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The last of a trio of obesity drugs that launched early in the last decade to crash

FDA Requests Belviq Be Pulled From The US Market Due To Cancer Risk

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The US Food and Drug Administration has requested that Eisai Co. Ltd. voluntarily withdraw the obesity pills Belviq and Belviq XR (lorcaserin) from the US market because of an increased risk of cancer. The announcement on 13 February comes after Eisai demonstrated the cardiovascular safety of Belviq in an outcomes trial, but that same trial showed an increased risk of cancer occurrence.

The FDA issued an alert in January notifying the public that it was assessing the safety of Belviq for a potential increased risk of cancer. In the 12,000-patient CAMELLIA-TIMI 61 trial, Eisai showed Belviq did not increase major cardiovascular events compared to placebo, but the drug did not improve cardiovascular outcomes either. At the time the data was first released in mid-2018, Eisai did not highlight cancer as a safety signal. *(Also see "Eisai's Obesity Drug Belviq Passes Cardiovascular Outcomes Test" - Scrip, 17 Jul, 2018.)* The FDA had required the cardiovascular outcomes trial (CVOT) as a post-approval commitment.

"Patients should stop using the medication Belviq and Belviq XR and talk to their health care professionals about other treatment options for weight loss," Center for Drug Evaluation and Research Janet Woodcock said in a statement. The agency did not recommend special cancer screening for patients who have taken Belviq outside of routine tests.

Belviq has not been a big commercial seller in the US, but Eisai had been hoping the positive cardiovascular outcomes trial could mark a new chapter for the troubled weight loss pill. The company reported nine-month revenues of ¥4.61bn ($42m) for Belviq in January.

NAIL IN COFFIN

Now, the FDA's request to remove the drug from the market feels like another nail in the coffin for a trio of obesity drugs that launched in the early part of the last decade with a lot of fanfare but failed commercially. *(Also see "10 Drug Launch Flops Of The Decade " - Scrip, 8 Jan, 2020.)* The big problem for the drugs was around the perceived modest efficacy and uncertain risks.

Belviq was the first of those drugs to reach the market in 2012. It was initially developed by Arena Pharmaceuticals and partnered with Eisai in 2010. *(Also see "Arena Scores Hefty Obesity Drug Deal With Eisai Ahead Of PDUFA Date" - Pink Sheet, 1 Jul, 2010.)* Arena handed over full commercial rights to the product to Eisai in 2017 to focus on other drugs.

Two other drugs followed behind Belviq: Vivus Inc.'s Qysmia (phentermine/topiramate) and Takeda Pharmaceutical Co. Ltd../Orexigen Therapeutics Inc.'s Contrave (naltrexone/bupropion). Orexigen eventually filed for bankruptcy, and while Vivus continues to market Qysmia, it only generated $9.5m in the third quarter of 2019.

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As Belviq Goes Off India Market, Patent Case May Fizzle:
https://bit.ly/2SSaZgw

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A passing nuisance or a real worry? (p18)

from the executive editor

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How worried are you about coronavirus? And if you do have any fears, do they relate more to your personal safety, or that of your business? I'm firmly in the not-worried-yet camp; a quick Amazon search for face masks ended with a closed laptop as soon as I saw their price, although I do admit to having upped the handwashing (both frequency and thoroughness).

Three years of studying microbiology at university may have left me with a healthy respect for viruses, but 20 years of covering pharma has engendered some faith, at least, in its ability to Do Something about the current outbreak. Fears over SARS, MERS and H1N1 waxed then waned, after all, and hopefully COVID-19 will be no different.

Such sanguinity appears shared by pharma heads. As we report in p18, only a few firms addressed the issue squarely during the Q4 reporting season and concerns at present are largely confined to China. With the obvious caveats firmly in place, most said the disruption was manageable and expected the outbreak to be relatively short-lived. And many are joining in efforts to tackle the disease.

Still, the arrival of an unknown infectious disease evokes deep-seated fears. Just today in the UK press, amid all the coronavirus updates, was news of the discovery in rural Lincolnshire of a mass grave of 14th century victims of the Black Death – the findings proving that it was not just the populous towns where the normal systems for burial broke down under the sheer volume of bodies as half the population of Europe was wiped out. A reminder, if any were needed, not to get too complacent.

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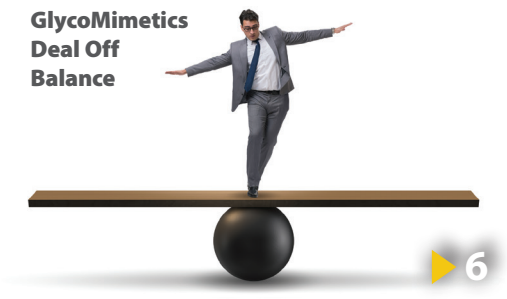

exclusive online content

89Bio's NASH Hopes Hang On Demonstrating Best-In-Class FGF21 Profile

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Recent entrants, including some big pharma players, threaten to make the fibroblast growth factor (FGF) analog class another crowded field of clinical development for non-alcoholic steatohepatitis, but 89bio Inc. thinks its mid-stage FGF21 analog could prove best in class with less frequent dosing than a Phase II FGF21 candidate at Bristol-Myers Squibb Co. and offer a better safety profile than NGM Biopharmaceuticals Inc.'s Phase IIb FGF19 analog.

Founded in Israel in May 2018 with the licensing of BIO89-100 (then called TEVA47948) from Teva, 89Bio now operates mainly out of San Francisco. It anticipates reporting out Phase IIa data for BIO89-100 in NASH during the second half of 2020 – the ongoing Phase Ib/IIa study is testing once-weekly and twice-weekly injectable dosing of the glycopegylated FGF21 analog. The firm also plans to soon initiate a Phase II study of the candidate in severe hypertriglyceridemia with data expected during the first half of 2020.

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AstraZeneca Returns To Growth, But Coronavirus Likely To Hit China Revenues

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AstraZeneca PLC has recorded its first full year of revenue growth in eight years, bouncing back thanks to its fast-growing new cancer drug portfolio and expansion in China. But CEO Pascal Soriot warned the Covid-19 virus outbreak could have an impact on 2020's numbers.

As the sixth successive quarter of growth, Q4 2019 marks the completion of the long turnaround process for Soriot and his senior team, and AstraZeneca is now tipped by analysts to be one of the standout growth stories in big pharma over the next five-10 years.

AstraZeneca's new HQ in Cambridge UK is still not complete but the business is now set for significant growth

Source: AZ

Total revenues for the year rose 10% to $24.3bn, with more approvals and further indications for existing products expected in 2020. But now that it's 'payback time' for investors, AstraZeneca is under pressure to meet those expectations of industry-leading growth.

