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Culture Change At GSK: 'We're Doing What We Said We'd Do'

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GlaxoSmithKline PLC is pressing ahead with a transformation in its culture, with new emphasis on clear decision-making and a focus on "smart risk taking" already making an impact, according to Hal Barron.

The company's chief scientific officer and president of R&D has been at the UK-headquartered firm for just under two years, after being hired by CEO Emma Walmsley to shake up its under-performing drug discovery and development divisions.

Speaking at the Endpoints News UK-BIO19 event in London, Barron was candid about the extent of culture change needed at the company when he joined in January 2018, with employees telling him that "decision-making is a disaster."

After extensive informal group talks with employees, Barron says it became clear that a woolly, consensus-driven approach to decision-making on R&D was handicapping the company – often leading to drugs being progressed without "killer" tests.

He has led a culture change among the company's 10,000 R&D employees in sites in Europe, North America and Asia, with each project – and even every meeting – having a clear "single accountable decision-maker."

At its recent Q2 results meeting the company highlighted its progress: in the last 12 months, it has advanced eight assets into Phase I, three assets into Phase II and four into Phase III.

In that period, GSK has also gained approval for three new medicines, including Dovato (dolutegravir/lamivudine) for HIV, Dectova (zanamivir) for flu and the Nucala (mepolizumab) pre-filled syringe for asthma. This is a clear uptick in launches, but the company must also demonstrate strong commercial execution with these products.

Barron told the London meeting that he was most pleased with the efforts of one R&D team, which had taken the initiative to run one further test on their own initiative – which proved that that molecule wasn't viable and should be discontinued. He said this illustrated the new attitude, and challenged the "progressing for its own sake" of R&D projects.

That's not to say Barron hasn't felt push-back against his new ideas, summed up in a handful of catchy phrases, including "Science X Technology X Culture".

Some employees seemed jaded at the idea of change, having seen radical new ideas quickly come and go many times before. Barron said this resulted in an attitude in some of "We heard your Science X Technology X Culture idea. You'll be gone in two years, we'll just wait it out."

He told host John Carroll, however, that two years down the line, his efforts to deliver on this strategy were winning doubters over.

"Somebody said to be me recently, 'you are actually doing the strategy we talked about,'" he said, indicating that belief in major change had been blunted by years of reorganization without a clear end goal.

Barron, whom Emma Wamsley enticed away from Google-funded anti-aging moonshot Calico, set out his research vision last year, and is now executing on it, adding high-profile partnerships. The company has a new

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from the editor

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The end of October approaches and the pressure to find a solution to the Brexit conundrum mounts. The biopharma sector is particularly sensitive to the final outcome. Even while the UK remains in the EU, the impacts have already been noticeable.

The European Medicines Agency, which has so benefited from the UK's contribution over its 24-year life, is struggling to carry out its program of work having shed nearly 20% of its staff in the move from London to Amsterdam. It has yet to resume most of the activities it suspended nearly a year ago, from guideline development to engaging in international activities.

Meanwhile, other countries' agencies are not standing still. While drug review times for new active substances in the EU stagnated in 2018, approval has been speeded up in Japan, Canada, Australia and the US. In the latter, average time to approval took 244 days, compared to 436 days in the EU, according to data from the UK's Centre for Innovation in Regulatory Science.

As for the UK's Medicines and Healthcare products Regulatory Agency, it still doesn't know what (if any) access it will have to EU clinical trial IT systems, databases, registers and reporting systems, although it does plan to implement or at least align with the EU Clinical Trials Regulation.

And in the short term, there remains much uncertainty around the risks to the supply of medicines in the event of the UK leaving without a deal, and a bureaucratic scramble to ensure businesses can continue to operate across the EU/UK border.

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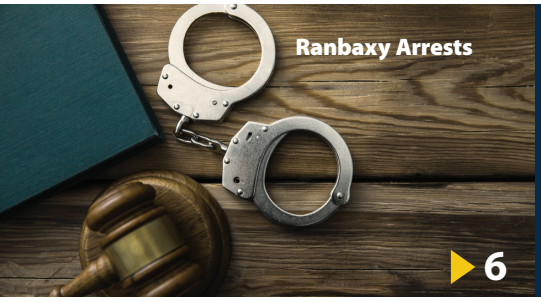

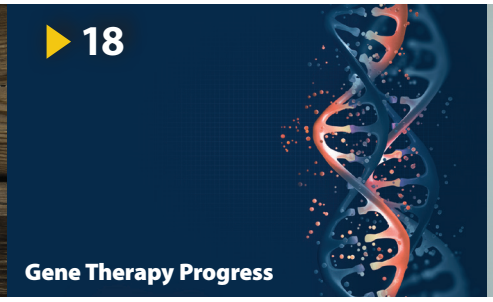

exclusive online content

Mystery Solved? GenSight's Gene Therapy Does Move Between Eyes

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Paris-based GenSight Biologics SA has been struggling to explain why its gene therapy for a rare eye disease helps improve vision in both eyes, even though it is only injected into one.

Now the company has unveiled compelling evidence from a study in primates to explain the phenomenon – and hopes it will help secure a first-in-class approval in Europe by 2021.

GenSight's lead candidate GS010 is in Phase III trials in Leber hereditary optic neuropathy (LHON), a rare mitochondrial disease that leads to irreversible blindness in teens and young adults.

Results from its largest late-stage trial, REVERSE, unveiled last month, showed a single intravitreal injection into one eye can help restore sight in 58% of the 36 patients in the study over a 96 week period.

However, the trial showed that eyes receiving the placebo improved nearly as much as those having the gene therapy. This has been a worrying puzzle for the company, with investors spooked when an earlier trial, RESCUE, first showed this pattern earlier this year.

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To read the rest of this story go to: https://bit.ly/2MGiZy5

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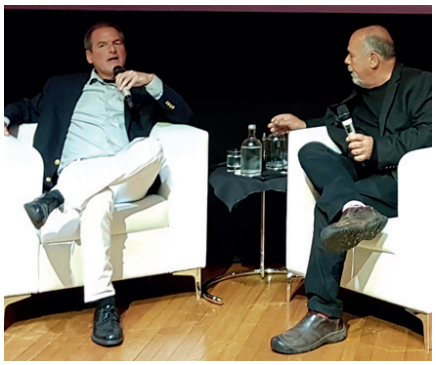
focus of science related to the immune system, the use of human genetics and the application of advanced technology such as functional genomics, machine learning and cell therapy.

Its partnerships include one with CRISPR pioneers, Jennifer Doudna and Jonathan Weissman, and another with genetics firm 23andMe.

Barron says all efforts are focused on improving the (industry-wide) 90% failure rate of molecules entering clinical trials, which he says hinges on moving away from animal models towards genetically validated human targets.

On 8 October GSK unveiled a new collaboration with Lyell, a US company focused on cell therapy, specifically exploring the concept of T-cell exhaustion, run by Rick Klausner (founder and co-director of Juno Therapeutics Inc. and co-founder of GRAIL). Klausner and Barron are convinced Lyell's research could unlock the potential of CAR-T and TCRT (chimeric antigen receptor and T-cell receptor modified T-cells) therapy in solid tumors, a breakthrough which would make the technology far more commercially and clinically valuable.



Hal Barron (l) and John Carroll

LEARNING FROM TESARO'S CULTURE

Another key strategic move by Barron was GSK's acquisition of US biotech Tesaro Inc., and its chief asset, PARP inhibitor drug Zejula (niraparib). Some analysts judged GSK to have overpaid when it spent $5.1bn on the company in December 2018, but this decision appears to be paying off, with recent data suggesting Zejula can mount a genuine challenge to AstraZeneca PLC's market leader Lynparza (olaparib).

Barron said the biotech's pipeline was also a hidden gem, and GSK has even abandoned assets in its pipeline in order to fund development of promising ones which had been languishing unfunded in Tesaro's pipeline. He claimed to be impressed by Tesaro's ethos, and said he wanted to replicate his experience at Genentech, when it was taken over by Roche. In that instance, Genentech was allowed to keep its independent status, and even influenced Roche's culture, rather than the other way round.

"I was very focused on how we use Tesaro to build our culture, It wasn't about acquiring Tesaro to conform them. It was how do we take the brilliant culture they created, and actually learn from it...because their culture was exactly what we were trying to achieve as part of risk taking, and not fearing failure."

Barron said he had also been impressed by the desire among GSK employees to move forward, and their dedication to science and to patients. Nevertheless, he acknowledged that the company still has a long way to go to restore its place in big pharma.

When GSK was created via a merger in 2000, it was the industry's second biggest company by revenue, with only Pfizer Inc. ahead of it. Since then, it has slid down the rankings, and stood at eighth in 2018, with analysts forecasting only minor improvements on this measure in the next five years.

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Pfizer's Abrocitinib Looks Competitive In Atopic Dermatitis

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Pfizer Inc. has expanded on the long lead it had with Xeljanz (tofacitinib) over competing Janus kinase (JAK) inhibitors by engineering more selective next-generation drugs in this class, including abrocitinib, for which the company presented the first detailed Phase III atopic dermatitis (AD) data on 12 October in a late-breakers session at the European Academy of Dermatology and Venereology (EADV) meeting in Madrid.

Positive top-line results already have been reported for abrocitinib, a selective inhibitor of JAK1, in two out of three Phase III clinical trials meant to support a US Food and Drug Administration filing in the second half of 2020 for the treatment of moderate-to-severe AD. Detailed data from the JADE MONO-1 study at EADV show an efficacy profile for the oral small molecule abrocitinib that may compare well with competitors in this itchy skin disease, including the blockbuster biologic Dupixent (dupilumab) from Sanofi and Regeneron Pharmaceuticals Inc.

Pfizer is submitting results from the JADE MONO-2 study for abrocitinib for possible presentation at the American Academy of Dermatology (AAD) meeting in March. Results from a third trial, JADE Compare, also tests abrocitinib versus placebo, but with a separate active comparator arm in which patients will be treated with Dupixent, with results expected in the first half of 2020. *(Also see "Pfizer Continues Positive Data Readouts For JAK Inhibitor Abrocitinib In Eczema" - Scrip, 27 Sep, 2019.)*

Michael Corbo, senior vice president and chief development officer for Pfizer's Inflammation & Immunology (I&I) unit, stressed in an interview with *Scrip* that there is need for new options, particularly for an oral therapy, which is not currently available. "There is a subset of patients who always will prefer oral therapy," Corbo said. "But also not every mechanism works for every patient. While dupilumab is a very good drug and it works well for patients, not all patients respond, so having an alternative mechanism is very important for patients with moderate to severe disease."

He said Pfizer also believes the rapid onset of action observed in Phase III trials for abrocitinib to date is going to be a differentiating factor for the drug versus other AD options. Most approved agents are topical treatments, including the company's phosphodiesterase-4 (PDE-4) inhibitor Eucrisa (crisaborole).

