mmol/L (38.7-mg/dL). The meta-analysis showed that the same level of risk reduction occurred when treating to lower targets with the newer drugs as was seen with the older statin trials.

In a subset of patients in CTTC statin studies with a mean LDL-C at baseline/control of 1.7 mmol/L (65.7 mg/dL), the relative risk for major vascular events per 1-mmol/L (38.7 mg/dL) reduction in LDL-C was 22%. In the studies of non-statin drugs on top of statins, the median baseline/control arm of LDL-C ranged from 1.6 mmol/L to 1.8 mmol/L (63 mg/dL to 70 mg/dL) and the relative risk reduction for major vascular events per 1-mmol/L (38.7-mg/dL) reduction in LDL-C was 21%.

Furthermore, LDL lowering "was not associated with an increased risk of serious adverse events, myalgias and/or myositis, elevation in the level of aminotransferases, new-onset diabetes, hemorrhagic stroke, or cancer," the article stated.

The authors noted that benefits were seen in patient populations starting as low as a median of 1.6 mmol/L (63 mg/dL) and achieving levels as low as a median of 0.5 mmol/L (21 mg/dL) – and there was no difference between the drug classes.

"The clinical benefit per millimoles per liter reduction in LDL-C was virtually identical for statins, ezetimibe, PCSK9 inhibition, and CETP inhibition, despite these drugs having different effects on other risk markers such as high-density lipoprotein cholesterol, lipoprotein(a), and high-sensitivity C-reactive protein. This observation reinforces the notion that the reduction in LDL-C (or more broadly, atherogenic apolipoproteinB-containing particles) is the primary driver of clinical benefit," the article states.

The article acknowledges that levels achieved in the non-statin studies are much lower than those advised in guidelines for high-risk patients, that is the range from 1.8 mmol/L to 2.6 mmol/L (from 70mg/dL to 100mg/dL). The authors concluded that the "thresholds as low as approximately 0.5 mmol/L or 20 mg/dL, would further reduce cardiovascular risk."

"What should we target? The data show a benefit all the way down to 21 mg/dL and it looked entirely safe," Sabatine said when he spoke with *Scrip*.

As for the AHA/ACC treatment guidelines, Sabatine said, "I think they are a little bit behind the times and hope in the next iteration … they can be a little more aggressive for the goal."

Sabatine expects vigorous discussion when the guidelines are presented. The results of the meta-analysis somewhat conflict with another meta-analysis published by Eliano Navarese of the Inova Vascular and Heart Institute of Northern Virginia and colleagues in JAMA Cardiology on April 17. That study found that more intensive LDL-C lowering was associated with a higher reduction in cardiovascular

mortality risk in studies, but only for those with LDL-C baseline levels over 100 mg/dL.

Sabatine told *Scrip* that this previously published trial "suffers from several important limitations," the main one of which is that it fails to take into account the magnitude of LDL-C reduction in a trial.

"It has been well-established that the clinical benefit is a function of the absolute reduction in LDL-C. Without normalizing each trial to that (as all the prior statin meta-analyses have done and as we did), then one cannot make a proper comparison," he explained.

Weill Cornell Medicine cardiologist Antonio Gotto said in an editorial accompanying Sabatine et. al.'s study that the meta-analysis was "extremely well done" and that the results are encouraging and make a "strong case" for updating the current AHA/ACC guidelines.

"Whether one calls it a target or a threshold, practicing physicians need some guidance as they venture into achieved levels of LDL-C levels that are as foreign as travel to outer space. I have confidence that the new guidelines will be closer to a global positioning system map rather than just a compass and the stars. Treating physicians should apply informed clinical judgment to each individual patient," Gotto said.

However, the assessment was not all positive, as Gotto acknowledged that in the excluded ODYSSEY outcomes study the greatest benefit was in those with LDL-C of 100 mg/dL or more.

In ODYSSEY, patients who had LDL-C levels at 100 mg/dL had a 24% lower rate of major adverse cardiovascular events (MACE), according to a pre-specified analysis, versus 15% overall, the latter of which is lower than the 21% figure reported for non-statin drugs in the meta-analysis. That raises a question about whether including the Praluent study would have dragged down the results for non-statins in those with lower baseline LDL-C.

But, as Gotto noted, the investigators did a calculation that showed that the inclusion of ODYSSEY would have had a minimal effect on the reported results.

Gotto also pointed out that there are some unknowns on the safety of targeting extremely low LDL-C. The PCSK9 inhibitors can drive LDL-C to extremely low levels – 15 mg/dL – though Praluent was discontinued in the ODYSSEY study at this threshold, he noted.

Furthermore, Gotto pointed out that while there have been no safety concerns to date with the PCSK9 inhibitors, the studies were relatively short so there may not have been time to detect uncommon adverse events; the risk of diabetes with statins was not fully described until 23 years after lovastatin was approved and millions of patients received the drug.

"The level of LDL-C in newborn humans has been reported at 22 to 45 mg/dL. Detecting adverse events when the LDL-C is reduced to levels less than those present at birth may require longer periods of follow-up than were included in the FOURIER and ODYSSEY outcomes trials. While it is possible to calculate how low LDL-C levels can be reduced while still detecting a cardiovascular benefit, one reaches a point of diminishing returns, and it is not clear how low it is safe to go," Gotto wrote.