Revenue growth for the full year and Q4 was led by targeted lung cancer drug Tagrisso (osimertinib), up 71% for the 12 months to $3.18bn, with Imfinzi (durvalumab) rising rapidly to $1.46bn and ovarian cancer therapy Lynparza (olaparib) breaking through the $1bn annual sales mark for the first time.

Nevertheless, these figures were just shy of analysts' expectations, as were sales of AstraZeneca's other current growth drivers, diabetes drug Farxiga (dapagliflozin), and severe asthma treatment Fasenra (benralizumab), though these were offset by a better-than-expected showing from aging respiratory blockbuster Symbicort (budesonide/formoterol).

For 2020, the company is forecasting revenue growth in the high-single to low-double digits, with core earnings per share expected to increase by a mid- to high-teens percentage.

The revenue forecasts are lower than hoped for by bullish investors, but one headwind being factored into these calculations is the ongoing coronavirus outbreak.

The virus, which is still not under control and has brought China to a standstill, is spreading globally. Given that much of AstraZeneca's growth is driven by China, the company says it was keeping an eye on developments, and expects to provide an update at the time of its Q1 results. "For 2020, we anticipate another year of strong growth. However, we also need to take into account the situation with the Coronavirus in China, so we anticipate total revenue to increase by high-single digit to a low-double digit percentage. And when it comes to core EPS, we anticipate an increase of mid- to high-teens percentage," Soriot said.

The latter half of 2019 saw a number of significant developments for the company, including US approval of Enhertu (trastuzumab deruxtecan) in breast cancer (co-marketed with Daiichi Sankyo) and Calquence (acalabrutinib) in leukemia, as well as several approvals in China at the end of the year, including Lynparza in first-line ovarian cancer. *(Also see "AZ Closer To Second Enhertu OK After Gastric Cancer Success" - Scrip, 27 Jan, 2020.)*

The company expects two significant new drug approvals this year in the US. First up is selumetinib is a novel treatment for pediatric patients with NF1 and symptomatic, inoperable plexiform neurofibromas, a rare and incurable genetic condition. The Food and Drug Administration is expected to make its decision in the second quarter of 2020.

Meanwhile AstraZeneca's partner FibroGen Inc. filed roxadustat with the FDA in December, a novel anemia treatment for patients with chronic kidney disease with blockbuster potential. Analysts forecast the drug could hit $5bn in peak annual sales, and the FDA is expected to announce its decision in the fourth quarter. *(Also see "AstraZeneca's Dobber On Ramping In Renal, Expanding In CV And Business Development " - Scrip, 21 Jan, 2020.)*

While the company has now returned to growth, it remains well behind the $33bn annual revenues it earned in 2010 before it headed into steep decline because of blockbuster expiries.

Soriot famously promised to reach sales of $40bn by 2023 when the company was fending off a takeover bid from Pfizer Inc. in 2014. Most analysts now believe the company will fall short of this aspiration, but Soriot and his team hope to generate new sources of growth to help them deliver on this promise.

The company is still paying off debts, including the bill for the construction of its new global headquarters in Cambridge, UK, but says improving its cash generation and leverage will be one of its key priorities in 2020. This points to the company gearing up for a possible re-entry to the mergers and acquisitions market, which could potentially help it meet its long-held growth target.

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Teva Edges Closer To Growth, But With A Big Overhang

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Teva Pharmaceutical Industries Ltd. is heading into the third year of a massive turnaround strategy that began under CEO Kåre Schultz in late 2017, and while the company made substantial progress on its goal of returning to earnings growth in 2020, the expectation for generic revenues continues to be moderate and there is a threat to the stability from opioid liability litigation.

Teva updated investors on its 2019 financial results and 2020 forecast on 12 February with earnings before interest, taxes, depreciation and amortization (EBITDA) forecast to be $4.5bn to $4.9bn in 2020, a range that is slightly below to slightly above 2019 EBITDA of $4.7bn in 2019. A year ago, Teva had guided investors to expect 2019 would be a trough year before returning to earnings growth in 2020, so it remains unclear if Teva will actually reach that goal. *(Also see "A Trough Year For Teva, With A Turning Point Targeted For 2020" - Scrip, 13 Feb, 2019.)*

Schultz said the guidance reflects necessary flexibility. "The low end is of course not what we're aiming for. That would never be the case, but it reflects the fact that there's always uncertainty in any business," he told a same-day conference call.

He pointed out that he has a long management track record of hitting guidance. "I have not missed the guidance of the company I've been working at for 62 quarters in a row. I'm not planning to start doing that now," he said.

The 2020 forecast also calls for revenues that are largely flat, which would be a substantial improvement for Teva. The company is forecasting revenues of $16.6bn to $17bn in 2020 compared to $16.9bn generated in 2019. The 2019 revenues represented a decline of 8% over 2018. The decline was mainly due to the eroding Copaxone (glatiramer) business and a decline in the US generics business.

The growth drivers for 2020 will be two of the company's newer specialty brands, Austedo (deutetrabenazine) for tardive dyskinesia and chorea associated with Huntington's disease and the CGRP migraine prevention drug Ajovy (fremanezumab). Teva expects Austedo revenues to grow from $412m in 2019 to $650m in 2020 and revenues of Ajovy to grow from $96m in 2019 to $250m in 2020.

The generics business, however, is expected to continue its flat to moderate growth, with North American generics revenues expected to be flat at around $4bn. The company pointed to the launch of its first biosimilar – Truxima (rituximab-abbs), a biosimilar of Roche's Rituxan – as another growth driver. The company did not break out sales of Truxima, which only launched in November, but said its market share is ranging between 12%-15%.

> "The low end is of course not what we're aiming for ... but it reflects the fact that there's always uncertainty in any business." – Kåre Schultz

LAUNCH UPDATES

The launch of Ajovy has been slow because of the competitive dynamics in the migraine space, with three similar drugs on the market. *(Also see "Market Snapshot: Migraine Prevention Therapies' Slow Road To Blockbuster Status" - Scrip, 23 Jan, 2020.)* Teva's product, administered through a prefilled syringe, is the only one that has not been available in an autoinjector, which has been a limitation. However, the US Food and Drug Administration approved an autoinjector device for Ajovy in late January, which the company expects will help to level the playing field.

"We think now that we have the autoinjector approved, as we prepare for launch, which we will do here in the next couple of months, we will have an offering that is really unmatched in the CGRP market," exec VP-North America commercial Brendan O'Grady said. Ajovy will be available in the prefilled syringe and the autoinjector and can be administered by patients or in physicians' offices, and it is the only CGRP that is available in quarterly dosing as well as monthly. The quarterly dosing option represents about 17% of the use and continues to grow, he said.

With Austedo, Teva is anticipating new data from a Phase III trial testing the drug in a potential new indication to relieve tics in people with Tourette's syndrome. The data will be reported in a few months, Teva said. The trial could be a big failure or a big success, Schultz said, noting, "it's anybody's guess."