One of the co-primary endpoints in JADE MONO-1 was the proportion of patients who at 12 weeks achieved an Investigator Global Assessment (IGA) score of 0 or 1 – clear or almost clear skin – and a two-point or greater improvement from baseline, which Corbo noted is the US FDA's standard for drug approvals in AD. The other co-primary endpoint was the proportion of patients with at least a 75% change from baseline in their Eczema Area and Severity Index (EASI) score.

Key secondary endpoints included the proportion of patients with a four-point or greater reduction in itch severity measured with the pruritus numerical rating scale (NRS) and the magnitude of decrease in the Pruritus and Symptoms Assessment for Atopic Dermatitis (PSAAD) – a patient-reported measurement scale developed by Pfizer. Among other secondary endpoints were the proportion of patients with at least a 90% change in EASI score (EASI 90) and the percentage change from baseline in SCORing Atopic Dermatitis (SCORAD) response at all scheduled time points.

DATA AT EADV SHOW SIGNIFICANCE ACROSS DOSES

Both once-daily abrocitinib doses – 100 mg and 200 mg – met the co-primary endpoints with statistical significance, however, Pfizer did not report the p-values. The company said the percentage changes in SCORAD were statistically significant for both doses of abrocitinib versus placebo at all time points.

JADE MONO-1 enrolled 387 AD patients aged 12 and up, including 154 patients in the 200 mg arm, 156 in the 100 mg arm and 77 in the placebo arm of the study.

In addition to abrocitinib's oral administration and selective JAK1 inhibition, Pfizer believes that its rapid onset of action will be a differentiating factor for its drug. Corbo said 50% of the patients treated with 200 mg of abrocitinib in JADE MONO-1 had a meaningful improvement in pruritis starting at two weeks on the drug.

"This is the thing keeping them up at night, preventing them from doing daily activities and it's really all-consuming when you have such intense itching," he noted. "We also do see rapid improvement in inflammation as well, but itching is a hallmark of the disease, and being able to see rapid responses in that is important."

Abrocitinib Vs. Placebo Response Rates In JADE MONO-1

	ABROCITINIB 200 MG	ABROCITINIB 100 MG	PLACEBO
IGA	43.8%	23.7%	7.9%
EASI 75	62.7%	39.7%	11.8%
NRS Four-Point Improvement	57.2%	37.7%	15.3%
EASI 90	38.6%	18.6%	5.3%

Rates Of Serious Adverse Events (SAEs) And Treatment Discontinuations Due To AEs

	ABROCITINIB 200 MG	ABROCITINIB 100 MG	PLACEBO
SAEs	3.2%	3.2%	1.9%
Discontinuations	5.8%	5.8%	9.1%

The US FDA granted a breakthrough therapy designation for abrocitinib in the treatment of moderate to severe AD in February 2018.

DATA LOOK COMPETITIVE VS. DUPIXENT AND LILLY'S OLUMIANT

Corbo admitted it's difficult to compare drugs across different clinical trials, but the JADE Compare trial with Dupixent as an active comparator should shed some light on abrocitinib's potentially differentiating features.

However, the Dupixent label notes that in two studies testing the interleukin-4 (IL-4)/IL-13 inhibitor as a monotherapy IGA response rates were 38% and 36% at 16 weeks, which is less than the 43.8% IGA response rate for abrocitinib 200 mg in JADE MONO-1 at 12 weeks. EASI 75 responses were 51% and 44% for Dupixent, also lower than the 62.7% EASI 75 response rate for abrocitinib 200 mg.

EASI 90 responses for Dupixent monotherapy were 36% and 30%, closer to abrocitinib 200 mg's 38.6%. Improvements in pruritis of four NRS points or more were 41% and 36% for Dupixent at 16 weeks versus 57.2% for abrocitinib 200 mg at 12 weeks.

Eli Lilly & Co.'s JAK1 and JAK2 inhibitor Olumiant (baricitinib) also is in Phase III for AD. EASI 75 rates at week 16 for Olumiant in the BREEZE-AD7 trial were 43.1% for the 2 mg dose and 47.7% for the 4 mg dose. NRS response rates were 38.1% for Olumiant 2 mg and 44% for the 4 mg dose. *(Also see "Lilly's Latest Olumiant Data Raise Question Of JAK Inhibitor Role In Atopic Dermatitis" - Scrip, 27 Aug, 2019.)*

ABROCITINIB SAFETY MAY STAND OUT IN JAK CLASS

BREEZE-AD7 was the third of five Phase III studies for Olumiant in AD to report and it raised an already concerning safety flag. One patient in the study, which studied Olumiant in combination with topical corticosteroids, had a pulmonary embolism. Cardiovascular concerns due to pulmonary emboli reported in a few patients treated with Olumiant in rheumatoid arthritis (RA) clinical trials are why the drug is approved in the US only at the lower 2 mg dose. *(Also see "Lilly Prices Olumiant For JAK Battle, But Misses Approval For Higher Dose" - Scrip, 2 Jun, 2018.)*

No patients treated with abrocitinib in JADE MONO-1 had any cardiovascular events.

"The adverse event rate was similar in both MONO-1 and MONO-2," Corbo said.

Short-lasting nausea (20.1% in the 200 mg arm, 9% in the 100 mg arm), headache (9.7%, 7.7%) and nasopharyngitis (11.7%, 14.7%) were the most common treatment-emergent adverse events (TEAEs) for abrocitinib, while the most common TEAE in the placebo group was dermatitis (16.9%).

Serious adverse events (SAEs) in the abrocitinib 200 mg group were inflammatory bowel disease (IBD), peritonsillitis, dehydration and two cases of asthma, while SAEs in the 100 mg group were retinal detachment, acute pancreatitis, dizziness and seizures. Aggravated dermatitis, meniscal degeneration and atopic dermatitis were SAEs in the placebo group.

"Of all of the serious adverse events, there was one in the 100 mg arm of acute pancreatitis in an alcoholic and there was

one case of inflammatory bowel disease reported in the 200 mg arm" that were deemed by the JADE MONO-1 investigators to be related to treatment with abrocitinib, Corbo said.

SAFETY AND EFFICACY BY DESIGN

Corbo noted that Pfizer has been working for several years now to design kinase inhibitors with more specificity to improve both efficacy and safety.

"We're really seeing the maturation of the investment that we've made in the science of the JAK pathway, both in biology and chemistry, which has led up to abrocitinib," he said.

Michael Vincent, senior vice president and chief scientific officer in Pfizer's I&I unit, said abrocitinib is the most advanced of the five assets in the company's immuno-kinase inhibitor portfolio, which are being tested across nine immune-mediated diseases in the I&I group's three main areas of focus – dermatology, gastroenterology and rheumatology.

The other four immuno-kinase inhibitors are: PF-06651600, a JAK3/TEC family kinase inhibitor in Phase III for alopecia areata (AA) and Phase II for vitiligo, Crohn's disease (CD) and ulcerative colitis (UC); PF-06700841, a tyrosine kinase 2 (TYK2)/JAK1 inhibitor with a topical formulation in Phase II for psoriasis and AD, and an oral formulation in Phase II for psoriatic arthritis, CD, UC, vitiligo, systemic lupus erythematosus (SLE) and AA; PF-06826647, a TYK2 inhibitor in Phase II for psoriasis; and PF-06650833, an IL-1 receptor-associated kinase 4 (IRAK4) in Phase II for RA.

"Our interest and our expertise in this area is really driven by tofacitinib, Xeljanz, which was approved six years ahead of any agent for rheumatoid arthritis," Vincent said. "That's given us really great capabilities in the biology of JAK inhibition as well as the chemistry required to come up with those unique assets."

"In addition, having a suite of molecules to choose from has enabled us to take a different approach than I think some others have taken with their JAK programs," he continued. "Rather than studying one inhibitor across a range of indications and hoping it works well in all of those, we've actually tried to target our particular unique kinase inhibitors to the pathophysiology of the underlying disease, so that we're matching the cytokines that are inhibited by that particular kinase with the pathology that's driven by cytokines in a particular disease."

For example, Dupixent inhibits the cytokines IL-4 and IL-13, but IL-31 also is an important cytokine in AD, because it stimulates nerve cells to drive the pruritis, or itching, that's a hallmark of the disease. Inhibition of JAK1 by drugs like abrocitinib modulates IL-4, IL-13 and IL-31 as well as interferon gamma.

"We think that's probably one of the reasons why, since JAK1 inhibits IL-31, that we have such a rapid and marked effect on itch in our patients," Vincent said.

Pfizer's next selective immuno-kinase inhibitor to report data will be the JAK3/TEC inhibitor PF-06651600. Two late-stage trials in alopecia are under way and a US FDA filing based on those studies is expected in 2021. Pfizer believes that the JAK3/TEC inhibitor and abrocitinib have the potential to exceed $1bn each in peak revenues across their targeted indications, Vincent said.

In addition to the three Phase III JADE studies for abrocitinib in adults and adolescents with AD, the company also plans to test the drug in pediatric patients – first in children aged 6-12 and then in 2- to 6-year-olds – after reviewing the adult and adolescent data with regulators. Dupixent was approved first in adults and more recently in adolescents, but Sanofi and Regeneron also now have positive results in children aged 6-11. *(Also see "Getting A Good Start: Sanofi Extends Dupixent's Potential To Younger Patients" - Scrip, 6 Aug, 2019.)*

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Ranbaxy Brothers Arrested, Downward Spiral Intensifies

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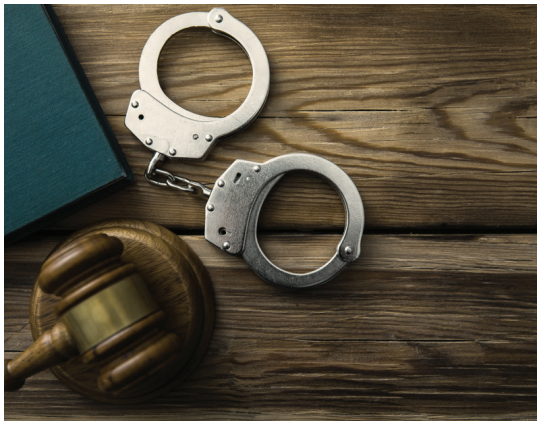
After mounting allegations of massive fraud and financial foul play, the Ranbaxy Singh brothers' chickens have come home to roost.

The brothers, Shivinder Singh and Malvinder Singh, who at one point owned the leading Indian drug firm, Ranbaxy Laboratories Ltd., were arrested by the Economic Offences Wing (EOW) of the Delhi Police following complaints of misappropriation of finances estimated at over INR23bn ($338m) at Religare Finvest Ltd (RFL).

The Singh brothers were the founders of the financial firm, Religare Enterprises Ltd (REL), of which RFL is the lending arm. Shivinder Singh was reported by the local media to have been detained on 10 October, with older sibling Malvinder being arrested thereafter in a late-night swoop. Some other top ex-REL/RFL officials were also detained.

Specific allegations against the Singh brothers and others pertain to their having had absolute control of REL and its subsidiaries and plunging RFL into financial distress by "disbursing loans to companies having no financial standing that were controlled by them" the reports added.