PCSK9 SPONSORS' POINT OF VIEW

The outlook for PCSK9 inhibitors has improved since the FOURIER outcomes data were released in March 2017 – and more recently as the companies agreed to cut prices. Amgen reported that Repatha sales in the second quarter of 2018 were up 78% year-over-year at $148m. *(Also see "Harper, Hooper Exit As Amgen Revenues Rise" - Scrip, 26 Jul, 2018.)* Sales of Sanofi/Regeneron's Praluent were up 61% at $74m during the same period.

"With outcomes data added to our label in the US in December and more recently in Europe and Japan, our teams have been speaking directly to the benefits of treating patients with Repatha," Anthony Hooper, executive vice president of global commercial operations, said during Amgen's July 26 earnings call.

BETTER ACCESS COMING?

As time goes on, the company expects better utilization management terms and better access with payers. Amgen has been offering outcomes-based contracts tied to the benefit seen in FOURIER, with the caveat that payers relax utilization criteria. *(Also see "Is Amgen's FOURIER Enough For Physicians, Payers To Expand Repatha Use?" - Scrip, 17 Mar, 2017.)* The company recently concluded negotiations to improve patient access in the US with several payers, including **CVS Health Corp.** and **Anthem Inc.**.

"As these changes take effect in the second half of this year, Amgen expects the proportion of commercial plans requiring documentation and the utilization management criteria to be cut in half, with the rest relying on simple physician attestation," Hooper said.

"The drug is proving to be something that physicians and cardiologists are prescribing consistently, continually and the demand from patients is still there," he noted during the call.

Asked to comment by *Scrip* on the meta-analysis by Sabatine and colleagues, Amgen said that the results are consistent with what it knows from the FOURIER study – that sustained reduction in LDL-C shows proven benefit in high-risk cardiovascular patients, even for those achieving low LDL-C levels with no new safety concerns reported.

"The results of the study support vigorous LDL-C reduction and we believe these important data should be reflected in the new guidelines," the company told *Scrip*.

During its earnings call on Aug. 2, Regeneron indicated things also were looking up for Praluent. Commercial Head Marion McCourt pointed out that during the second quarter, the company announced it would lower the net price of Praluent in exchange for straightforward physician prescribing and more affordable patient access.

Praluent was chosen as the exclusive PCSK9 inhibitor on the **Express Scripts Holding Co.** national formulary, which includes 20 million individuals. *(Also see "Let's Make A Deal: Sanofi/Regeneron Extend A Hand On Praluent, Express Scripts Takes It" - Scrip, 1 May, 2018.)*

"The agreement took effect on July 1, so it is too early for us to assess the impact. This is a competitive space with many decisions yet to be made. We continue to engage with other payers and remain committed to minimizing barriers related to access and affordability for patients," McCourt said.

Pushed on what it will take to see broad adoption of the PCSK9 class, Regeneron CEO Leonard Schleifer said that barriers against use are slowly being removed, but the "tipping point" may come with practice guidelines demanding that for patients with cardiovascular disease who can't get their LDL down to an appropriate level with the existing therapies, it will be standard practice – not optional – to go to a PCSK9 inhibitor. "That probably will be the tipping point, but we'll see," Schleifer said.

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Tazemetostat Setbacks Hit Epizyme

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Epigenetic cancer therapy specialist **Epizyme Inc.** has ended development of its lead product tazemetostat as a monotherapy or in combination with prednisolone for diffuse large B-cell lymphoma, or DLBCL. The company has also pushed back the expected timeline for submitting its US NDA for the drug's first indication of epithelioid sarcoma. And it disappointed investors in offering no clear timeline for the resolution of a partial clinical hold on trials of the drug during its second-quarter investor call.

The termination came after an evaluation of the level of clinical activity in the three DLBCL cohorts of a Phase II trial in relapsed and refractory follicular lymphoma (FL) and DLBCL; the company emphasized that results from two further cohorts of FL patients have been positive. "We continue to be excited by these FL data," said president and CEO Robert Bazemore on the conference call.

He also mentioned the evolving treatment landscape for DLBCL as influencing the decision. According to Informa's Biomedtracker database there are 12 products in active Phase III and II/III programs for the cancer, and recent approvals have included **Novartis AG** and **Gilead Sciences Inc.**'s CAR-T therapies, respectively *Kymriah* (tisagenlecleucel) and *Yescarta* (axicabtagene ciloleucel), as well as **Merck & Co. Inc.**'s anti-PD-1 checkpoint inhibitor *Keytruda* (pembrolizumab).

The executive sought to draw a distinction between the two conditions, noting that DLBCL is a more aggressive disease that is usually treated with combination therapy approaches in all lines of therapy. "In addition, the patients we have enrolled in our [DLBCL] study are heavily pretreated and highly refractory to previous treatments," he said.

DELAYED NDA IN EPITHELIOID SARCOMA

Meanwhile, the main reason for the delay in filing for FDA approval of tazemetostat for the rare condition epithelioid sarcoma was the need to collect more mature durability of response data. Epizyme had said it would file an NDA in the fourth quarter of 2018; it is now scheduling the filing for the first half of 2019.