Neurocrine Biosciences Inc.'s rival drug Ingrezza failed to show a benefit in Tourette's syndrome so there is some uncertainty around Teva's potential for a more successful outcome.

Altogether, Teva has made notable strides in its turnaround strategy, which has resulted in an entire restructuring of its expenses, reducing its manufacturing footprint, cutting thousands of employees and paying off billions in debt.

Teva has reduced its manufacturing network from 80 facilities to less than 60 and is continuing to consolidate, Schultz reported. Teva has reduced its debt from $35bn in 2017 to $24.9bn at the end of 2019. The company successfully refinanced in the fourth quarter so that it can manage payments that were coming due in the next three years, he said.

OPIOID RISK OUTSTANDING

As Teva makes slow and steady progress on its financial stabilization, there is one big uncertainty that continues to weigh on the company – opioid liability litigation and how much Teva could have to pay to settle lawsuits in the US.

The chief executive did not have an update on that front, aside from reiterating his comments at the J.P. Morgan Healthcare conference, that he is "cautiously optimistic" on the outlook for a broad settlement ahead of a case heading to trial in mid-March. *(Also see "J.P. Morgan Notebook Day 1: No Big Deals, But Plenty Of Pipeline, Commercial Highlights" - Scrip, 14 Jan, 2020.)* Teva has proposed a national settlement framework that would allow the company to settle much of the ongoing litigation with a $250m upfront payment and a $23bn supply of the opioid addiction treatment Suboxone (buprenorphine/naloxone) tablets over 10 years. *(Also see "J.P. Morgan Notebook Day 1: No Big Deals, But Plenty Of Pipeline, Commercial Highlights" - Scrip, 14 Jan, 2020.)*

The opioid liability issue and persistent generic challenges weighed on analysts, even as they acknowledged the substantial progress Teva has made.

"It is increasingly clear that management has the business stabilized and has executed remarkably well in eliminating the necessary cost structure while maintain exceptional performance in both its launch of Austedo, as well as maintaining the revenue in its various generic franchises," Cowen analyst Ken Cacciatore in a same-day note.

"However, given the share price correction and current valuation, we believe nearly all of these favorable trends are already factored, and yet this excludes any potential opioid or drug liability risks," he cautioned.

Bernstein analyst Ronny Gal warned investors, "We understand the recovery... but don't fall in-love with the model. Teva needs a sustainable business model and it's not quite there yet."

The company's stock opened up 6% at $13.09 on the positive news.

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Ipsen Upbeat Despite Palovarotene Program Pain

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On balance, 2019 was a decent one for Ipsen

The shine has been taken off the strong sales growth at Ipsen in 2019 by the regulatory and clinical woes of palovarotene, the rare disease drug the French drugmaker had such high hopes for when it acquired Canada's Clementia Pharmaceuticals Inc. last year.

It was a year ago that Ipsen agreed to pay $1.04bn up front plus an additional deferred amount of $263m to buy Montreal-based Clementia and get hold control of palovarotene. The drug, a retinoic acid receptor gamma selective agonist, was touted as a potential treatment for a number of orphan diseases, especially fibrodysplasia ossificans progressiva (FOP) and multiple osteochondromas (MO).

At the time of the purchase, which completed in April last year, Ipsen chief commercial officer Harout Semerjian told *Scrip* that palovarotene was "a largely de-risked asset with limited competition." Having received fast-track, breakthrough therapy and rare pediatric disease designations for FOP from the US Food and Drug Administration, a US submission was expected in the second half of last year, for a potential launch in mid-2020.

However plans for a filing were consigned to the dustbin at the end of 2019 when the FDA slapped a partial clinical hold on Ipsen's palovarotene clinical trials in FOP and MO in children less than 14 years old, due to bone growth concerns. Things got even worse last month when the company revealed that it had paused dosing patients on the back of a futility analysis which indicated that the Phase III FOP trial called MOVE was unlikely to meet its primary efficacy endpoint.

The setbacks in the palovarotene program led Ipsen to take a pre-tax partial impairment of €669m in the fourth quarter. Ipsen also cut its sales estimates in 2022 to around €2.8bn, down from previous guidance of €3.2bn, assuming that there will be no revenues from palovarotene.

Still Ipsen is not giving up on palovarotene just yet, saying it will conduct further assessments of the MOVE dataset, address the FDA's questions "and define next steps for the clinical program to bring palovarotene to patients as quickly as possible."

New CEO Aymeric Le Chatelier, who took the helm when David Meek left to join FerGene days after the first bit of bad palovarotene news in December, told analysts on 13 February that "we really understand this is an important topic and that there are still many outstanding questions." He added, "It is clear that we remain highly committed to building a successful rare disease franchise [and] are extremely determined and motivated to bring the first therapeutic treatment option to the FOP patient community."

Beyond palovarotene, he highlighted a licensing deal signed in October for Blueprint Medicines Corp.'s BLU-782, an ALK2 inhibitor in Phase I development for the treatment of FOP. It is "addressing the underlying cause of the disease," Le Chatelier

said, noting that a Phase II trial is expected to begin later this year.

Ipsen's enthusiasm is not shared by the investment community. Jefferies issued a note on 13 February saying, "We see few opportunities to mitigate pessimistic sentiment and relieve pressure on the shares, exacerbated by the recent regulatory and clinical setbacks for palovarotene and the departure of CEO David Meek."

The palovarotene problems overshadowed what was a very healthy 2019 on the sales front for Ipsen. Turnover was up by 14.8% to €2.58bn, thanks to another strong performance for cancer drugs Somatuline (lanreotide), Cabometyx (cabozantinib), Onivyde (irinotecan liposome injection) and Decapeptyl (triptorelin), as well as the dermal filler and spasticity treatment Dysport (abobotulinumtoxinA).

Ipsen is reliant on Somatuline, approved for neuroendocrine tumors (NET) and its only billion euro drug. Le Chatelier noted that sales in Europe continued to grow in the double digits despite the first entry of generics of Novartis AG's rival product Sandostatin LAR (octreotide), adding that "there has been minimal impact to date and no impact on pricing so far [but] in 2020, we expect more pricing pressure and additional launches across Europe."

Somatuline itself could face generic competition from 2021 in Europe but Le Chatelier pointed out that a new injector-friendly device continued to be well received by the NET patient community in Europe and elsewhere, giving it the edge over Sandostatin LAR.

Le Chatelier said 2019 was an excellent year and "despite the recent palovarotene setback, the fundamentals of our business remain strong with a growing specialty care franchise and a sound financial structure including attractive cash flow generation. We are committed to the disciplined execution of our strategy, delivering solid mid-single digit growth in 2020."