A district court in Delhi, on 11 October, is said to have permitted four-day police custody in the case for the brothers and some other officials; Malvinder Singh has also moved the Delhi High court in the case, seeking that the first information report against him be quashed and



apparently claiming that the EOW does not have jurisdiction to probe the case. Younger brother Shivinder has claimed to be a victim of the fraud. *Scrip* could not

immediately directly reach the accused or their representatives in the case for further comments.

SAD SAGA OF GREED AND AVARICE

The tightening of the noose on the Singh brothers comes amid a long list of charges against them including by the Japanese drug giant Daiichi Sankyo Co. Ltd., which is seeking the enforcement of the INR35bn damages award by an arbitration tribunal in Singapore in 2016. Incriminating details in the arbitration order against the former Ranbaxy top brass led by the Singh brothers had previously put the spotlight on allegations of misrepresentation of critical information concerning the US Department of Justice and US FDA investigations against the Indian company at the time of its 2008 takeover by Daiichi Sankyo. In 2014, Daiichi divested Ranbaxy to Sun Pharmaceutical Industries Ltd..

India's Supreme Court earlier this year urged the brothers to work out a strategy to pay the sum due to the Japanese drug firm. The latest position on the case could not immediately be ascertained, though hearings in the case are believed to have concluded. *(Also see "India's Top Court Tells Singhs To Come Up With Plan To Pay Daiichi, Uphold Nation's 'Honor'" - Scrip, 18 Mar, 2019.)* Last month, the Delhi High Court is reported to have directed 55 garnishee parties, including Radha Soami Satsang Beas (RSSB), guru, and Gurinder Singh Dhillion, who is said to be related to the Singh brothers, to deposit large sums apparently due to RHC Holdings, the flagship firm of the Singh brothers, towards ongoing execution proceedings in the Daiichi arbitration case. Malvinder had claimed that paying the amount owed to Daiichi hinged on recovery of these dues.

Not many in the pharma industry had kind words for the brothers, though. "The Singh brothers' pernicious fall from grace and a business empire so assiduously built by their father the late Parvinder Singh now in ruins is a sad saga of greed and avarice topped by unethical behavior. The story is unfolding inch by inch and yet a mile to go," an industry veteran told *Scrip*.

> "The Singh brothers' pernicious fall from grace and a business empire so assiduously built by their father the late Parvinder Singh now in ruins is a sad saga of greed and avarice topped by unethical behavior." – industry veteran

Ranbaxy, the beacon of the Indian pharma industry, is now a "brand decimated," the official declared.

Others said that with their "integrity in tatters," the news of alleged financial embezzlement and attempts to escape from paying penalties to Daiichi Sankyo were the "final nails" in the coffin for the brothers.

"The arrest and the efforts towards possible conviction seems to have ended speculation that the rich and powerful can get away with murder," an industry expert said, adding that bringing such once-powerful tycoons to justice will do India's global image a "world of good".

MISAPPROPRIATION OF FUNDS

The latest enforcement action against the Singh brothers, who have been at daggers drawn for a while now, is no major surprise. *(Also see "All Downhill: Ranbaxy Singh Brothers Trade Charges, Blows" - Scrip, 7 Dec, 2018.)(Also see "Ranbaxy Family Feud: Transparency And Ethics "Continuously Negated" Says Younger Brother" - Scrip, 5 Sep, 2018.)*

The writing has been on the wall for some time now, some analysts said, adding that it would, however, be interesting to watch if speedy action follows or if the case "drags along indefinitely."

REL and RFL in December filed a complaint with India's Ministry of Corporate Affairs against the Singh brothers as well as REL's former chair and managing director, Sunil Godhwani, among others seeking investigation into various suspicious transactions at REL and its subsidiaries. The complaint followed internal inquiries (including an independent forensic review) by the new RFL board and management. REL was controlled by the Singh brothers until February 2018 and the boards of both REL and RFL were re-constituted after their departure.

These inquiries had flagged possible siphoning and misappropriation of funds of REL and its subsidiaries estimated at INR22.30bn through loans to entities that are "controlled by, connected to or known to" the founders or their associates. These entities then deliberately defaulted on such loans. Illegal issuance and redemption of preference shares to benefit founder group entities, which resulted in "undue gains" of about INR2.90bn to the founders, were also unearthed. The frauds were said to have occurred from 2008-2017.

RFL had also similarly filed a criminal complaint with the Economic Offences Wing of the Delhi Police against the Singh brothers and Godhwani, among others, after inquiries by the new RFL board and management revealed siphoning and misappropriation of funds of RFL estimated at INR7.70bn. The Enforcement Directorate had raided the Singh brothers in August 2019.

In March this year, the Securities and Exchange Board of India directed hospital chain Fortis Healthcare and Fortis Hospitals Ltd (FHsL) to pursue efforts to recover funds allegedly diverted by the brothers and certain entities. The Singh brothers were the founders of Fortis Healthcare, in which Malaysian IHH Healthcare Berhad now owns a controlling holding.

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Early Indian Promise For A Cut-Price CAR-T Therapy

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India may be lagging its Asian peers in the area of cell and gene therapy but pockets of promise have emerged, with a spin-out backed by the Indian Institute of Technology (IIT), Bombay and the US National Cancer Institute hoping to deliver a cut-price CAR-T cell product.

Dr Rahul Purwar, an associate professor in the department of bioscience and bioengineering at the institute in Mumbai and founder of ImmunoACT Pvt. Ltd., underscored that India must develop its indigenous CAR-T cell platform given the promise of the therapy and the rise in the incidence of cancer in the country. Deaths from the disease were estimated at over 700,000 in 2018.

Purwar also highlighted the "geographic disparity" in CAR-T trials, where China and the US have the highest number of clinical studies underway, way ahead of other countries. The number of CAR-T trials globally has swelled from three in 2010 to about 460 in 2019, he noted.

Addressing Informa Markets' recent Biopharma Conclave in Mumbai, Purwar noted that the CAR-T platform is no longer just limited to hematological malignancies and can have an effect on solid tumors and beyond oncology.

He referred to the recent study by researchers at Penn Medicine in the US which suggested that the CAR-T approach may be harnessed to treat heart disease. The pioneering study, published in *Nature* last month, found that the immunotherapy reduced cardiac fibrosis and restored heart function in mice after cardiac injury.

Penn Medicine's Abramson Cancer Center had earlier developed what went on to became Novartis AG's Kymriah (tisagenlecleucel), the world's first approved CAR T-cell therapy.

LOWERING THE COST OF THERAPY

However, Purwar noted that CAR-T therapies at current prices are beyond the reach of most Indian patients. Kymriah and Gilead Sciences Inc.'s Yescarta (axicabtagene ciloleucel) both are reported to have US list prices of $373,000 in diffuse large B-cell lymphoma; for B-cell acute lymphoblastic leukemia, Kymriah costs $475,000. *(Also see "Medicare Add-On Payments For CAR-T Should Reflect 80% Of Actual Costs, CMS Told" - Pink Sheet, 1 Jul, 2019.)*

Purwar, who holds a PhD (molecular medicine) from the Hannover Medical School, Germany, and has been a research fellow at Harvard Medical School in the US, said that his firm is developing an indigenous CAR-T cell therapy which aims to lower costs by over 90% and also a CAR-T cell platform which can used for "other targets/malignancies."

"With this in objective mind, we have collaborated with the Tata Memorial Hospital, All India Institute of Medical Sciences and the US National Cancer Institute is our 'knowledge partner (subject matter expertise)'; ImmunoACT was started for clinical translation," Purwar said at the meeting.

Purwar also shared some interesting cost-related aspects for CAR-T therapies, suggesting that the cost of manufacturing these could lie between $50,000-75,000 per patient. But importantly, the large chunk of these costs goes towards labor for manufacturing/quality control and then the GMP facility; the cost of goods sold is a relatively small component.

"The point I want to convey is that's how India is nicely placed in the area to make things affordable," Purwar said. *(Also see "Gene And Cell Therapies In Asia: Indian Environment Evolving But Multiple Issues Unresolved" - Scrip, 29 Sep, 2019.)*

> CAR–T therapies at current prices are beyond the reach of most Indian patients.

REGULATORY APPROVAL FOR INDIA TRIALS

Speaking to *Scrip* on the sidelines of the conclave, Purwar explained that his firm's first product is a CD-19-targeting therapy for B-ALL (acute lymphoblastic leukemia), for which it has done ex vivo studies and demonstrated efficacy.

"We developed all the QC [quality control] assays and we are now continuing with animal studies and the next step is to seek approval from the Drugs Controller General of India for clinical trials," Purwar said.

He expects to submit the paperwork to the regulator by the end of this year and start clinical trials by mid-2020. "We can manufacture CD19+ CAR-T cells in enough numbers required for clinical dosage," Purwar added in his presentation at the conclave.

On whether data generated in India would be acceptable in other geographies, Purwar emphasized that his firm has followed US FDA guidelines for the clinical work. "Regarding the development process we have done everything as per international standards."

INITIAL FUNDING

Securing funding for such cutting-edge research has, however, not always been easy in India.

Purwar said that initial funding came from the Tata Trust and some of it from the Wadhwani Research Centre for Bioengineering. IIT Bombay, the department of biotechnology and the Council of Scientific and Industrial Research are also among those who provided funding.

Purwar hasn't approached venture capital firms as yet, but maintained that the general response of the industry has been good. "But as you know Indian industry is skeptical about taking such risks since the [ImmunoACT] CAR-T cell therapy hasn't seen the clinic. Once we have it in the clinic and the first patient treated successfully then I think everyone will show interest."

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Drugs With 'Unsupported Price Increases' Add $5bn To US Spending – ICER

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Seven out of nine high cost prescription drugs with significant price increases from the fourth quarter of 2016 through the final quarter of 2018 were not supported by evidence of any additional net clinical benefit, the Institute for Clinical and Economic Review concludes in a report released 8 October.

Furthermore, net prices for the seven drugs "were responsible for increasing total US drug spending by more than $5.1bn from 2017-2018," ICER said, which supports arguments that policymakers should work to restrict such practices. Average net price increases for the period ranged from nearly 10% to 32.5% across the seven products (see chart).

Increases from the fourth quarter 2016 through fourth quarter 2018

DRUG	WAC INCREASE	AVERAGE NET PRICE INCREASE	US SPENDING IMPACT OF NET PRICE INCREASE, 2017 AND 2018
AbbVie's Humira	19.1%	15.9%	$1,865m
Genentech's Rituxan	17.0%	23.6%	$806m
Pfizer's Lyrica	28.3%	22.2%	$688m
Gilead's Truvada	14.3%	23.1%	$550m
Amgen's Neulasta	14.6%	13.4%	$489m
Eli Lilly's Cialis	26.2%	32.5%	$403m
Biogen's Tecfidera	16.7%	9.8%	$313m

The drug whose price increases accounted for the greatest single impact on spending was AbbVie's Humira (adalimumab). The average US price for Humira rose 15.9% over the period, after accounting for rebates and other concessions, "ultimately costing American patients and insurers an estimated $1.86bn more than what would have been spent if Humira's price had not increased," according to ICER.