"We understand that because there are no drugs approved in this disease and because the drugs that are used to treat them are typically the broader soft tissue sarcoma drugs, the response to these drugs are quite modest both in terms of the response rate, but also the durability of the benefit. And so, we think, it's to our benefit, particularly given that this is the first filing for tazemetostat for any indication, to have as robust a package as we can," said Bazemore.

PARTIAL CLINICAL HOLD

The other reason for the delay is the partial clinical hold that was placed on trials of the oral EZH2 inhibitor in the US, Germany and France in the second quarter following a safety report of a pediatric patient developing a secondary T-cell lymphoblastic lymphoma. The company said it had re-obtained the informed consent of all the patients in its clinical trials and updated its content form on the basis of the safety report. It has completed an assessment of tazemetostat safety data and clinical activity across its clinical trials and convened an external panel to review and validate this assessment.

Epizyme has "more or less finalized our position now and in the coming weeks we're going to be discussing that and trying to make sure we have alignment with the FDA on it, before we submit our complete response," Bazemore said. However, he stopped short of issuing a clear timeline for when the company expect to resolve the issue.

THE FL AND DLBCL COHORTS

Two of the cohorts in the Phase FL/DLBCL trial are investigating tazemetostat as monotherapy in relapsed or refractory FL patients with EZH2 mutations and in relapsed or refractory FL patients with wild-type EZH2. Positive interim data on both cohorts were presented at the European Hematology Association meeting in June.

In FL patients with EZH2 activating mutations, treatment with tazemetostat resulted in a 71% objective response rate, and all patients achieved at least some reduction in tumor volume.

In FL patients with wild-type EZH2, treatment with tazemetostat resulted in a 33% objective response rate with "a substantial majority of patients"achiving at least some reduction in tumor volume.

In relapsed/refractory DLBCL, there are three cohorts: two investigating tazemetostat monotherapy, one of which is in patients with EZH2 mutations and the other in patients with wild-type EZH2. A third cohort is investigating tazemetostat in combination with prednisolone in patients with wild-type EZH2.

Results from the DLBCL will be reported at a medical meeting later in 2018, the firm said.

Epizyme has not completely ruled out further development of tazemetostat in DLBCL, and it may look at combining it with other therapies, apart from prednisolone.

It is already conducting Phase Ib safety and tolerability studies of tazemetostat with R-CHOP as a front-line treatment regimen for high-risk DLBCL patients; its partner the Lymphoma Study Association will present data at a medical meeting later this year. Tazemetostat is also being investigated in combination with **Roche**'s PD-L1 inhibitor *Tecentriq* (atezolizumab) in relapsed/refractory DLBCL in another Phase Ib study with safety and pharmacokinetics primary endpoints and efficacy secondary endpoints. Data from that study are expected in 2019.

However, analysts at Leerink were skeptical about these prospects, writing in a Aug. 2 note: "realistically, we do not have much confidence in the prospect of the combinations with either RCHOP or Tecentriq, as there has been no proof-of-concept data and the studies will likely be stretched to several years even if the combinations do provide meaningful clinical benefit."

Meanwhile, the firm plans to "re-engage with FDA to define the registration path of the treatment of relapsed/refractory FL" once the partial clinical hold has been resolved, Epizyme's CEO noted.

Epizyme focuses on discovering and developing small molecule inhibitors of histone methyltransferases, histone acetyltransferases and helicases, which regulate gene expression. Its share price dropped by 23.8% to $9,90, giving it a market cap of $688m on Aug. 2 after its Q2 update.

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Otsuka's Guadecitabine Fails in ASTRAL-1 But AML Studies Continue

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Astex Pharmaceuticals Inc./Otsuka Holdings Co. Ltd.'s potential next-generation leukemia therapy, guadecitabine, has missed its co-primary endpoints in the Phase III ASTRAL-1 study in older patients with previously untreated acute myeloid leukemia (AML).

Top-line data from the study, comparing guadecitabine with the physician's choice of therapy – azacitidine (**Celgene Corp./Nippon Shinyaku Co. Ltd.**'s *Vidaza*), decitabine (Otsuka/**Johnson & Johnson**'s *Dacogen*) or low-dose cytarabine – found that the investigational agent missed the complete response rate and overall survival co-primary endpoints, Astex and its parent company, Otsuka, reported on July 30.

However, the trial included a difficult-to-treat patient population, and the Phase III evaluation of guadecitabine continues in other patient groups in other Phase III studies, the companies say. The effects of guadecitabine on secondary endpoints and its safety profile in ASTRAL-1 will be reported at a later date, added executives from Pleasanton, CA-based Astex Pharmaceuticals, which was acquired by Otsuka in 2013 for around $886m.

The AML therapeutic area is expected to see considerable growth over the next several years, as newer agents like guadecitabine and others reach the market, according to Datamonitor Healthcare analysts. An annual growth rate of around 30% and a market value that will rise from $153m in 2016 to $1.6bn in 2025 will be driven by the launch of new AML therapies across a range of treatment settings, as well as an increase in disease prevalence, the analysts say.