As for the M&A strategy, he noted that while the last two major deals – Clementia and BLU-782 – were in rare diseases, oncology and neuroscience remain areas of interest. "You could expect us to announce something in any of these three therapeutic areas going forward." *(Also see "Ipsen CBO: We Are Seeking Fresh Rare Disease Buys" - Scrip, 25 Nov, 2019.)*

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Strong Sales For Ipsen

DRUG	FY19 SALES €M	% CER
Somatuline	1,031.6	18.3
Decapeptyl	407.4	8.8
Dysport	388.3	10.2
Cabometyx	242.2	63.5
Onivyde	134.7	16.9

Source: Ipsen

Pfizer Ends Pact With GlycoMimetics After SCD Failure

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Six months after the failure of a Phase III study evaluating rivipansel for the treatment of vaso-occlusive crisis in sickle cell disease (SCD) patients, Pfizer Inc. has told licensor GlycoMimetics Inc. that it will tear up their 2011 agreement to develop the drug.

GlycoMimetics in a filing with the US Securities and Exchange Commission dated 5 February said Pfizer's decision meant it would regain all rights to the respective assets and incur no termination penalties related to the end of the partnership. Pfizer licensed the pan-selectin inhibitor from GlycoMimetics in October 2011 in a $340m deal. *(Also see "GlycoMimetics makes good with $340m sickle cell drug deal with Pfizer" - Scrip, 12 Oct, 2011.)*

The NASDAQ-listed biotech said in the SEC filing that it would determine "what, if any, next steps" to take with respect to rivipansel, its lead drug candidate also known as GMI-1070, after reviewing the Phase III data more completely. The collaboration officially ends on 5 April.

Pfizer's decision comes after its Phase III RESET clinical trial evaluating rivipansel in SCD failed in August 2019 to meet its primary and key secondary efficacy endpoints.

GlycoMimetics is a US-based clinical-stage biotech focused on the discovery and development of novel glycomimetic drugs to address unmet medical needs. Aside from rivipansel which was developed for the treatment of vaso–occlusive crisis in sickle cell disease, its chief assets comprise GMI–1271, an E–selectin antagonist, which is being evaluated in a Phase I/II clinical trial as a potential treatment for acute myeloid leukemia and also in a Phase I clinical trial for the treatment of multiple myeloma. The Maryland-based company is also developing a Phase I clinical trial drug candidate, GMI–1359, a combined CXCR4 and E–selectin antagonist that has received orphan drug designation and rare pediatric disease designation from the US Food and Drug Administration for the treatment of osteosarcoma, a rare cancer affecting about 900 adolescents a year in the US.

News of Pfizer's contract exit spooked investors and pulled GlycoMimetics volatile share price down further, and analysts predicted more declines would follow. The company does not have revenues and finances its operations through equity financings.

Analysts at PriceTarget Research in a note to investors on 5 February said, "GlycoMimetics is expected to be a major value eraser, reflecting capital returns that are forecasted to fall short of the cost of capital." PriceTarget Research has consequently assigned its lowest rating to the company.

SCD is the most common inherited blood disorder in the US, affecting about 100,000 people. In SCD, a gene mutation causes the production of abnormal, flattened, sickle-shaped red blood cells that prevent blood flow and cause painful attacks, fatigue, organ damage and stroke. The pain episodes, known as vascular occlusion or VOC, often require hospitalization.

There are few options for SCD treatment, aside from regular blood transfusions. But late 2019 saw the launch of the first treatments to address the underlying cause of the disease.

Global Blood Therapeutics Inc.in late 2019 launched its first commercial drug, Oxbryta (voxelotor), for the treatment of SCD after securing FDA approval on 25 November, just ten days after Novartis AG's Adakveo (crizanlizumab) was approved by the FDA. The two drugs work differently and carry different indications, however. *(Also see "Global Blood Therapeutics' Oxbryta Approved Broadly For Sickle Cell Disease " - Scrip, 25 Nov, 2019.)*

And there are several gene therapies in the clinic that show promise. *(Also see "Sickle Cell Disease Market Snapshot: "The Time Has Come" " - Scrip, 31 Oct, 2019.)* One is LentiGlobin which US-based bluebird bio Inc. hopes can provide a potential cure for patients with sickle cell anemia via a single infusion by replacing the missing gene for anti-sickling hemoglobin, HbAT87Q.

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It's A Deal, Finally: Dr Reddy's Snaps Up Wockhardt's Branded Gx Business

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Wockhardt Ltd. has divested parts of its branded generics business in India and certain international territories to Dr. Reddy's Laboratories Ltd. for INR18.50bn ($260m), ending long-running speculation around an imminent deal that is expected to help the Mumbai-based firm pare debt and provide liquidity for its remaining operations.

A deal has long been in the making and rumored suitors for the financially strained Wockhardt included private equity players such as Apax Partners, Blackstone, Carlyle and KKR, among others, at varying points in time. Indian peer Cipla Ltd. was also thought to be interested in certain assets of Wockhardt. *(Also see "Cipla Rumored Frontrunner For Wockhardt Deal" - Generics Bulletin, 2 Dec, 2019.)*

Dr Reddy's will now acquire selected divisions of Wockhardt's branded generics business in India and a few other international territories (namely Nepal, Sri Lanka, Bhutan and Maldives). A portfolio of 62 brands in multiple therapy areas including respiratory, neurology, dermatol-

ogy, gastroenterology, pain and vaccines, along with related sales and marketing teams and a manufacturing plant located in Baddi, Himachal Pradesh, inclusive of all employees, will be transferred to Dr Reddy's under the deal.

The business undertaking is being transferred on a slump sale basis and the transaction is expected to close in the first quarter of the financial year 2020-21, the companies said.

Dr Reddy's has long hinted that it is looking for acquisition opportunities, with a particular interest in emerging markets and India. *(Also see "Dr Reddy's Posts Surprise Q3 Loss But Strong Operating Results Boost Shares" - Scrip, 28 Jan, 2020.)*

Dr Reddy's co-chairman and managing director G V Prasad said that India was an important market for the firm and the Wockhardt deal would help in "considerably scaling up our domestic business."

"We believe the portfolio holds a lot of potential and will get an impetus under Dr Reddy's," Prasad said.

ADEQUATE LIQUIDITY FOR REMAINING OPERATIONS

The deal has been struck at approximately 3.8 times of annualized revenue of the business being sold by Wockhardt. The business being transferred reported revenue from operations of INR3.77bn, which is about 15% of the firm's consolidated revenue for the nine months ended 31 December 2019. *(Also see "Wockhardt Will Raise Funds With Restructuring" - Generics Bulletin, 3 Feb, 2020.)*

Habil Khorakiwala, Wockhardt's founder chair, said that deal was in sync with the firm's strategic plan to shift from acute therapeutic areas to more chronic therapy segments like diabetes, CNS, etc., and also to its niche antibiotic portfolio of NCEs (new chemical entities).

"The divestment will also ensure adequate liquidity to bring in robust growth in the chronic domestic branded business, international operations, investments in biosimilars for the US market, apart from the company's global clinical trials of breakthrough anti-infectives and R&D activities," Khorakiwala said.