The report also found that two costly drugs with big increases, Gilead's Genvoya (elvitegravir, cobicistat, emtricitabine, and tenofovir alafenamide) and Celgene's Revlimid (lenalidomide), were supported by new clinical evidence.

However, ICER cautions that the finding does not necessarily mean the evidence could justify a price increase because it has not conducted a full economic analysis of the data. The first annual ICER report on "unsupported price increases" is meant "to provide the public and policymakers an explicit and independent approach to determine whether price increases could potentially be supported by new clinical evidence," ICER chief medical officer David Rind said in a release.

ICER'S LIST OF DRUGS WITH UNJUSTIFIED PRICE INCREASES

"If new evidence emerges that shows a treatment may be more beneficial than what was previously understood, perhaps that new evidence could warrant some level of price increase. For seven of the nine drugs we reviewed, however, we found that the prices increases lacked justification in new evidence," Rind added.

The report does not recommend any particular policy but could help shape legislative efforts in both the House and Senate aimed at curbing increases with price inflation rebates. *(Also see "House Draft Drug Pricing Bill Offers Aggressive Policies But Near-Term Prospects Look Weak" - Pink Sheet, 10 Sep, 2019.)*

PRICING BILLS HAVE NO EVIDENCE REQUIREMENT

Drug pricing bills being shepherded through Congress by Senate Finance Committee Chairman Chuck Grassley, R-IA, and House Speaker Nancy Pelosi, D-CA, would require manufacturer rebates for drugs covered by Medicare if prices rise faster than inflation. However, the legislation does not direct HHS to evaluate whether the increases are supported by new clinical evidence.

In addition, although some states, including California and Vermont, have passed pricing transparency laws requiring manufacturers to justify increases, the ICER initiative is the first aimed at establishing a systematic approach to determine whether increases are justified by new clinical evidence or other factors. In developing the list of drugs to evaluate, ICER identified products with the largest US sales revenue in 2018 and then narrowed the list to those with wholesale acquisition cost increases at rates of more than twice the medical Consumer Price Index across 2017 and 2018.

The list was further narrowed to the top 10 treatments that had estimated net price increases responsible for the biggest boost in US spending over those two years. ICER used data from SSR Health to estimate net prices per unit. SSR Health combines available data on unit sales with data published in manufacturers' earnings reports on US sales. The revenue numbers are net of discounts, rebates, concessions to wholesalers and distributors, and patient assistance programs.

MANUFACTURER FEEDBACK ON PRICES LED TO SOME CHANGES

Two manufacturers disputed ICER's net price calculations with their own data. Amgen challenged estimates for Neulasta (pegfilgrastim) and Enbrel (etanercept) and Biogen argued with figures used for Avonex (interferon-beta 1a). In response, ICER removed Enbrel and Avonex from the final list but retained Neulasta.

Data reviewed for the report came from manufacturer submissions or an ICER systematic review. ICER evaluated

randomized clinical trials, high quality comparative observational studies, and, for low frequency harms, large uncontrolled studies. For drugs with multiple indications, evidence was sought for indications responsible for at least 10% of a drug's utilization.

The report cites several reasons why ICER rejected evidence that might support a price increase. They include the fact that the evidence pertained to an indication that accounts for less than 10% of use or included previously known information about the treatment.

Also considered problematic were studies that used the drug in all comparison arms, studies in which the intervention or outcomes were outside the scope of the report, single-arm studies that did not meet ICER's criteria for assessing efficacy or instances where the data was in the form of an abstract, with limited information on study design.

Manufacturers submitted data to ICER for most of the nine drugs in the final list, with the exception of Pfizer and Eli Lilly, which declined to provide data for Lyrica (pregabalin) and Cialis (tadalafil).

"In the case of Cialis," Lilly told ICER, "the patent has expired, and low-cost generic manufacturers can and do replicate the science. As a result, this invention is highly accessible and at a very low cost."

The Pharmaceutical Research and Manufacturers of America sharply criticized the report in a statement. "This is a flawed report that cherry picks a few medicines in an effort to advance the false narrative that spending on medicines is increasing, which is not consistent with current data," PhRMA argued.

"By focusing on a small set of medicines that do not yet have generic equivalents, the report ignores the fact that medicines are the only part of our health care system with built in cost containment due to future competition from generics and biosimilars."

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Gilead's O'Day Regime Has New R&D Structure

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Along with the hiring of former Genentech Inc. exec Merdad Parsey as chief medical officer, Gilead Sciences Inc. has reorganized its research and development organization to report directly to CEO Daniel O'Day.

O'Day has held the lead position at Gilead since March, after serving as CEO for pharmaceuticals at Genentech parent company Roche. *(Also see "Gilead To Let Kite Fly Free; O'Day Says It Will Become Separate Business Unit" - Scrip, 2 May, 2019.)* O'Day's hiring was said to help Gilead along as it shifts attention toward oncology – a specialty that Parsey also brings to the table.

But Gilead is going through a rough transition period, adjusting to the loss of longstanding leadership like John Martin and John Milligan, who had been in place since the mid-90s. R&D chief Norbert Bischofberger, the architect of Gilead's infectious disease success, left in 2018 after 30 years. *(Also see "Gilead's R&D Leadership Change Is End Of Bischofberger Era" - Scrip, 12 Mar, 2018.)*

Throughout this, the company has been under pressure as its mega-blockbuster hepatitis C business slowed down, its core HIV business matures and its first foray into oncology – the CAR-T therapy Yescarta gained through its 2017 acquisition of Kite Therapeutics – gets off to a slow start. *(Also see "Gilead To Let Kite Fly Free; O'Day Says It Will Become Separate Business Unit" - Scrip, 2 May, 2019.)*

Continuous personnel changes left the company reeling; John McHutchison and Andrew Cheng were promoted to fill in for Bischofberger, but both have left Gilead. Oncology director Alessandro Riva, hired from Novartis in 2017, was lured away by India-based Glenmark after only two years at Gilead. *(Also see "Glenmark's Coup: Gilead's Riva Now CEO Of Spin-Out Innovation Firm" - Scrip, 6 Mar, 2019.)*

Parsey, who had been SVP in charge of early clinical development for Genentech's Research and Early Development group (gRED), will head up Gilead's global clinical development. The company said that current research EVP William Lee will remain with Gilead, but will no longer report to a chief scientific officer. Instead, both Lee and Parsey will each report directly to O'Day.

When O'Day came to Gilead in early 2019, Morningstar analyst Karen Andersen suggested that after months of unsteadiness, Gilead could find stability with O'Day, who had previously been with Roche for three decades. *(Also see "Gilead Lures Roche Pharma CEO O'Day As CEO; Genentech's CEO Will Replace Him " - Scrip, 10 Dec, 2018.)*

Andersen also expressed concern at the time that Gilead could "lack the scientific expertise needed to guide accretive mergers or acquisitions," something Parsey's appointment could help with. Gilead told *Scrip* that having the

Gilead's Pipeline

	PHASE I	PHASE II	PHASE III
HIV/AIDS	GS-6207 (Capsid Inhibitor)	GS-9131 (NRTI)	Emtricitabine and tenofovir alafenamide (for PrEP)
	Vesatolimod (TLR-7 agonist)		
	GS-9722 (bNab)		
Liver Diseases	GS-4224 (PD-L1) for Hep B	Cilofexor (FXR agonist) for NASH	Cilofexor (FXR agonist) for Primary Sclerosing Cholangitis
		Cilofexor (FXR agonist) for Primary Biliary Cirrhosis	
		Firsocostat (ACC Inhibitor) for NASH	
		GS-9688 (TLR-8 agonist) for Hep B	
Hematology/Oncology	Axicabtagene ciloeucel Trial: ZUMA-11 for DLBCL (41BB)	Axicabtagene ciloleucel Trial: ZUMA-5 for Indolent NHL	Axicabtagene ciloleucel Trial: ZUMA-7 for 2nd line DLBCL
	KTE-X19 Trial: ZUMA-8 for CLL	Axicabtagene ciloleucel Trial: ZUMA-6 for DLBCL (PD-L1 mAb)	
	KITE-718 (MAGE A3/A6) for Solid Tumor	Axicabtagene ciloeucel Trial: ZUMA-12 for 1st line DLBCL	
	KITE-439 (HPV E7) for Solid Tumor	KTE-X19 Trial: ZUMA-2 for MCL	
	GS-1423 (Bi-specific antibody) Solid Tumor	KTE-X19 Trial: ZUMA-3 for Adult ALL	
		KTE-X19 Trial: ZUMA-4 for Pediatric ALL	
Inflammatory/Respiratory	GS-4875 (TPL2 Inhibitor) for Inflammatory Bowel Disease	Filgotinib (JAK1 inhibitor) inflammatory diseases	Filgotinib (JAK1 inhibitor) for rheumatoid arthritis
		GS-9876 (Syk inhibitor) for Sjogren's Syndrome	Filgotinib (JAK1 inhibitor) for ulcerative colitis
		GS-9876 (Syk inhibitor) for Lupus	Filgotinib (JAK1 inhibitor) for Crohn's disease
		Selonsertib (ASK-1 inhibitor) for DKD	

research arm report directly to O'Day would provide "a degree of autonomy in following the science."

CHALLENGES AHEAD FOR NEW R&D ORG

The new organization takes over a relatively young pipeline, and must get past some challenges seen in the past year.

As the HCV market slows, Gilead has turned its attention to other liver diseases. There were setbacks earlier this year when non-alcoholic steatohepatitis (NASH) drug selonsertib, an ASK1 inhibitor, failed in two trials. *(Also see "Another NASH Failure: Gilead's Hits Keep Coming" - Scrip, 25 Apr, 2019.)* The company hasn't given up, however, with the ACC inhibitor firsocostat and FXR agonist cilofexor both in Phase II trials in NASH, with the latter also being studied for primary biliary cirrhosis and primary sclerosing cholangitis. Gilead is also studying a TLR8 agonist, GS-9688, in Phase II and a PD-1 inhibitor, GS-4224, in Phase I for HBV.

Gilead's HIV pipeline includes three Phase I drugs: the capsid inhibitor GS-6207, TLR-7 agonist vesatolimod and a broadly neutralizing antibody to HIV, GS-9722. Currently in Phase II is GS-9131, a nucleoside reverse transcriptase inhibitor (NRTI). Gilead has a combination of two NRTIs, tenofovir alafenamide (TAF) and emtricitabine, currently under US Food & Drug Administration review for PrEP, although efficacy concerns dog the new formulation.