Underlying the diversity of approaches being pursued in AML, they believe there are nearly a dozen different drug classes likely to be approved up to 2025, with FMS-like tyrosine kinase 3 (FLT3) inhibitors making the largest contribution to growth. Just two weeks ago, **Agios Pharmaceuticals Inc.**'s IDH1 inhibitor, *Tibsovo* (ivosidenib), was approved in the US for relapsed or refractory AML patients testing positive for an IDH1 mutation, while Agios and Celgene gained US FDA approval for the IDH2 inhibitor, *Idhifa* (enasidenib), in August 2017. *(Also see "Tibsovo Approval Makes Agios' Second AML Approval In A Year; Priced At $26k For 30 Days" - Scrip, 20 Jul, 2018.)*

Although on the face of it the top-line data from ASTRAL-1 were a disappointment, the study was still considered worthwhile

Novartis AG's FLT3 inhibitor, *Rydapt* (midostaurin), was approved for AML in 2017 in the US and Europe.

Daiichi Sankyo Co. Ltd.'s FLT3 inhibitor, quizartinib, has demonstrated an overall survival benefit as a single agent compared with chemotherapy in the pivotal QuANTUM-R study of relapsed/refractory AML-patients with FLT3-ITD mutations, giving the company a potential foot in the door for the indication. *(Also see "Daiichi's Phase III Quizartinib Data Pave Way In Niche AML Market" - Scrip, 18 Jun, 2018.)*

Other potential therapies include **Astellas Pharma Inc.**'s gilteritinib, which is in Phase III studies, and **Cyclacel Pharmaceuticals Inc.**'s sapacitabine, that missed an overall survival endpoint in the SEAMLESS Phase III study reported last year but is continuing in clinical development.

DATA COLLECTION IMPORTANT

Although on the face of it the top-line data from ASTRAL-1 were a disappointment, the study was still considered worthwhile because of the clinical and genetic data generated by what was the largest global prospective study in this group of patients.

AML patients aged under 60 years are usually treated first with intensive induction chemotherapy, a strategy associated with a 60-80% complete response rate, but in older patients the response rate to induction therapy drops below 50%, and median survival can be less than one year.

ASTRAL-1 involved 815 patients from 24 countries with previously-untreated AML ineligible to receive intensive induction chemotherapy, often because of their age or co-morbidities, who were treated with subcutaneous guadecitabine for five days, or iv or sc azacitidine for five or seven days, or low-dose subcutaneous cytarabine for 10 days, in 28-day cycles.

Guadecitabine was designed to be resistant to breakdown by the enzyme cytidine deaminase, thereby prolonging exposure of cancer cells to the active metabolite, the DNA hypomethylating agent, decitabine. The metabolite inhibits DNA methyltransferase, thereby preventing the silencing of tumor suppressor genes and tumor-associated antigens by aberrant DNA methylation, and sensitizing tumor cells to other anticancer agents.

The promise of this anticancer activity has meant that two further Phase III studies are continuing: ASTRAL-2 is a randomized open-label study in patients with relapsed or refractory AML following intensive chemotherapy, and ASTRAL-3 is a randomized open-label study in myelodysplastic syndromes (MDS) or chronic myelomonocytic leukemia (CMML) after the failure of treatment of azacitidine, decitabine, or both. The agent is also being evaluated in other anticancers, either alone or in combination with chemotherapy or immunotherapy.

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Here's What Competition Looks Like In India's Humira Biosimilars Market

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The Indian market for biosimilar versions of **AbbVie Inc.**'s blockbuster biologic *Humira* (adalimumab) appears to have witnessed significant activity – there are an estimated seven brands already jostling for share. The segment has also seen an expanding patient pool and improved access amid interesting pricing dynamics.

First off the block was **Zydus Cadila**'s biosimilar adalimumab (marketed as *Exemptia*); launched in December 2014, Exemptia claimed to be a "fingerprint match" with the originator product in terms of safety, purity and potency. It was followed by **Torrent Pharmaceuticals Ltd.**'s version of adalimumab (marketed as *Adfrar*) launched in 2016. Torrent's product is part of a licensing pact with another Indian firm, **Reliance Life Sciences**, which has its own adalimumab brand, *AdaliRel*.

2018 saw the arrival of **Hetero Drugs Ltd.**'s biosimilar Humira, marketed as *Mabura*, while **Glenmark Pharmaceuticals Ltd.** sealed a licensing pact with Zydus Cadila to launch another adalimumab brand, *Adaly*. **Cipla Ltd.** too has since jumped into the fray with an in-licensed version of adalimumab, *Plamumab*. Some online pharmacies also list the availability of *Envira* (adalimumab) from local firm **Emcure Pharmaceuticals Ltd.**, though details on this could not immediately be ascertained. Humira itself as the original branded product is currently not sold on the Indian market.

Zydus' Exemptia is said to hold a market share of 65% in the adalimumab segment, significantly ahead of the other players. There are also signs of an expanding patient base for Exemptia - in early 2016 around 2,000 patients were said to be on the product. Details in the firm's the 2016-17 annual report, however, noted that more than 7,000 patients have been on Exemptia.

BETTER ACCESS AND MATURING MARKET

Experts note how the Indian biosimilars market has been evolving – in recent years multiple such products for individual innovator biologics, especially the high value monoclonal antibodies such as adalimumab, bevacizumab, trastuzumab and rituximab, have all been approved.