Wockhardt had recently received regulatory approval in India for two indigenously developed novel antibiotics, essentially broad spectrum anti-MRSA drugs, which it claims provide a far better safety profile than existing therapies.

DEBT PILE

The deal is expected to bring much needed relief to Wockhardt, which has been grappling with financial turbulence and manufacturing compliance issues; the firm had a debt pile of INR33.62bn (including secured, unsecured and preference capital) for the fiscal year 2019. During the nine months ended 31 December 2019 the company repaid INR7.68bn towards various long-term debt obligations "as per schedule." Gross debt-equity ratio as on 31 December 2019 stood at 0.95.

Rating agencies have previously highlighted the significantly elevated refinancing risks for Wockhardt in the second half of fiscal year 2020 due to its weak liquidity position to service impending debt maturities. In August 2019, credit rating agency India Ratings and Research noted that in the absence of a "meaningful recovery" in operating performance, Wockhardt had witnessed continuous depletion in cash balances for servicing debt obligations. "Furthermore, the agency expects weak free cash flow (FY19: negative INR1.30bn; FY18: INR3.32bn) generation in FY20," India Ratings and Research said at the time.

Wockhardt's financial troubles came to a head when its debt pile mounted after it made a string of overseas acquisitions and then certain currency hedging bets went awry in 2008. Wockhardt defaulted on repayments of its $110m foreign currency convertible bonds in 2009. The company approached the corporate debt restructuring (CDR) cell through ICICI Bank Limited in April 2009 to restructure its debts through the CDR mechanism; it has since exited the CDR process.

'MORE AND MORE WITH LESS AND LESS'

Interestingly, reflecting on the financial setbacks in his recent autobiography, chairman Habil Khorakiwala maintained that what was heartening to note was that "financial troubles were not a result of wrong business decisions or faulty transactions but merely of faulty financial management."

Wockhardt had then gone on to divest some of its "best" assets and businesses (including animal healthcare and nutrition) to not just restore the firm's financial health but also to take it on a "new growth path," chair Khorakiwala noted in the autobiography, Odyssey of Courage.

"The philosophy was simple. Divest from non-core business to strengthen core business. I encapsulated this philosophy in the motto: more and more with less and less," Khorakiwala said in the book. Clearly, he will now have to walk the talk with what remains of Wockhardt.

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A Positive Outlook For Deals, With Election Year Caveats

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The biopharma deals and financing environment is poised to be healthy in 2020 despite the uncertainty around a US presidential election year, according to industry deal-making experts at the BIO CEO & Investor conference in New York 10-11 February.

Advancements in science and strong business fundamentals should continue deal momentum, transaction advisers said during a deals panel, but they did offer some caveats related to the US election in November.

Financial adviser Eric Tokat of Centerview Partners, which advised Spark Therapeutics Inc. in its merger with Roche last year, said the industry is in the midst of a new era of deal-making that is being driven by science.

"Historically, large pharma mergers were driven by efficiency, cost-cutting, cash flow, diversification. In this era, the drivers are a bit different than we have seen in the past," he said. The science-driven nature of deal-making today should continue the momentum behind smaller bolt-on deals in 2020, he predicted. "I do anticipate more of the $1bn-$5bn or $1bn-$10bn deals."

However, as the election approaches later in the year, there could be some pullback, he said. But for now, "no one seems to have priced in any potential risk of an election year derailing anything."

J.P. Morgan vice chairman Philip Ross agreed that "it's not priced in," but he speculated that more uncertainty could come later in the year when the Democratic nominee is selected. Growing uncertainty could impact the financing and IPO environment, with activity weighted to the first part of the year, he said.

"Everyone is kind of lining up right now to say there is less uncertainty today," Ross said. "There are a lot of people pushing pretty hard." After the US Labor Day holiday, there will be a small window for raising capital before the focus will shift to the election, he added. A similar sentiment was echoed by investors and advisers at the J.P. Morgan Healthcare conference in January. *(Also see "Finance Watch: Expect A Busy First Half For 2020 IPOs" - Scrip, 23 Jan, 2020.)*

Raymond James managing director Andrew Gitkin said, "My sense is that boards and executives are trying to manage around the election and trying to bring forward financings."

"What could derail the positive momentum for biotech this year, according to Tokat, is if the Democrats nominate a far-left progressive candidate like Elizabeth Warren or Bernie Sanders, who could be more likely to advocate for sweeping drug-pricing policy changes, and their potential election as president.

"I do think low likelihood, but if it does happen, I think we are going to have a very different biotech valuation and a lot of unhappy investors," Tokat said. If there is a radical political change and a big market correction, it could result in a deal-making reset as biotech will need time to adjust to lower valuations, he said.

FTC SCRUTINY ON DEALS

Another lingering uncertainty is around the US Federal Trade Commission and potential for increased scrutiny of deals. Tokat, who worked on the Spark/Roche merger that was hung up by an FTC review, said that if the administration flips that will be yet another element of uncertainty.

"I think people will just be more careful," he said, but industry is already very aware of anti-competitive hurdles. Still, he said the FTC's lengthy review of the Spark deal was a surprise.

"There was zero discussion in the board room around potential risk of antitrust," he said of that deal. Roche's acquisition of Spark closed in December after a lengthy 10-month investigation into how Roche's marketing of Hemlibra (emicizumab) for hemophilia A might have anti-competitive implications for the development of Spark's gene therapies for hemophilia.

J.P. Morgan's Ross, who advised Celgene Corp. on its merger with Bristol-Myers Squibb Co., said similarly Bristol's move to divest Celgene's Otezla (apremilast) because of FTC scrutiny was somewhat unexpected. "We did all the diligence. We evaluated TYK2. It's a really cool mechanism and asset, but to say all the airtime was taken in the room on Otezla, it wasn't," he said. Celgene ended up selling Otezla to Amgen Inc. for $13.4bn in August so that it could get the merger with BMS completed faster. The FTC had expressed concerns about overlap with one of Bristol's late-stage pipeline assets, another inhibitor of tyrosine kinase 2 (TYK2). *(Also see "Amgen's $13.4bn Otezla Buy Helps Bristol/Celgene Merger Close By Year-End" - Scrip, 26 Aug, 2019.)*

In terms of therapeutic areas of focus for deals, it is likely to remain centered around two core areas: oncology and rare disease, the panelists at BIO CEO said. That is partly driven by supply and demand, Tokat said, because 50% of the companies with over $1bn in market cap are working in oncology and rare disease.

"CNS continues to be interesting. The key theme is disease-modifying, curative, transformative," he said.