With five cancer drugs in Phase I and six in Phase II, Gilead is well on its way to establishing itself in oncology. Studies include cell therapy, immuno-oncology and targeted therapies to treat non-Hodgkin lymphoma and acute lymphoblastic leukemia in adults and children. (*See chart above.*)

Gilead is also looking into treatments for inflammatory, respiratory and autoimmune disorders with a total of eight programs. The syk inhibitor GS-9876 is in Phase I to treat irritable bowel disease, and in Phase II for lupus and Sjogren's syndrome. The failed NASH drug selonsertib is also in Phase II, for diabetic kidney disease. Gilead's most advanced inflammatory asset is the JAK1 inhibitor filgotinib, being developed for several diseases, but partner Galapagos has already filed for European approval in rheumatoid arthritis.

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UCB To Buy Ra for $2.1bn And Plays Down Antitrust Fears

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UCB Group looks to have done a very smart bit of business by agreeing to buy Ra Pharmaceuticals Inc. for $2.1bn and get access to the potential blockbuster zilucoplan for the neuromuscular condition myasthenia gravis (MG) and other rare diseases.

The Belgian drugmaker is paying $48 a share in cash for Cambridge, MA-based Ra, which represents a 111% premium to the latter's stock price on 9 October. The jewel in Ra's crown is zilucoplan, a once-daily self-administered, subcutaneous peptide inhibitor of C5, which is in Phase III for the treatment of generalized MG with top-line results expected in early 2021.

UCB already has an MG drug in Phase III development, the FcRN inhibitor rozanolixizumab, but the company sees the two products as complementary. Analysts at Deutsche Bank agreed, pointing to physician feedback in an investor note on 10 October which suggested "multiple treatment options are required for management of patients and the drugs are likely to be complementary given different mechanisms of action and potential for use in both acute and chronic treatment."

If all goes well in the Phase III trials for zilucoplan, it would go up against another C5 inhibitor and one of the highest-priced drugs in the world, Alexion Pharmaceuticals Inc.'s Soliris (eculizumab). In late 2017, the latter became the only therapy approved in the US specifically to treat MG, which affects almost 200,000 patients in the US, Europe and Japan; patients experience a variety of symptoms, including drooping eyelids and double vision as well as severe muscular weakness.

The Deutsche Bank team noted that zilucoplan's mechanism has been de-risked by the approval of Soliris, and they claimed that use of the Alexion drug in the MG indication is "limited by its very high price and intravenous administration." In December 2018, following the announcement of positive Phase II data on zilucoplan, BMO Capital Markets analyst Matthew Luchini predicted pricing at about $225,000 a year for Ra's drug, significantly lower than Soliris's annual cost of roughly $500,000.

There are a number of other players eyeing MG, including Alexion itself. The Soliris follow-on Ultomiris (ravulizumab) is in Phase III for that indication, as is argenx SE's modified antibody fragment efgartigimod.

Zilucoplan is "a pipeline in a product"

UCB also stressed that aside from MG, zilucoplan is "a pipeline in a product." The drug is set to go into Phase II trials for immune-mediated necrotizing myopathy and analysts at Jefferies issued a note saying that the data "could potentially serve as a basis for potential accelerated regulatory filing given lack of approved therapies."

Zilucoplan is also being studied for amyotrophic lateral sclerosis "and other tissue-based complement-mediated disorders with high unmet medical need," UCB noted. Ra has also been developing an extended release formulation of zilucoplan, as well as a potential first-in-class oral small molecule C5 inhibitor.

CEO Jean-Christophe Tellier said Ra was "an excellent strategic fit addressing multiple areas of UCB's patient value growth strategy." He added that the acquisition "will add to our strong internal growth opportunities – six potential product launches in the next five years, strengthening our neurology and immunology franchises with late and early-state pipeline projects."

He also stressed that UCB was getting hold of Ra's "highly productive" Extreme-Diversity platform which enables the production of synthetic macrocyclic peptides "combining the diversity and specificity of antibodies with the pharmacological properties of small molecules." UCB will maintain Ra's operations in Boston as an innovation hub.

FEW FEARS ABOUT FTC

The transaction is expected to close by the end of the first quarter of 2020 but there are concerns that timeline may be optimistic. There has recently been increased antitrust scrutiny in the US on a number of M&A deals involving overlapping therapeutic areas, notably Celgene Corp. being forced to sell its psoriasis drug Otezla (apremilast) to Amgen Inc. for $13.4bn to win US Federal Trade Commission approval for its merger with Bristol-Myers Squibb Co.. *(Also see "Amgen's $13.4bn Otezla Buy Helps Bristol/Celgene Merger Close By Year-End" - Scrip, 26 Aug, 2019.)*

The repeated delays to Roche's proposed acquisition of Spark Therapeutics Inc. could also be pertinent. The deadline for the tendering of shares in that planned $4.8bn deal has recently been moved to 30 October to allow additional time for review of the transaction, unveiled back in February, by both the FTC and the UK Competition and Markets Authority. *(Also see "Deal Watch: Another Delay For Roche/Spark, While FTC Ups AbbVie/Allergan Merger Scrutiny" - Scrip, 3 Oct, 2019.)*

UCB believes that despite zilucoplan and rozanolixizumab both being in development for MG, their different mechanisms of action should mean they do not cause the FTC and other regulators any concerns. Tellier said on a conference call that "despite the environment," the firm was confident it could answer any questions and obtain all the required antitrust approvals before the end of Q1 next year.

While acknowledging antitrust concerns, analysts have backed UCB's move with Deutsche Bank saying that the acquisition "is attractive for shareholders, adding a Phase III asset with

strong proof-of-concept that could launch in 2022, leveraging UCB's existing sales and marketing organisation and planned investments behind rozanolixizumab."

The broker added that "most importantly, the deal should help secure and further accelerate the company's potential return to growth following its current investment phase, offsetting impact from expected pressure on its legacy business." UCB's epilepsy drug Vimpat (lacosamide) goes off-patent in 2023, while its immunology big-seller Cimzia (certolizumab pegol) will start losing protection in the new few years.

Deutsche Bank concluded by saying that "in order to justify the deal, we believe zilucoplan would need to deliver peak sales of $500m-$600m. This seems realistic to us."

Analysts at Credit Suisse issued a note saying the acquisition is "strategically sound given the existing focus at UCB on MG with rozanolixizumab." They added that the deal "will supplement what is already a rich late-stage pipeline" which along with the MG drugs includes the IL-17A and IL-17F inhibitor bimekizumab for psoriasis, axial spondyloarthritis and psoriatic arthritis and the epilepsy drug padsevonil.

Credit Suisse said that getting hold of the US firm's discovery platform is an important addition to the value of the transaction. It concluded by claiming that given the significant premium offered by UCB, "we do not expect any additional bidders for Ra to emerge." If Ra backs out, it will pay a termination fee of $75m.

UCB is the third European mid-sized pharma company to seek out US companies for acquisitions in less than a month. September saw Swedish Orphan Biovitrum AB agree to buy Dova Pharmaceuticals Inc. in a deal valued at $915m and Denmark's Lundbeck Inc. ink a $1.95bn deal to acquire migraine drug developer Alder BioPharmaceuticals Inc. *(Also see "Sobi Targets Thrombocytopenia In $915m Swoop For Dova " - Scrip, 30 Sep, 2019.) (Also see "Lundbeck CEO: Alder Buy Will Boost Pipeline" - Scrip, 16 Sep, 2019.)*

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Label Battles: Beovu And Eylea Contest Begins In AMD

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Regeneron Pharmaceuticals Inc.'s share price slid 8 October after rival Novartis AG won approval from the US Food and Drug Administration (FDA) for its injectable Beovu (brolucizumab) for treating wet age-related macular degeneration, amid views the VEGF inhibitor's attractive profile could undermine sales of Eylea (aflibercept). But some analysts said the sell-off had been overdone.

Investors were reacting to Novartis's news on 8 October that it won approval for its new injectable Beovu for use to treat wet age-related macular degeneration (AMD), a condition which can eventually lead to blindness and affects around 20 million people worldwide.

Novartis used a priority review voucher in its submission, which was mainly based on two head-to-head Phase III trials – HAWK and HARRIER – in which Beovu showed non-inferiority to Eylea when dosed every 12 weeks, versus bi-monthly dosing for Eylea.

"Beovu is the first FDA-approved anti-VEGF to offer both greater fluid resolution versus aflibercept and the ability to maintain eligible wet AMD patients on a three-month dosing interval immediately after a three-month loading phase, with uncompromised efficacy," Novartis said when announcing the FDA's decision.

Novartis's CEO Vas Narasimhan has described the VEGF antibody therapy as one of the biggest potential growth drivers in the Swiss company's pipeline. Its approval will allow Novartis – a leading player in the European ophthalmology market, where it holds marketing rights for VEGF-A targeting Lucentis (ranibizumab) – to gain a significant foothold in the US market.

The launch of Beovu could, some analysts say, have significant implications for Regeneron and Roche, which market the AMD therapies Eylea and Lucentis, respectively, in the US. Novartis, which owns Lucentis, sells it outside the US, while Roche markets the drug in the US.

A report by OptumRx Inc. released in September said analysts and physicians believe Beovu will reach annual sales over $1bn globally by 2021 and become the most profitable AMD drug by 2026.

But Regeneron has been pushing back: since completion of the HAWK and HARRIER trials it has made progress at dampening Beovu's potential dosing advantage. FDA approved a supplemental BLA for Eylea in August for dosing every 12 weeks after the first year of treatment. And the Beovu label indicates a higher rate of intraocular inflammation compared with Eylea, giving Regeneron a way to argue its corner on safety, some observers said.

Baird Equity Research said the battle between Beovu and Eylea will focus on their respective labels, and Beovu's does not present a knock-out proposition.

"We think the [Beovu] label provides little reason to see a substantial switch away [from Eylea] as efficacy and dosing look similar, and safety looks marginally worse," Baird said on 8 October in a note.

"We think investors are currently overestimating the impact of Beovu on Eylea and believe the absence of a significantly differentiated label should help [Regeneron] shares rebound," Baird concluded.

Analysts at SVBLeerink agreed. In a same day reaction note to investors SVBLeerink said the Beovu label "provides no clear advice to physicians on treatment duration selection."

"Importantly, which was not specifically disclosed in the previous Phase III trial readouts, Beovu's label shows higher safety liabilities than Eylea, with an intraocular inflammation rate four times as high as the control arm (4% vs. 1%).

"This is likely to be the main defense used by Regeneron to retain market share for Eylea in AMD." Datamonitor Healthcare analyst Tara Hansen said that "for the patients who benefit from Beovu and are able to maintain that 12-week dosing schedule, it is definitely an attractive alternative to Eylea. However, I think the issue will be identifying those patients.

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Lilly Expands Migraine Franchise With Reyvow Approval

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Eli Lilly & Co. has its second US approval in migraine in a little over one year, as the US Food and Drug Administration okayed Reyvow (lasmiditan) for the acute treatment of migraine on 11 October.

The approval is the second part of a franchise build-out for Lilly in migraine, which saw preventive drug Emgality (galcanezumab) approved in September 2018.

The Indianapolis pharma told *Scrip* that that it will price Reyvow closer to launch and offer patient assistance programs. Lilly plans on a "value-based price" that will encourage access to a novel treatment option for migraine, the company added.