"Competition triggered by the availability of multiple biosimilars not only provides more options to the prescribers and patients, but also helps bring down the prices. These are definite steps towards better access and maturing of the market," Dr. Charu Manaktala, senior medical director and head of Asia Pacific Biosimilars Centre of Excellence, **IQVIA**, told *Scrip*.

Manaktala said that physicians in India had been prescribing alternate copy versions of innovator biologics even before the country's specific biosimilars regulatory pathways were put in place.

"Post 2012, and especially with the recent trend towards companies developing/filing the same biosimilars in the advanced markets such as the EU, and the availability of additional clinical data from global clinical studies, prescriber confidence will be built further," she predicted.

In 2012, India outlined its first set of guidelines on similar biologics, lending much-needed clarity to the approval pathway for such products; the guidelines were revised in 2016.

Interestingly, most Indian players appear to have aligned the prices of their adalimumab biosimilars in the region of around INR22,000-25,000 ($320-364) except for the Cipla brand, which is priced at around INR16,072, details on online pharmacy sites in India indicated. Typically, though, the price to patients is believed to be much lower, given various patient assistance programs and other discounts.

Zydus Cadila confirmed to *Scrip* that for patients who are on a patient assistance program through doctor referrals, the actual cost of Exemptia ranges from INR11,000-14,000. Cipla's Plamumab is believed to be available at prices lower than Exemptia, though the Mumbai-based company declined to comment on product-related issues or pricing.

Some experts, however, suggest that the trade discounts seen in the Indian biosimilars space typically come with a caveat – the offer is valid only if you buy a minimum quantity of the product.

"I think these discounts/offers will continue, driven by competition and duration of the therapy. For chronic it will be higher," Dr. Subita Srimal, partner at ProGrow Pharma Partners, an Indian life sciences advisory firm, told *Scrip*.

PRICES RELATIVELY LOW

The India biosimilar adalimumab prices are also a fraction of Humira's price internationally – a prefilled carton with two syringes is reported to cost around $2,500 in the US. Adalimumab biosimilars are also expected to launch this October in Europe, while an at-risk launch of a US Humira biosimilar, some analysts predict, could potentially happen by late 2020.

Industry experts had previously explained that the price advantage of biosimilars is perhaps more valuable in an out-of-pocket market like India, where physicians generally try to "economize" and prescribe adalimumab for around six months to bring down/control the severity of the symptoms, after which the patient can be "tapered off" the biologic and maintained on oral/conventional therapies.

Srimal also noted that currently the price of certain mature biosimilars, such as of breast cancer drug trastuzumab (*Herceptin*), are "marginally different" and the innovator also manages to "match the price through free samples" based on the drug dose. She expects this trend to continue.

"If there is a marginal difference most physicians based on the patient [if in the high income category] push the innovator compound," she added.

The India pricing dynamics are also interesting in view of general expectations that price erosion for biosimilars is likely to be less dramatic in emerging markets, as regulatory requirements become more harmonized and costs climb.

IQVIA's Manaktala explained that the application of global, harmonized regulatory standards translates into increased development costs, especially due to the need for procuring large quantities of innovator biologic (as the reference product) as well for the conduct of clinical trials.

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Anima Biotech: Lighting The Way In Protein Translation

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Anima Biotech Inc. is a pioneer of translation control therapeutics, a new class of drugs that control protein translation. It is led by Yochi Slonim, a software and technology entrepreneur by background and a convert to the excitement of the biotech business.

When Slonim was introduced to the idea of translation control therapeutics 12 years ago, he had just sold his third software company and was looking for ways to reinvest into start-ups that were looking at big problems, not just solving issues for banks or insurance companies. He was introduced to biotech by Zeev Smilansky, his co-founder in the company, by an idea for creating drugs for undruggable diseases and was so fascinated by the idea that he became the seed investor in the company.

Anima Biotech CEO, Yochi Slonim

THE BIG IDEA

Smilansky's big idea was to cause ribosomes to broadcast light pulses as they assemble the protein. Light pulses from within the ribosomes that will show in pictures, or even videos, when, where and how much of any target protein they are making. "That was a fascinating idea, the light coming out of the ribosomes, and I was imagining images that would look like the Milky Way on a cloudy night, you can look and see in clouds of light how the ribosomes are producing the proteins," Slonim told *Scrip*.

When the ribosomes produce the protein, the process shows as glowing light . A screening system is then put in place whereby Anima tries out hundreds of thousands of molecules, inserted into the cells to see if these have any effect on the light. If a certain molecule increases or decreases the light, this is controlling the production of that protein.

The molecules do not bind to the protein, however, but they find a way to control the protein's production indirectly by targeting the regulatory mechanisms around mRNA translation. It is not just about the amount of light, it is also about the location of light. For example, in neuroscience, there is a huge importance attached to where the proteins are made.

Anima initially collaborated with the biochemistry lab at the University of Pennsylvania, because they had certain technologies that were relevant to that challenge. Anima built a completely automated screening system around that core technology, which shows the translation of the proteins through light coming out of the ribosomes. For each 100,000 compounds, about 50 million images are generated and each image gives 70 different parameters that are sampled out of the image. "This gives you billions and billions of data points that, through machine learning and artificial intelligence technologies and image processing analysis, we are basically coming up with the images that show you the active compounds; the hits, the ones that control the light," explained Slonim.