Raymond James' Gitkin said he is also seeing a lot of interest around big data, and around manufacturing technology, given increased emphasis on gene therapy and cell therapy. *(Also see "Gene Therapy Companies Among Top M&A Targets In 2020 " - Scrip, 2 Jan, 2020.)*

"Everyone talks about cell and gene therapy and that is the next generation," said Geoff Meyerson, CEO and founder of Locust Walk, a transaction advisory firm. "But if you look at the deals that are actually getting done, there are still an awful lot of small molecule deals getting done and there are a lot of small molecules getting approved by the FDA."

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Sandoz Optimistic On Biosimilars As It Reprioritizes US Portfolio

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Sandoz International GMBH is shrinking the size of its US footprint as it prioritizes complex generics and biosimilars in the region and divests much of its small molecule generics portfolio to India's Aurobindo Pharma Ltd. US President Carol Lynch talked about the changing dynamics for the US business and the company's positive outlook for biosimilars in an interview with *Scrip* at the BIO CEO & Investor conference in New York on 10 February.

"We are looking forward to closing the transaction and when that's behind us, then obviously we've got a smaller business in terms of the areas we are focusing on, but also a smaller company as well to support that," Lynch said. "We did most of that restructuring last year, so we are in great shape to try to grow as we move forward."

Source: Sandoz

Sandoz US President Carol Lynch

Novartis, which owns Sandoz, announced the deal with Aurobindo in 2018, agreeing to divest its US dermatology and generic US oral solids portfolio in a deal worth around $1bn. That deal is still yet to close, with Novartis guiding most recently that it is on track to close in the first quarter, pending regulatory approval.

Once the Aurobindo sale is finalized, Sandoz's US portfolio will be focused on complex small molecules, biosimilars and sterile injectables. Global traditional generic drugs will remain core to Sandoz, but Lynch said the footprint will vary regionally.

The US generics market has been a challenging one for the sector broadly, with fewer big blockbusters going off patent and consolidation among purchasers driving intense price pressure. *(Also see "Generic Drug Sector Struggles Even As The Need For Cheaper Drugs Grows" - Scrip, 10 Aug, 2018.)* The US business has been dragging down Sandoz global performance. In 2019, Sandoz revenues were

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CONTINUED FROM PAGE 11

$2.5bn, representing 1% growth; excluding the US, Sandoz revenues would have grown 8%. For 2020, Sandoz sales are expected to grow low-single digits, though Lynch declined to break out the expectations for the US business.

The US will represent about 15% of Sandoz' sales after the realignment, but with a stronger growth trajectory that will begin to materialize in 2021, she said. About 750 positions within Sandoz were impacted by the deal, but many of those were in manufacturing or other technical roles that will transfer to Aurobindo.

ERELZI AND ZIEXTENZO ARE POTENTIAL GROWTH DRIVERS

How 2020 unfolds for the US business depends on key catalysts. One of the big uncertainties revolves around the potential launch of a biosimilar version of Amgen's Enbrel (etanercept). The biosimilar, Erelzi (etancercept-szzs), was approved by the US Food and Drug Administration but has not launched in the US because of patent litigation. A US district court ruled against Sandoz and in favor of Amgen last year, but Sandoz is appealing the decision, with an appeals court hearing slated to begin on 4 March. Sandoz hopes to be the first to market in the US with a biosimilar version of Enbrel.

In the meantime, the company is focused on the launch of Ziextenzo (pegfilgrastim-bmez), a biosimilar of Amgen's Neulasta, which was approved by the FDA in November. *(Also see "Sandoz Is Satisfied With US Pegfilgrastim Start" - Generics Bulletin, 28 Nov, 2019.)* It is the third biosimilar of Neulasta on the US market, so the launch represents an interesting test case for how a multi-biosimilar market might unfold.

Sandoz is hoping to leverage its position in the market with Zarxio (filgrastim-sndz), a short-acting product and the first biosimilar to launch in the US, in 2015. With its longer history in the market, Zarxio has been one of the most successful biosimilar launches commercially in the US, having achieved a number one market share by volume three years after launch, according to Sandoz.

Lynch said Ziextenzo has already made some notable inroads when it comes to market access. "When we come to customers, we are a known entity," she said. "We've got a great reputation not only for the way we do business, but also the fact that we've got good quality reliability in terms of our supply chain, and that's really important when they are switching patients."

The company is also leveraging the commercial experience with Zarxio to invest fewer resources behind the launch. This is a critical element of being successful in biosimilars, an area that needs to function differently from the branded space to be profitable, Lynch explained.

"We have less resources behind pegfilgrastim at launch than we had with Zarxio because of course that path has already been carved now and we can just follow our footsteps," she said. "You have to be judicious about how you invest your money and be really clear at the time exactly about why you are doing this and to what end."

AN INFLECTION POINT FOR BIOSIMILARS

While the US biosimilar market has been slower to get off the ground than many players had anticipated, Lynch said biosimilars appear to be turning a corner commercially.

"I think we are at an inflection point now with the biosimilars in the US," Lynch said. The sheer number of new biosimilars hitting the market is helping to fuel momentum as payers and physicians gain experience with the products, she said. Several new biosimilars of drugs like Herceptin (trastazumab), Rituxan (rituximab) and Avastin (bevacizumab) have recently launched.

"It just means that everyone is gaining in confidence, whether it is from the payer side to the buy-and-bill side with how to make it work in your practice to the patients getting familiar with the products," she said.

Lynch also said payers are starting to broaden the market access to biosimilars. One of the big challenges for biosimilars has been going up against the high volumes, and thus high rebates, that come with long-standing mature brands. For example, Pfizer and Merck & Co. have struggled to make inroads with their respective Remicade (infliximab) biosimilars Inflectra and Renflexis because of Johnson & Johnsons's defensive rebating initiative for Remicade.

Lynch said payers appear to be trying to figure out the logistics to resolve the rebate wall hurdle because their own long-term financial forecasts include big savings from biosimilars, and that is motivating them to make changes.

"The conversations actually are not as difficult as you might imagine in some cases," she said. "There is a lot of pressure generally in the system that people need to do the right thing. There is so much discussion ongoing, especially in an election year, around the cost of health care and here is a solution in biosimilars that is available and not being used."

Some policy initiatives have been put forward in the US to support biosimilar uptake that Sandoz supports. One Lynch highlighted, which appears to have some bipartisan support, is a Medicare change that would increase reimbursement for biosimilars from an average sales price plus 6% to ASP plus 8% for five years. Another is a proposal by the Centers for Medicare and Medicaid Services that would allow plans to add a second preferred specialty drug formulary tier with lower cost sharing starting in 2021 to encourage uptake. *(Also see "Medicare Part D Plans May Add 'Preferred' Specialty Tiers To Lower Costs" - Pink Sheet, 6 Feb, 2020.)*

WHAT COMES NEXT?

Another area Sandoz is looking to make a big entry into is insulins. The company announced an agreement in December 2018 with the Chinese insulin supplier Gan & Lee to bring a portfolio of biosimilar insulins to market in the US, including insulin glargine, insulin lispro and insulin aspart.