Lilly originally discovered lasmiditan, a selective agonist of the 5HT1F receptor in the trigeminal nerve pathway, but out-licensed the molecule to CoLucid Pharmaceuticals Inc. in 2005. It then got the candidate back in January 2017 when it bought out CoLucid for $960m. *(Also see "Lilly Pays Nearly $1bn To Regain Migraine Candidate It Once Sold For $1m" - Scrip, 18 Jan, 2017.)* The oral therapy already had succeeded in the Phase III SAMURAI trial in acute migraine when Lilly brought it back in-house.

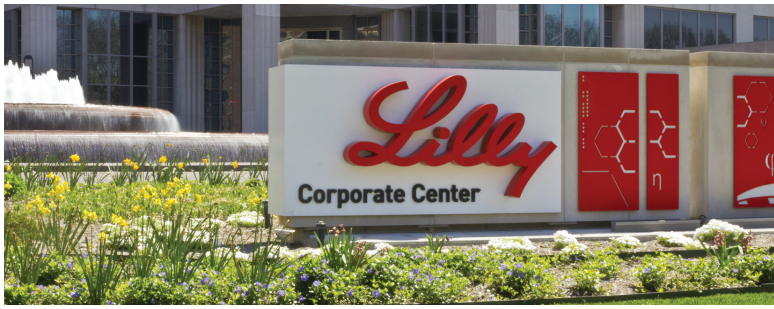
Chief scientific officer Daniel Skovronsky spoke of Emgality and lasmiditan as a franchise strategy for migraine during the Barclay's Global Healthcare Conference in March, noting that Emgality is being studied for a supplemental indication in cluster headache.

Former Lilly Bio-Medicines president Christi Shaw said during the pharma's earnings call on 6 February that Emgality and Reyvow would complement each other in several ways, including the latter offering a therapeutic option for patients who have trouble tolerating drugs from the CGRP class. Shaw left Lilly in July to become the new CEO of Kite Pharma Inc., the oncology cell therapy subsidiary of Gilead Sciences Inc.*(Also see "Shaw Leaves Lilly To Helm Gilead's Kite" - Scrip, 11 Jul, 2019.)*

"If you look at the marketplace … with the 36m patients who suffer from migraine, there's about 16m of those that are diagnosed and 6m that suffer from acute migraines and are taking therapy. And that is overlapping only somewhat with the prevention market," she noted.

"So, as you look at prevention, CGRPs versus acute use, there's obviously a huge need for both distinctly," Shaw continued. "And CGRPs also obviously don't clear 100% of all patients of their migraines, so … the use obviously may overlap there. And we think lasmiditan has a really great positioning versus the oral CGRPs. If you're taking a preventive CGRP, you may want to look at a different mechanism if you have to add to that. And then if we look at the acute marketplace, so many patients have fallen out of the market because of lack of efficacy or they can't tolerate the safety, so lasmiditan will be a great option for them."

In its statement on the approval, Lilly noted that up to 40% of migraine sufferers do not get adequate relief from their initial acute therapy. Lilly will likely soon face direct competition from oral anti-CGRP drugs for acute migraine treatment, however, as Allergan PLC has ubrogepant under review at the FDA, while Biohaven Pharmaceutical Holding Co. Ltd. has rimegepant also under FDA review. *(Also see "Biohaven's Oral Rimegepant Poised To Alter Migraine Market" - Scrip, 11 Jul, 2019.)* Beyond ubrogepant, Allergan has a second oral CGRP drug, atogepant, in Phase III for the prevention of migraine headaches.



Allergan's blockbuster neuromodulator Botox (onabotulinumtoxinA) also is approved as a preventive doctor-injected therapy for chronic migraine, or patients with 15 or more headaches per months. Emgality and the two other anti-CGRP biologics approved for migraine prevention are cleared for patients with chronic as well as episodic migraine, or 14 headaches or less per month. Botox, most commonly known for its wrinkle-reducing indications, was the main attraction for AbbVie Inc., which is acquiring Allergan for $63bn. *(Also see "AbbVie Pounces On Chance To Buy Revenues In $63bn Mega-Deal For Allergan" - Scrip, 25 Jun, 2019.)*

Lilly's new drug Reyvow is indicated for short-term acute (on-demand) treatment of migraine with or without aura. It is not indicated to prevent migraine. The label warns of a risk of driving impairment and advises patients not to drive or operate machinery for at least eight hours after taking the medication. The drug can cause central nerve system depression, which can lead to dizziness and sedation – the most common side effects reported in clinical trials were dizziness, fatigue, paresthesia and sedation. The label also warns against taking Reyvow with alcohol or anything that depresses the CNS.

Patients can be prescribed an oral dose of 50mg, 100mg or 200mg, according to the label.

Approval was based on a pair of Phase III randomized, placebo-controlled studies in 3,177 adult patients with a history of migraine. Treatment with Reyvow resulted in statistically significant improvement, including pain resolution and resolution of the most bothersome symptom within two hours, compared to placebo.

On 30 July, Lilly reported that Emgality yielded $34.3m in sales during the second quarter, bringing its 2019 total sales to $48.5m.

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Finalists 2019

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Best Contract Research Organization – Full-Service Providers

The Scrip Awards for Best Contract Research Organization acknowledge the critical role that CROs play in drug development. This Award is for those companies which provide the full range of services to their clients.

CMIC
CMIC was the first clinical CRO in Japan and is now involved in nearly 80% of new drug development and filings in the country. Over the last 25 years, CMIC has developed its unique "Pharmaceutical Value Creator" business model and now offers services that encompass the entire pharma value-chain. CMIC has bases in 10 countries, including the US, South Korea, China and Singapore.

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Covance supports clinical trial activity in about 100 countries through its industry-leading central laboratory and preclinical and clinical development businesses, generating more safety and efficacy data than any other company to support approvals. Covance collaborated on 93% of the novel drugs approved by the US FDA in 2018, including 94% of the rare and orphan disease drugs and 94% of the oncology drugs.

ICON
ICON contributed to the development of 21 new drugs in 2018/19 and its clinical study execution capabilities have led to the approval of 18 of the world's top 20 best-selling drugs. ICON has exceeded sponsor expectations and beaten industry medians through strong collaboration and detailed planning during start-up, careful site selection and monitoring progress of enrolment and in-depth global regulatory expertise.

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IQVIA is a global provider of advanced analytics, technology solutions, and contract research services to the life sciences industry with operations in more than 100 countries. Since introducing its CORE-powered clinical development model, IQVIA has won around $3.7bn in study contracts. In several studies, it has seen significant improvements in patient recruitment, including enrolment rates that were 13-30% faster.

PPD
PPD demonstrated industry leadership by building on the breadth and depth of its client solutions in the 12 months. It expanded in China, deployed unique site and patient access services, increased its laboratory services and capacity, innovated in data analytics and technology, and entered into partnerships with other industry leaders. PPD was involved in 66 drugs approved in the US, Europe and China in the 12 months.

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Best Contract Research Organization – Specialist Providers

The Scrip Awards for Best Contract Research Organization acknowledge the critical role that CROs play in drug development. This Award is for those companies which provide specialist services to their clients.

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Cardinal Health Regulatory Sciences (CHRS) is a regulatory consultancy that provides a full range of services, from regulatory strategy and development support, to operational functions such as submissions and publishing. Over 40 years, CHRS has supported more than 500 product approvals worldwide, and is currently working on projects in more than 180 countries across the globe.

METRION BIOSCIENCES
Granta Park, Cambridge-based Metrion Biosciences is an ion-channel focused drug discovery CRO delivering expertise in a wide range of preclinical ion channel drug discovery services. It has a track record of delivering quality data in a timely and cost-effective manner, through its various long-standing partnerships and collaborations, and has achieved a significant increase in fee-for-service sales year on year since its inception.

MMS HOLDINGS
This data-focused CRO takes a scientific approach to complex trial data and regulatory submission challenges and maintains a 97% customer satisfaction rating. In the past year, MMS has co-founded the Health Analytics Collective with MIT, Julia Computing, and the Center for Translational Medicine at the University of Maryland Baltimore to use real-world evidence to shorten the approval process.

PHARPOINT RESEARCH
PharPoint Research offers clinical operations, data management, and biostatistics services. With a 92% client repeat rate, its data management team works to get data prepared and locked as it comes in, shortening the time from LPLV to database lock. PharPoint's biostatistics programs are custom developed, independently verified, and designed to be portable for transfer and use by sponsors.

QUANTICATE
Quanticate is one of the world's largest CROs focused on the collection, analysis and reporting of clinical study data which has allowed it to develop a high level of expertise for biometrics. Its 'Coded to Care' program adds value through quality, timeliness and innovation, with 100% on-time delivery and no re-work seen across its partnerships.

RXGEN
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Pharma Will Embrace Basket And Umbrella Trials, Despite Challenges

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Clinical trial design has undergone a rapid transformation in the last five or so years, especially in oncology, and that evolution is set to continue.

That was the conclusion from a panel of biopharma and cancer charity-funded research leaders last week – with so-called "basket" and "umbrella" studies seen as part of this future.

As oncology research grows ever more precise in targeting mutation-based subgroups, and biopharma explores an almost infinite number of drug combinations in cancer, the need to find a new streamlined clinical trial model is urgent.

This led the US Food and Drug Administration's Janet Woodcock to declare clinical trials "broken" two years ago, and now industry leaders are coming round to the idea – while highlighting the major logistical challenges.

Speaking at the Endpoints UKBIO19 meeting in London on 8 October, Christian Itin, CEO of cell therapy biotech Autolus Ltd, said it was obvious that a new approach was needed.

While the use of Phase II and even single arm studies are now regularly being accepted by regulators as registration trials, he said the existing paradigm was holding back progress.

"We have to make sure that we can learn fast. One of the frustrating things in conventional trial design is that we're moving in a sequential fashion," he said.

"Fields like oncology are really remarkable in terms of the explosion of approaches and products that are being tested. You realize there's no way we can get the answers if we cannot do this [study drugs] in a parallel way."

He added that the onward march of precision medicine was producing more mutation and biomarker targeting drugs and fragmenting the population. This creates major new challenges in identification and recruitment of these patients to trials.

One of the biggest clinical trial milestones of recent times was last year's approval of Bayer AG/Loxo Oncology Inc.'s Vitrakvi (larotrectinib), a groundbreaking drug on two fronts.

Firstly, it was the first drug to gain its first approval as a treatment treat for tumors regardless of where they are in the body (Merck & Co. Inc.'s Keytruda gaining a similar indication as a supplementary approval). *(Also see "FDA Nod For Loxo/Bayer Tissue Agnostic Drug Marks Paradigm Shift In Cancer " - Scrip, 27 Nov, 2018.)*

The drug can treat adult or pediatric patients with any solid tumors that have a neurotrophic receptor tyrosine kinase (NTRK) gene fusion.

Secondly, and more frequently overlooked, it was the first drug to gain FDA approval via a series of so-called basket studies. These are part of a novel group of study designs known as master protocol trials, along with umbrella and platform trials.