Anima's technology is capable of visualizing and monitoring the production of any protein in living cells, in real time, and to identify and discover compounds that control the production in a specific way. Specificity is important here, Slonim said, because to harness this technology it is imperative to know if you can control one protein or all the proteins in the cell. "You want compounds that do not have many side effects and our technology can tell us what other proteins' production is impacted by a given compound," he explained.

There are important differences between Anima's strategy and protein degradation companies such as **Arvinas Inc.** or interfering RNA (iRNA) companies like **Alnylam Pharmaceuticals Inc.**, added Slonim. "Instead of trying to knock down the mRNA as a target, or degrade proteins, we have a way to control the production by ribosomes of proteins from that mRNA, the translation of the mRNA into a protein. And with small molecules. It's like finding the master switches and the detailed specific switches of the production machinery and basically targeting them with small molecules. Nobody has ever done that before."

Slonim said that this strategy is applicable to 85% of known proteins. "It's bigger than small interfering RNA (siRNA). If you take an Alnylam and **Moderna Therapeutics LLC** together, it's the breadth of what we can do, but we can do this in small molecules. Think about the opportunity in that."

ELI LILLY INTEREST

In July, Anima Biotech and **Eli Lilly & Co.** inked an exclusive deal for the discovery and development of translation inhibitors for several target proteins by using Anima's Translation Control Therapeutics platform. The multi-year agreement is structured around several undisclosed Lilly targets. Anima will use its technology platform to discover lead candidates that are translation inhibitors of the targets. Lilly will be responsible for clinical development and commercialization of products resulting from the collaboration.

Anima will receive $30m in upfront payments and $14m in research funding. The biotech is also eligible to receive up to $1bn if all future development and commercial milestones are achieved. Anima will additionally be entitled to low- to mid-single digit tiered royalties on sales of any Lilly products resulting from the collaboration.

"Lilly could be the first, and maybe the only one, with drugs against those targets," according to Slonim. He noted that the company will use the capital to fund its own pipeline and continue its partnership strategy. Slonim wants to partner with additional pharma partners because he is very realistic about how many targets Anima could work on by itself, saying that its "less than 1%" of what

Anima Biotech Quick Facts

- **Founded: In 2015,** after long research in collaboration with the University of Pennsylvania
- **Leadership: Yochi Slonim,** CEO; Zeev Smilanksy, chief scientific officer; Iris Alroy, vice president of R&D; David Sheppard, head of chemistry; Yossi Oulu, vice president of digital technologies; Avi Eliassaf, chief operating officer; Yuval Tsadik, vice president of finance
- **Therapeutic focus: Current pipeline** in fibrosis, oncology, viral infections, and neuroscience, specifically Huntington's disease.
- **Funding: Private investors**
- **Partnerships: Eli Lilly,** Duke University, Oxford University, Scripps Research Institute, and many more academic partnerships

the industry could do with this new technology. "We are going to run as fast as we can on both fronts, grow our own pipeline and form more partnerships."

PIPELINE OPPORTUNITIES

The company is running a fibrosis program, looking specifically at lung fibrosis, liver fibrosis and scleroderma. The program goes after the production of collagen that differentiates between the bad production, which is out of control, and the steady state production, which is good.

The second program is for respiratory syncytial virus (RSV), for which Anima has, again, a different approach. "We don't go after the virus, we go after the translation of the viral proteins by the ribosomes of our own cells, of the host cells. It's a different idea," said Slonim. "We already have molecules that are translation inhibitors of the RSV and they were proven to reduce the viral loads in the cells, so they are effective. But we are now thinking that maybe we've uncovered the general mechanism by which viruses are basically controlling the ribosomes, hijacking them to produce their own proteins, and this is a mechanism that is shared by many viruses. Anima is now in the process of testing those compounds against a panel of many viruses. "If that proves to be the case, then maybe we've discovered that the ultimate antiviral drug," he said.

The third program is in oncology, using its technology to see how the protein c-myc is over-expressed and to control that production. Neuroscience is an important therapy area within the pipeline, specifically Huntington's disease.

Slonim is considering out-licensing these assets because it is easy to "come up with new ones." There are currently "a couple" of discussions around this topic, and this is how Slonim sees the pipeline being fueled in the future. Because of the speed at which Anima can use its platform to create assets, it can strategize its pipeline to what is the biggest need in the industry.

Anima can expand its pipeline very quickly because its screening technology does not require it to develop anything against the chemistry of a target protein, meaning it can collaborate easily. Once the company settles on a given target, it takes just six months to have validated molecules in cellular models of the disease that are controlling the translation of that protein.

"The thing that is so difficult for the industry is that everybody is looking at the protein and if the protein is a hard target, it means that you are starting an extremely long and difficult process of building or discovering a molecule that will bind to the target," Slonim said. "That's like a fortress that you are mounting the forces against it. And we don't have to develop anything against the protein itself, we just look for those modulators of the light that is generated by our proprietary biology and analyzed with our software. It is a different concept altogether."

This concept means that Anima can target many proteins and the investment in a single discovery project is "dramatically lower" than the industry is used to. Slonim says that cost and efficiency is not the crux of the matter there, but the ability to find drugs that nobody else can, to find drugs that work differently by controlling the production of protein, instead of binding to protein. And Anima, he said, can also do this "very fast" against its partners' targets.