"This is a space we want to play in," Lynch said, pointing to the high need for cheaper alternatives. The company has not disclosed a timeline for getting biosimilar insulins to market.

The FDA is in the midst of reclassifying insulins as biologics, along with some other protein products that were originally approved as drugs, which will open up the biosimilars pathway. *(Also see "Countdown To Transition: US FDA Says 91 Drugs Will Become Biologics In March 2020" - Pink*

Sheet, 27 Sep, 2019.) The transition, which has been in the works for years since it was required under the Biologics Price Competition and Innovation Act (BPCIA) in 2009, will finally go into effect on the 20 March. The change could have implications for some insulin products that have already been filed or approved by the FDA, and Lynch said she is watching closely to see if the agency reclassifies any of those products as interchangeable biosimilars.

Another area Sandoz may consider moving into via a partnership or licensing arrangement is in the oncology space beyond supportive care products like Zarxio and Ziextenzo, where Lynch said Sandoz has a portfolio gap it is looking to fill.

Sandoz markets versions of Rituxan outside the US but backed out of a plan to commercialize the cancer drug in the US in November 2018 after the FDA requested additional information on the application. The company said it believed the marketplace needs would be satisfied before it could generate the necessary data. *(Also see "Novartis Gives Up On Rituxan Biosimilar For US Market" - Scrip, 5 Nov, 2018.)*

More recently, the company announced in February that it will discontinue development of an Advair (fluticasone/salmeterol) generic, a small molecule drug combination that is considered complex because it is delivered through a device to the lungs. Sandoz had been working on the product for nearly 10 years but so far only one generic version of GlaxoSmithKline's Advair has reached the market, Mylan's Wixela Inhub. *(Also see "Mylan Launches Advair Generic Wixela At 70% Discount To GSK's Branded Drug List Price" - Scrip, 12 Feb, 2019.)*

Lynch said Sandoz is still interested in the respiratory therapeutic area because of the high bar to market and the big need in asthma and chronic obstructive pulmonary disease for affordable treatments.

"This is what we like, things that are really hard to do, because it means that few people can do it," she said. "We will have some hiccups along the way, but we will have successes." Working in biosimilars means acknowledging the higher costs and risks in development and mitigating those risks as much as possible, she said. "It's part and parcel with the business. You don't win on everything."

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Novartis And UK Launch Partnership On Groundbreaking Cardiovascular Prevention Trial

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A new partnership between Novartis AG and the UK government has been launched, to tap into the country's expertise in clinical trials and healthcare data, and to prove the value of Novartis' next blockbuster-in-waiting, cardiovascular treatment inclisiran.

The Swiss big pharma company acquired the RNA interfering therapy along with its developer The Medicines Company for $9.7bn last year, and is betting big on its potential to transform the treatment of cardiovascular disease.

Inclisiran has produced some impressive results in Phase III trials, showing it cut "bad" LDL cholesterol in patients with atherosclerosis, and is administered by injection just once every six months.

The opening of Novartis UK's new headquarters in White City, London. L-R: Vas Narasimhan, Novartis CEO; Mari Scheiffele general manager UK & Ireland, Novartis Oncology; health secretary Matt Hancock; Haseeb Ahmad, Managing Director, UK, Ireland and Nordics, Novartis Pharmaceuticals and country president, Novartis UK.

Novartis filed with the US Food and Drug Administration in December with approval expected later this year (with approval in Europe to follow that) but its biggest test will be cardiovascular disease prevention trial (CVOT) trials, which must prove compelling if the drug is to be the heart disease game-changer Novartis thinks it can be.

Meanwhile the UK, newly departed from the European Union, is keen to promote itself as a global destination for biopharma investment, and struck the deal with Novartis last year to prove its credentials.

Novartis is planning to make the UK its global center for a primary prevention study with inclisiran, building on the methods used to recruit 500,000 patients into the UK Biobank and to conduct ORION-4, the ongoing study for patients who have already had a heart attack or stroke.

The ORION-4 study will see the UK as the global trial co-ordinator, with Novartis working in partnership with the Nuffield Department of Population Health at Oxford University, the NHS and the National Institute for Health Research (NIHR) as part of this program.

The innovative collaboration between the pharma company and the country's national health system (NHS) also pioneers the use of a world-first, population health model to a large at-risk patient population with atherosclerotic cardiovascular disease.

The plan is that once the drug gains marketing approval, and presuming a positive recommendation by England's cost watchdog the National Institute for Health and Care Excellence (NICE), an ambitious proposed population-level agreement would commence.

This would provide access to treatment for secondary prevention in patients with atherosclerotic cardiovascular disease (ASCVD) as part of a program for those not reaching their LDL-C target on statins alone – something which the partners say could help to significantly cut deaths due to cardiovascular disease.

The plan was hatched last year by the UK's life science leader Sir John Bell with Novartis CEO Vas Narasimhan, and first unveiled at the J.P. Morgan healthcare conference in San Francisco in January.

They came together again on 11 February in London to launch the project, with Novartis also announcing investment in its digital health 'Biome' project, and with UK health secretary Matt Hancock on hand to officially open the company's new UK headquarters in West London.

"As a company working to improve and extend human life, we're optimistic about today's announcement and what this could mean in the ongoing battle against cardiovascular disease—the world's leading cause of death and disability. We see the UK, with its deep commitment to life sciences, as an attractive place to reimagine medicine," commented Vas Narasimhan.

The Novartis CEO says the potential of the NHS tie-up is considerable, with around 1.8 million patients in the UK who would be eligible from a secondary prevention standpoint from launch.

The real test will be the results of the outcomes study in 2024. If this proves the efficacy of inclisiran, Novartis believes there is a potential to further expand beyond this initial population.

But the partnership will not just be a test of Novartis's medicine, but also of the UK's ability to create a modern healthcare system and a pharma-friendly environment post Brexit.

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Strong Early Promise For Takeda 'Off The Shelf' CAR-NK Therapy

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The outcomes of a small Phase I/IIa trial with a novel type of chimeric antigen receptor (CAR) therapy are generating excitement from investigators and licensee Takeda Pharmaceutical Co. Ltd., given the potential practical benefits over existing CAR-T treatments.

The major Japanese firm last November entered in an agreement with the University of Texas's MD Anderson Cancer Center to develop cord blood-derived, CAR-directed natural killer (NK) cell therapies "armored" with interleukin-15, for B-cell malignancies and other cancers. *(Also see "Asia Deal Watch: Ambrx, NovoCodex Partner On Second ADC Candidate, For CD70-Positive Cancers" - Scrip, 6 Nov, 2019.)*

Results from an initial 11-patient trial in relapsed/refractory CD19-positive non-Hodgkin's lymphoma (six patients) and chronic lymphocytic leukemia (CLL; five patients) have just been published in the *New England Journal of Medicine* (2020; 382:545-553), and build on the company's optimism around the therapy (designated TAK-007) at its US investor day last year.