Basket trials differ to conventional clinical trials in that they generally evaluate one therapy against many diseases, while an umbrella trial tests many therapies on one disease.

Finally, a platform study is similar to an umbrella trial, as it focuses on multiple drugs on a single disease, but uses a decision algorithm to let therapies enter and exit the trial.

REGULATORS OPEN TO NEW APPROACHES

Also on the panel was MorphoSys AG chief development officer Malte Peters. He lauded the FDA's open-minded approach to accepting his company's single arm trial of its lymphoma candidate tafasitamab as a registration trial when it unexpectedly produced compelling efficacy data earlier this year.

He agreed with the logic of basket and umbrella studies, but said the "logistical challenge" of setting these trials up shouldn't be underestimated.

"For everybody, these studies are more difficult to conduct. Logistically, to find, let's say, 1-2% of patients who have a gene mutation and tumour X, is not easy," he said.

"So you have to find a system that allows for finding patients, including going beyond the big university hospitals. Because we need small hospitals, and maybe GPs [primary care doctors] to have access to screening and sequencing technology to allow these patients to be discovered and diagnosed correctly."

He said achieving this was difficult for one company, but even more complex if two-three drug companies were to collaborate, as regulators are urging.

"So, logistically, this is not easy. But recent experience shows you can overcome these hurdles. And I think we're seeing great progress, and we're going to see more of this in the future."

Oncologist and lymphoma expert Peter Johnson of Southampton University and Cancer Research UK was also present. He said many of CRUK's trials were now using the umbrella design, looking at single drugs across multiple tumor types, such as multiple cell lung cancer, pancreatic cancer and bladder cancer.

"I think this is the most efficient way of increasing capacity, this evolution," he said. "Because the massive resource you have to burn to establish the proper molecular characterization is probably beyond the scope of one individual player, given the return on investment in terms of the very small proportion of patients to treat."

The FDA is pushing ahead with efforts to encourage greater uptake of these and other novel trial designs and methodologies,with the European Medicines Agency advancing similar plans. *(Also see "EU Addresses Complex Clinical Trial Designs In New Guideline" - Pink Sheet, 11 Mar, 2019.)*

It launched the Complex Innovative Trial Designs (CID) Pilot Meeting Program in 2018, with a novel trial in pain medication from Eli Lilly & Co. being accepted on to the pilot in September.

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Audentes' Gene Therapy Allows Ventilator Independence For Rare Disease

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New data on Audentes Therapeutics Inc.'s lead gene therapy, AT132, in patients with X-linked myotubular myopathy have de-risked the product's development program, say analysts, and the San Francisco, CA-based biotech is planning on filing a US BLA in mid-2020 and a EU marketing application in the second half of 2020.

AT132 comprises an AAV8 vector containing a functional copy of the *MTM1* gene; the AAV8 vector is thought to target skeletal muscle after intravenous administration, where the enclosed gene increases expression of the enzyme myotubularin in patients with MTM1 mutations. The preclinical development of AT132 was conducted in collaboration with France's non-profit research organization, Genethon, and US academic researchers.

Up to the 7 August 2019 cut-off date, all six patients treated with AT132 in cohort 1 (1 x 10^{14} viral genomes/kg) and the first patient treated with AT132 in cohort 2 (3 x 10^{14} vg/kg) achieved ventilator independence, and all seven treated patients were able to rise to a standing position, or walk, Dr James Dowling of the Hospital for Sick Children, Toronto, reported at the recent annual congress of the World Muscle Society, held in Copenhagen, Denmark.

APPROVED GENE THERAPIES WORLDWIDE

These regulatory victories helped swell the number of gene therapy candidates in the pipeline to the point where there are now around 1,000. Gene therapy has remounted the podium as the third largest category in the overall pipeline, according to the drug database Pharmaprojects, lagging only two cancer groupings.

There was one new serious adverse event since data were last presented in May 2019, in a cohort 2 patient who developed joint swelling which resolved without treatment, but otherwise AT132 was well tolerated, the researcher reported. Up to the cut-off date, 12 patients were enrolled in the ASPIRO study, and a further two patients have since entered the study.

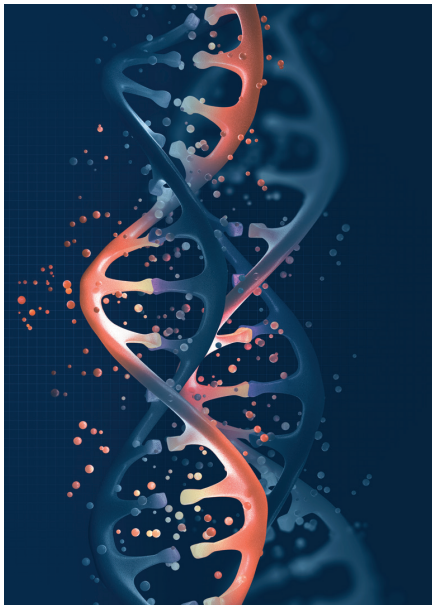
The company noted that ventilator dependence was considered to be closely correlated with morbidity and mortality in XLMTM patients, and it intended to complete enrolment and follow-up of patients at the 3 x 10^{14}vg/kg dose.

STRONG INFRASTRUCTURE

"We find the updates on ventilator dependence and motor milestones to de-risk the upcoming expansion cohort study that will confirm the safety and efficacy of AT132 and support regulatory fillings worldwide," commented SVBLeerink analysts. "The company's strong infrastructure in manufacturing is ready to support commercial roll-out of AT132, if approved," they added.

Analysts at BMO Capital Markets noted that the therapy was promising: "We believe AT132 continues to look better with time as more patients achieve ventilator independence (seven patients versus four reported at the American Society of Gene and Cell Therapy in May) and motor milestones."

In a talk at the Morgan Stanley Healthcare Conference last month, Audentes president and COO Natalie Holles reported that the decision Audentes made early on to invest in bringing GMP manufacturing in-house had "turned out to be a tremendous strategic advantage for us as a company allowing us to move really quickly through both preclinical and clinical development."



"We recently added a plasmid manufacturing suite to our manufacturing operations as well," she noted. "We were finding that plasmid was a costly and time ineffective part of our manufacturing process that we wanted to control internally, that's allowed us to accelerate even further." Audentes believes it has sufficient capacity to supply the global market for MTM.

"To my knowledge, none of our competitors in the space have the breadth, the experience or the productivity that we do in manufacturing," commented Holles.

AT132 has regenerative medicine and advanced therapy (RMAT), rare pediatric disease, fast-track and orphan drug designations from the US FDA, and priority medicine (PRIME) and orphan drug designations by the EU's European Medicines Agency.

Audentes is developing a series of gene therapy products: a US IND for AT845, a gene replacement therapy for the lysosomal enzyme, GAA, in the treatment of Pompe disease, was expected to be submitted in the third quarter.

AT702, an AAV-antisense product, that induces exon-2 skipping to treat Duchenne muscular dystrophy and is manufactured by the Nationwide Children's Hospital, is expected to start patient dosing in the 2019 fourth quarter. Audentes-manufactured AT702 is expected to be the subject of an IND in the first quarter of 2020.

Around half of all boys with X-linked myotubular myopathy die within the first 18 months of life from extreme muscle weakness and respiratory failure, caused by *MTM1* gene mutations that produce dysfunctional myotubularin; in survivors, around a quarter of boys die by age 10. The incidence of the condition is estimated to be around one in 40,000 to one in 50,000 newborn males.

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'Buy China' In Procurement Schemes – Should You Worry?

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As the People's Republic of China celebrates the 70th birthday of its foundation and President Xi Jinping vows to strengthen communist rule, many are worrying that any increased dominance of state-owned enterprises (SOEs) will put international companies at a disadvantage, just at the time the government is expanding centralized procurement schemes to more health products.

The SOE has a long history in China and although many SOEs have now transformed into holding companies, many still enjoy a controlling market share in certain industry sectors such as financial services, civil engineering and education.

Despite a relatively lower presence for SOEs in the pharma and medical device areas, roughly 70% of respondents to a recent survey conducted by the EU Chamber of Commerce in China (EUCCC) said SOEs were present in the health product sector. 18% of pharma respondents saw SOEs controlling at least 50% of the market.

In effect, the dominant role of SOEs has been at the core of trade barrier arguments made by the US Trade Representative under its annual Special 301 investigation, which cited the influence of SOEs 124 times in its March 2018 report. Many Chinese SOEs and government-backed investment companies were also named and subject to more scrutiny under the Committee on Foreign Investment in the United States review.

"While winning a public procurement bid in China when competing against an SOE can be an incredibly difficult proposition for any company, the legal distinction drawn between foreign and domestic companies puts foreign enterprises at a further disadvantage," warned the EUCCC's new Business Climate Report, released on 24 September in Beijing.

'BUY CHINA' FAVORING LOCAL FIRMS?

There are already signs of a trend of hospitals being encouraged to buy products from domestic companies in the medical devices sector, which may potentially spread to the pharma industry.

During the latest expanded round of the "4+7" drug procurement scheme covering major cities, the bidding results announced on 25 September showed a move towards even lower prices than in the previous round. One of the bid-winning drug products, risperidone from Qilu Pharmaceutical Co. Ltd., was priced at just CNY0.05 ($0.007) per tablet, while an amlodipine product from Sinopharma Rongsheng was CNY0.06.

The extremely low prices not only forced international drug makers to aggressively slash their pricing to compete but also pushed other domestic firms to further reduce their already low prices.

Tellingly, Qilu was formerly a state-owned enterprise until it transformed into a stock-holding company, and Rongsheng is a subsidiary of Sinopharm Group Co. Ltd., a huge state-owned and publicly listed group.

Interestingly, Qilu also bagged the second-highest total number of winning bids among all 4+7 participants, scoring for seven out of 25 products.

Despite these statistics however, the government is explicitly promoting fair competition. A 2017 State Council document (No.5) stated that products manufactured by foreign companies in China "will be treated equally in public procurement bids." Still, "many local procurement policies include a provision that hospitals are encouraged to buy domestically-made medical devices as long as they meet quality requirements, and even explicitly stipulate the purchase of 'domestic brands,'" noted the EUCCC report.

Nevertheless, in the medtech sector, the bidding authority in Shenzhen designated specific ratios for domestic brands in its latest procurement round for CT and MRI machines. The city bordering Hong Kong in August required hospitals to procure 30% (seven) of their CT units and 40% (10) of MRI units from domestic manufacturers. These are defined as non-foreign owned enterprises nor joint ventures with domestic firms.

HOW TO REMAIN COMPETITIVE

In the pharma procurement scheme, multinationals either need to match the prices of domestic firms or offer another competitive advantage to win, industry observers say.

Sanofi, for one, decided to cut its prices to compete, lowering the level of Plavix (clopidogrel) to below the previous winning price offered by Shenzhen Salubris Pharmaceuticals Co. Ltd. The French group subsequently won the bid for the 75mg tablet formulation.