"Disruptive at multiple levels" is how Slonim described both the idea and technology behind Anima. "It's an idea that is very powerful and conceptually very simple. Why go after the proteins after they are made, when they are so different from each other?" he asked. "Instead of that, let's go one step before they are formed, go in and understand how they are made and let's find the mechanisms to control that. If that works, then it's the answer to hundreds or thousands of diseases. That's huge, that's the opportunity. This is not only about knocking them down, it's about either decreasing or increasing proteins that are missing. It's like the Holy Grail; this is everything in one place."

NO VENTURE FUNDING

There is no venture capital involved in funding Anima, but the company has raised over $30m in private investment from people Slonim knew from his previous companies. Even before the Lilly deal, Slonim says that Anima was capable of running for a "couple of years" on its own.

Anima is in a unique position, as a new company with a mature, tried and tested technology. It has been working with 17 scientific partners and has published 14 peer-reviewed articles. It has five patents covering the platform and two additional patents are pending.

Slonim believes it will be at least three or four years of no competition because of the high barriers to entry, namely the combination of novel biology with proprietary software and overall, the multidisciplinary nature of the company which combines biology, chemistry, bioinformatics, image processing, big data algorithms, machine learning, artificial intelligence and cloud technologies. Its technology is protected by "very strong" patents. If another company has the same idea, "they will have to figure out a different way" to proceed, he said.

Published online 1 August 2018

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 27 July–2 August 2018

LEAD COMPANY/PARTNER	COMPOUND	INDICATION	COMMENTS
PHASE III INTERIM/TOP-LINE RESULTS			
Otsuka Holdings Co. Ltd.	guadecitabine	acute myeloid leukemia	ASTRAL-1; missed primary endpoints but evaluation continues.
RedHill Biopharma Ltd.	RHB-104 (rifabutin, clarithromycin, clofazimine)	Crohn's disease	MAP US; met primary and secondary endpoints.
Tonix Pharmaceuticals Holding Corp.	*Tonmya* (cyclobenzaprine) sublingual tablets	post-traumatic stress syndrome	HONOR; lack of efficacy at interim assessment, study halted.
Kyowa Hakko Kirin Co. Ltd.	romiplostim	aplastic anemia	Met primary endpoint in Japan, South Korea clinical study.
PHASE III INITIATED			
Pfizer Inc./Merck KGAA	*Bavencio* (avelumab)	ovarian cancer	JAVELIN Ovarian PARP; combined with talazoparib.
Athersys Inc.	*MultiStem* cell therapy	ischemic stroke	MASTERS-2; a single iv dose.
Mycovia Pharmaceuticals	VT-1161, oral	vulvovaginal candidiasis	VIOLET; recurrent disease.
Kala Pharmaceuticals Inc.	KPI-121, 0.25%	dry eye disease	STRIDE 3; short-term treatment.
PHASE II INTERIM/TOP-LINE RESULTS			
Theravance Biopharma Inc.	TD-9855	neurogenic orthostatic hypotension	Improvement in disease symptoms.
Teva Pharmaceutical Industries Ltd./ Active Biotech AB	*Nerventra* (laquinimod)	Huntington's disease	LEGATO-HD; missed primary endpoint.
Presbyopia Therapies	PRX-100 ophthalmic solution	presbyopia	Improved near visual function.
Celtaxsys Inc.	acebilustat	cystic fibrosis	EMPIRE CF; improved pulmonary exacerbations.
UPDATED PHASE II RESULTS			
RXi Pharmaceuticals Corp./ Ethicor Pharma Ltd.	RXI-109	ophthalmic wound healing	Well tolerated, improved symptoms.
Asterias Biotherapeutics Inc.	AST-OPC1, progenitor cells	cervical spinal cord injury	SCiStar; encouraging results.
BeiGene Ltd./Celgene Corp.	tislelizumab	Hodgkin's lymphoma	Encouraging clinical results.
Medivir AB	MIV-711	knee osteoarthritis	Positive effects on joint structure.
Spring Bank Pharmaceuticals Inc.	inarigivir	hepatitis B	ACHIEVE; positive results, well tolerated.
PHASE II INITIATION			
BioLineRx Ltd.	AGI-134	solid tumors	A glycolipid-based immunotherapy.
Verona Pharma PLC	RPL554, nebulized	chronic obstructive pulmonary disease	As add-on therapy to LAMA/LABA.
Neuralstem Inc.	NSI-566, neural stem cells	ischaemic stroke	To take place in Beijing, China.
Immunomedics Inc.	sacituzumab govitecan	bladder cancer	TROPHY U-01; in metastatic disease.
eFFECTOR Therapeutics Inc.	tomivosertib (eFT508)	solid tumors	Combined with checkpoint inhibitors.
NicOx SA	NCX 470	glaucoma	nitric oxide donating prostaglandin analog.

Source: Biomedtracker

Boehringer Takes Out Option For CF Gene Therapy

KEVIN GROGAN kevin.grogan@informa.com

A long-time leader in the respiratory field, **Boehringer Ingelheim GMBH** has teamed up with the UK Cystic Fibrosis Gene Therapy Consortium (GTC) and **Oxford BioMedica PLC** to develop a long-term treatment aimed at correcting the underlying genetic causes of the devastating lung disease.

The German group has received an option to license the exclusive global rights to develop, manufacture, register and commercialize a lentiviral vector-based gene therapy for CF. The product is the result of 17 years of research by the GTC, which consists of Imperial College London and the Universities of Oxford and Edinburgh, and its co-ordinator Eric Alton said in a statement the consortium had built on its non-viral gene therapy experience to develop a new viral vector-based product.

It is currently funded by the Health Innovation Challenge Fund (a partnership between the Wellcome Trust and the UK's Department of Health and Social Care) and the Cystic Fibrosis Trust. The GTC has been working for over a decade with Japanese biotechnology company **ID Pharma**, previously known as DNAVEC Corp, to develop the product to a stage where it can now undergo toxicology testing and larger-scale manufacturing. The novel lentiviral vector will be manufactured by Oxford BioMedica, the acknowledged leader in that field, Alton noted - the UK firm's technology is used to manufacture **Novartis AG**' CAR-T therapy *Kymriah* (tisagenlecleucel).

On its website, the GTC stressed that "we can of course offer no guarantee of success, building this programme will not happen overnight and the therapy will only be focused on the problems occurring in the lungs." However, the consortium added that "we believe this new partnership of three world-leading organizations has the greatest chance of realizing a parallel new therapeutic pathway for CF patients, and better still, one that will add to the improvements already being seen with small molecule treatments."

It went on to say that "currently we envisage the effect of a single dose lasting for many months or even longer and it is unlikely that gene therapy will suffer from drug-drug interactions."

Clive Wood, head of discovery research at BI, said that through this collaboration, "we are joining forces with some of the top talents in this disease space to propel treatment advances forward." He cited the company's existing expertise "as a leader for nearly a century" in respiratory diseases and with "the gene therapy knowledge of our partners, we aim to unlock unprecedented opportunities for patients with this devastating disease."

As for CF, **Vertex Pharmaceuticals Inc.** is the principal player with its CFTR modulators *Orkambi* (lumacaftor/ivacaftor) and *Kalydeco* (ivacaftor). Earlier this year, the FDA approved the company's *Symdeko* (tezacaftor), which restores CFTR gene function by moving the protein into the correct position on the cell surface, and the drug is also being developed as a base therapy for a triple combination with next-generation CFTR modulators in its pipeline.

Vertex is currently embroiled in a price battle in the UK for Orkambi. Last month, it rejected a counter reimbursement offer the National Health Service in England had put forward, saying it is unacceptable and threatens the company's ability to invest in R&D.

The offer from the NHS works out at around £14,000 per patient. This, according to Vertex, is close to a 90% discount on the price Germany pays for Orkambi.

Published online 6 August 2018

Leading immuno-oncology pioneer, ***Daniel Chen***, has been appointed chief medical officer, a newly created position, at Mountain View, California-based **IGM Biosciences**, to lead its clinical development activities. Chen was formerly global head of cancer immunotherapy development at Genentech/Roche. IGM Biosciences, which is evaluating IgM antibodies as therapeutic agents, has also added antibody engineering expert, ***William Strohl***, to its board of directors.

Cell Medica, which has offices in London and Houston, has named ***Chris Nowers*** as CEO and executive director, following the decision of ***Gregg Sando*** to step down. Nowers joins from Kite Pharma, where he was head of Europe, and he has previously held senior positions at Avantogen Oncology, Amgen and Bristol-Myers Squibb. Cell Medica is active in the CAR-T space, and is developing NKT cells engineered to express IL-15 to retain anticancer potency, as cancer therapies.

The publicly listed Berlin, Germany-based **Mologen AG**, has appointed ***Ignacio Faus*** as CEO and a member of its executive board. Faus has 25 years' experience in the life sciences industry, including co-founding Palau Pharma and as a director of several biotech and private equity firms. Mologen is developing DNA-based TLR9-agonists, and its lead immune-oncology agent, lefitolimod, is in a pivotal clinical trial in colorectal cancer.

Navitor Pharmaceuticals Inc, a US biopharma targeting the mTORC1 pathway, has appointed ***Thomas Hughes*** as CEO. Hughes is the former CEO of Zafgen , and has been a scientific advisor to Navitor since its seed stage. Former CEO George Vlasuk remains president and will become chief scientific officer. Navitor recently started a Phase I study of its lead candidate, NV-5138, for treatment-resistant depression.

Faraz Ali has joined South San Francisco, CA-based **Tenaya Therapeutics** as CEO, having most recently been chief business officer at Regenxbio, and before that was vice president at bluebird bio. Tenaya was founded in 2016 and is a preclinical-stage biotech that has a lead gene therapy program focused on reprogramming cardiac fibroblasts into cardiomyocytes to regenerate heart tissue.

Lawrence Kenyon, **Oncobiologics Inc.**'s CFO and corporate secretary, has been named president and CEO and has joined the company's board; he will remain CFO until a replacement is appointed to that position. Kenyon was appointed interim CEO in June 2018, having joined Oncobiologics as CFO and secretary in Sept. 2015, and having previously held senior positions at Arno Therapeutics, Tamir Biotechnology and Par Pharmaceutical. Oncobiologics' lead novel MAb candidate, ONS-5010, is expected to enter the clinic in 2018.

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