During the latest 4+7 round, makers of six products didn't lower prices but still managed to win bids. One of these was the lung cancer drug Iressa (gefitinib) from AstraZeneca PLC, which along with Qilu was one of only two companies to have passed official bioequivalence testing for a gefitinib product. The foregoing of a winner takes all system in the round also allowed both the companies to win.

Similarly, fosinopril had only one non-originator bidding company that had cleared bioequivalence testing Zhejiang Huahai Pharmaceuticals Co. Ltd., who with originator Bristol-Myers Squibb Co. won bids. BMS has held over 80% of the market for the hypertension drug.

As the government is expected to continue to roll out centralized procurement schemes, and amid shrinking market shares and the rising cost of non-participation, price-matching or other unique competitive advantages will need to be pursued.

Meanwhile, the EUCCC called in its report for "competitive neutrality" that ends the distinction between foreign and local ownership and offers a level playing ground.

"During the procurement process, the government should give priority to patients' clinical needs, and conduct evidence and value-based procurement," the European group stressed.

Published online 8 October 2019

An EU Plan To Pair Pharma With Life Science VCs

KEVIN GROGAN kevin.grogan@informa.com

Building a framework that connects big pharma, venture capital and biotech start-ups is the ambitious goal of a new project being pioneered by two agencies of the European Union.

The European Investment Fund (EIF) and EIT Health are linking up in a move that will see both institutions pool their respective network of partners in order to attract private investment finance for companies in the healthcare sector. The pact will enable the EIF (part of the European Investment Bank) and EIT Health to develop the Venture Centre of Excellence which the partners claim represents the first collaborative framework on a pan-European scale aimed at fostering relations between corporates from the pharma and medtech sectors and managers of European life science VC funds.

Jan-Philipp Beck, CEO of EIT Health told *Scrip* that the seeds for the collaboration were sown 18 months ago at a European Commission workshop. The plan is to provide a platform "with which we can essentially try to syndicate deals between corporate investors and VCs that are backed by the EIF." He noted that EIT Health has around 40 corporate partners including all the main big pharma players and "we want to get a large proportion of those involved in this platform."

As for the EIF, it is the largest investor in European life science venture capital "and the sector's most active limited partner with €2bn in commitments, close to 100% market coverage and an annual volume of around €300m," Beck said. The two agencies working together "is a tremendous opportunity to mobilize the investment needed to scale."

The collaboration requires critical mass, he argued, saying that "the more corporates you have that are willing to play this game and are interested, the more VCs you have and the better it is. That's how we will need to set this up over the next few months." He stressed that "we're not trying to raise the funds. It might be simpler to say, 'hey let's just raise a super duper, mega large life sciences fund' but it wouldn't work," given the different priorities of corporate pharma funds and VCs.

Jan-Philipp Beck

"What has the highest likelihood to succeed is this kind of a platform that would try to syndicate deals on a deal-by-deal basis. Is that difficult? Yes? Will it certainly succeed? No. Is it worth a try? I think most definitely. It is worth trying to use that mechanism to get critical mass in Europe and help promising companies that otherwise might be driven across the Atlantic for funds."

So what will grab the attention of big pharma enough to participate in the platform? Beck said that "in areas where they know they are going and are already making large, large investments, they don't need anyone else. However, we've also seen companies trying to get more traction in the early-stage community, often with no strings attached."

He added, "I think there is an appetite for saying 'this might not be maybe core to our business yet, this is something where we don't really know where it's going, but why don't we try to get a foot in the door'. Corporate pharma can de-risk that step through co-investment and still shape it, contribute to it but at the same time, also not be the only one. That's what we try to build on."

Beck has noted interest in particular in the digital therapeutic space. "There's all this connection between diagnostics and pharma, new things are moving and emerging but there's a great deal of uncertainty." He added that "we need to be able to provide exciting deal flow and identify those companies that are exciting. Otherwise, it's not going to be very interesting for anyone."

Beck said in Europe, research was still "incredibly local and regional and if we can make a contribution to connect better across borders, I think that would be also fantastic." EIT Health also runs the InnoStars initiative to tap into scientific expertise in countries that are not perceived as hotspots of innovation such as Hungary, Italy, Poland and Portugal.

He hopes that the Venture Centre of Excellence will led to more success stories for European biotechs similar to that of Peptomyc, a Spanish start-up focused on the development of a new generation of cell penetrating peptides targeting the Myc oncoprotein for cancer treatment.

Peptomyc, founded in 2014, struggled to gain early-stage investment but Beck said that Laura Soucek (its co-founder and CEO) was a scientist by training and "benefitted from many of our programs aimed at teaching entrepreneurial and business skills, as well as accessing financing for early stage innovation." Having recently secured more funding from the EU Horizon 2020 program, the Barcelona-based firm's first product, OMO-103, will move into human trials in 2020.

Other EIT Health-supported firms include Sweden's Gedea Biotech which has developed pHyph, a product that is already used as an approved food additive and is in clinical trials for vaginal fungal infection and bacterial vaginosis. Gedea "is being supported by our accelerator to allow them to scale out and reach patients across multiple markets," Beck said, as is Swiss biotech Tolremo Therapeutics, which is making medicines that can be combined with multiple existing oncology drugs to prevent resistance development in several types of cancer. *Published online 8 October 2019*

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.

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PIPELINE WATCH, 4–10 OCTOBER 2019

Event Type	Lead Company/Partner	Drug Name	Indication	Comments	Change To LOA (%)	LOA (%)
Phase III Published Results	AstraZeneca PLC	Imfinzi (durvalumab)	Small Cell Lung Cancer	CASPIAN; The Lancet, 4 Oct, 2019	0	39
Phase III Updated Results	VBI Vaccines Inc.	Sci-B-Vac	Hepatitis B Prophylaxis	PROTECT; Met Immunogenicity Endpoints	0	67
Phase III Updated Results	Gilead Sciences/Galapagos	filgotinib	Rheumatoid Arthritis	FINCH 1,3; Durable Responses At 52 Weeks	0	72
Phase III Updated Results	Myovant Sciences Ltd.	relugolix	Uterine Fibroids	LIBERTY 1,2; Met Efficacy Endpoints	0	79
Phase III Top-Line Results	Helixmith Co., Ltd.	Engensis (donaperminogene seltoplasmid)	Diabetic Peripheral Neuropathy	VMDN-003b; Met Primary & Secondary Endpoints	0	44
Phase III Top-Line Results	Novartis AG	Cosentyx (secukinumab)	Psoriatic Arthritis	ACHILLES, PDUS; Sustained Improvement	100	100
Phase III Trial Initiation	AnGes/Mitsubishi Tanabe	AMG0001 (beperminogene perplasmid)	Peripheral Arterial Disease	Resting Pain; In Japan	0	11
Phase III Trial Initiation	Dermira/Almirall	lebrikizumab	Atopic Dermatitis	Moderate To Severe Disease	38	65
Phase III Trial Initiation	Mithra Pharmaceuticals SA	Donesta (estetrol)	Menopause	E4 Comfort; In North America	36	66
Phase IIb/III Trial Initiation	Anavex Life Sciences Corp.	blarcamesine (ANAVEX 2-73)	Alzheimer's Disease, Early	ATTENTION-AD; Long-Term Extension	0	58
Phase III Trial Announcement	GlaxoSmithKline/Seattle Genetics	belantamab mafodotin (GSK2857916)	Multiple Myeloma	DREAMM-9 (w/VRd); Newly Diagnosed Patients	0	16

Source: Biomedtracker | Informa, 2019

Bayer/Ionis Advance Next-Generation Antithrombotic

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An investigational antisense product, IONIS-FXI-L_{Rx}, is progressing into Phase II studies in a collaboration between Bayer AG and US biotech Ionis Pharmaceuticals Inc., the companies announced on 9 October.

The move follows positive clinical results with the product, Bayer noted. IONIS-FXI-L_{Rx} is designed to reduce the production of the blood clotting factor, Factor XI, in the liver. The company is aiming to develop a next generation of antithrombotic agents which might be associated with little or no bleeding risk.

Germany headquartered Bayer already has a considerable development and commercial experience in antithrombotics with the oral anticoagulant, Xarelto (rivaroxaban), being its top-selling pharmaceutical product. In the first half of 2019, Xarelto had sales of €1.94bn, up by 14% compared with the first half of 2018.

With the move to Phase II, Bayer will be responsible for all development, regulatory and commercialization activities and costs associated with IONIS-FXI-L_{Rx} under an agreement signed in 2015.

Ionis has received more than $185m under that agreement, including a $10m milestone payment it earned with Bayer's continuation decision. The US biotech is eligible to receive additional milestone payments as IONIS-FXI-L_{Rx} advances toward the market, as well as tiered royalties in the low to high twenty percent range on gross margins.

Ionis has made significant strides in the scientific understanding of thrombosis formation: "Ionis was first to validate Factor XI and the intrinsic coagulation pathway as a novel antithrombotic strategy," noted its COO, Brett Monia. "Our antisense medicine targeting Factor XI demonstrates potent antithrombotic activity with little to no bleeding in multiple patient populations. This enables, for the first time, the potential to separate antithrombotic activity from bleeding risk," Monia added.

High levels of Factor XI increase the risk of blood clot formation inside blood vessels, leading to heart attacks and strokes, while low levels of Factor XI are associated with a lower incidence of thrombosis-related events, but little to no increase in bleeding risk.

IONIS-FXI-L_{Rx} has the potential to be used especially in patients at high risk for thrombosis and at high risk of bleeding.

Separately, Bayer announced on 10 October the launch of LifeHub UK, which will drive the development of artificial intelligence (AI) in radiology and imaging in order to detect disease and improve data-driven drug discovery.

It's the seventh of Bayer's global network of LifeHubs, and the UK AIM-quoted clinical AI company, Sensyne Health PLC, which entered into a collaboration with Bayer earlier this year, will be one of the first to be involved in the LifeHub, based in Reading's Green Park.

Published online 11 October 2019

APPOINTMENTS

Executive	To Company	New Role	From Company	Previous Role	Effective Date
Kevin Buchi	BioSpecifics Technologies Corp	Chief Executive Officer and Director	Dicerna Pharmaceuticals	Chairman	10-Oct-19
Alex Wang	Everest Medicines	Head, International Business	Abbott Singapore	General Manager, Point of Care	16-Sep-19
Daniel Weng	Everest Medicines	Vice President, Finance	Amgen China	Head, Finance	16-Sep-19
Frank Grams	Everest Medicines	Senior Vice President, Alliance Management and Head, Business Development, Europe	Sanofi	Vice President, Global Head, Alliance Management, General Medicines and Emerging Markets and Global Head, R&D Alliance Management	16-Sep-19
Sophia Zhu	Everest Medicines	Senior Vice President, Portfolio Development and Strategic Planning	Sanofi China	Head, Strategic Portfolio Development, Specialty Care	16-Sep-19
Merdad Parsey	Gilead Sciences Inc	Chief Medical Officer	Genentech Inc	Senior Vice President, Early Childhood Development	1-Nov-19

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