HIGH RESPONSE RATE

Patients in the trial had received three to 11 lines of prior therapy and nine were given a form of the CAR-NK therapy partially matched to individual HLA (human leukocyte antigen) type. There was no such matching for the other two, as allowed by protocol.

The single infusion involved three doses ($1x10^5$, $1x10^6$ or $1x10^7$ cells per kg) after lympho-depleting therapy (fludarabine and cyclophosphamide).

Eight patients (73%) responded, of which seven (four with lymphoma and three with CLL) had a complete response, with no evidence of disease at a median follow-up of 13.8 months. One CLL patient had remission of the Richter's transformation component but persistent disease.

Responses in all the eight patients were evident within a month and duration of response was confirmed out to one-year post-infusion, and five of the responding patients received discretionary post-remission therapy after the 30-day assessment.

Any side-effects were seen to be related mainly to the prior lympho-depleting therapy and no patients experienced cytokine release syndrome (a well-known risk with standard CAR-T therapy that can require specialist care), neurotoxicity or graft-versus-host disease, and there was no increase in inflammatory cytokines.

MD Anderson's lead developer of the CAR-NK platform, Dr Katy Rezvani, said investigators were "encouraged by the results" and that further larger trials are now being planned. At present, Takeda and the program's partners have said TAK-007 will move into multi-center pivotal studies in 2021.

MULTIPLE PRACTICAL BENEFITS

Promising efficacy and safety aside, the CAR-NK approach has a number of other important potential benefits over standard CAR-Ts.

As they are isolated from cord blood from healthy donors, the allogeneic NK cells can be prepared and stored in advance of therapy, independent of the receiving patient and thus allowing "off the shelf" use.

The lack of a need for HLA matching avoids the requirement in CAR-T therapies to make a "tailored" product for each individual patient.

This involves the more complex and time-consuming extraction and genetic modification of a patient's own T cells needed in existing CAR-T therapy, which can take weeks of manufacturing processes.

Novartis AG's Kymriah (tisagenlecleucel) and Gilead Sciences Inc./Kite Pharma Inc.'s Yescarta (axicabtagene ciloleucel) are already approved in a number of markets as anti-CD19 CAR-T therapies for various lymphomas.

"This may pave the way for a truly off-the-shelf product."

In the reported trial, the NK cells were transduced with a retroviral vector expressing genes encoding for the anti-CD19 CAR, "armored" with immunocytokine interleukin-15 (which improves proliferation and survival of the CAR-NK cells) and used inducible caspase 9 as a "safety switch" to trigger CAR-NK cell apoptosis with rimiducid in the event of serious side effects.

In addition, "Due to the nature of the [CAR-NK] therapy, we've actually be able to administer it in an outpatient setting," Rezvani said. Potential provision of the new CAR-NK immunotherapy in this or a community care setting would simplify considerably the hospital-based process required for current CAR-T therapies.

The researchers said they showed that more than 100 doses of CAR-NK cells can be produced from a single cord blood unit. This along with the minimal HLA matching requirements "may pave the way for a truly off-the-shelf product that could increase treatment accessibility for many more patients," they said in the *NEJM* article.

UP TO FOUR CANDIDATES

Under its deal with MD Anderson, Takeda has the exclusive rights to develop and commercialize up to four CAR-NK programs, including the CD19 therapy and B-cell maturation antigen (BCMA)-targeted CAR NK cells.

The CD19 (TAK-007) program has already been designated as the company's lead cell therapy candidate in oncology, R&D head Andy Plump has said.

The Japanese firm will be responsible for development, manufacturing and commercialization, and MD Anderson is eligible for undisclosed milestones and tiered sales royalties in addition to the upfront fee.

The newly reported trial was funded by The Leukemia & Lymphoma Society, MD Anderson's Lymphoma Moon Shot program and the US National Institutes of Health.

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Another Alzheimer's Setback As Roche And Lilly Drugs Fail

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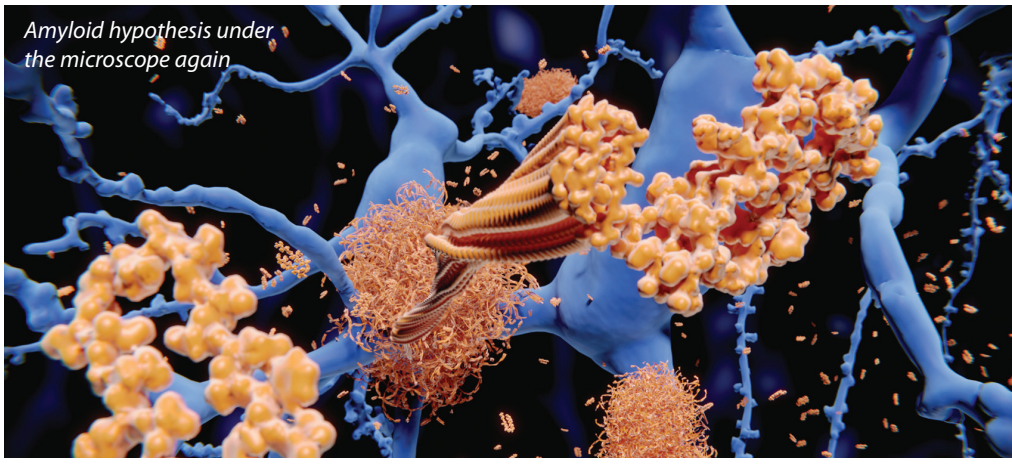
The theory that beta-amyloid (Abeta) is the main cause of Alzheimer's has taken yet another bashing after a closely watched trial evaluating Eli Lilly & Co.'s solanezumab and Roche's gantenerumab in people in the early stages of a rare, inherited form of the disease yielded disappointing results.



Amyloid hypothesis under the microscope again

The Phase II/III Dominantly Inherited Alzheimer Network Trials Unit (DIAN-TU) study run by Washington University evaluated the two drugs, which have both suffered failures in a variety of disease settings, in 194 people with autosomal dominant Alzheimer's disease who come from families that carry a genetic mutation that causes early-onset Alzheimer's dementia. Such people experience declines in memory and thinking skills starting in their 50s, 40s or even 30s and researchers noted that people who inherit the mutation were "all but guaranteed to develop symptoms at about the same age their parents did."

The participants were randomly assigned to receive solanezumab, gantenerumab or placebo and the initial analysis indicated that neither drug met the primary outcome of the study, the slowing of cognitive decline as measured by "multiple tests of thinking and memory." Details of DIAN-TU will be presented in April at the Advances in Alzheimer's and Parkinson's Therapies meeting in Vienna, Austria.

"Although the drugs we evaluated were not successful, the trial will move us forward in understanding Alzheimer's," said principal investigator Randall Bateman. He argued that the trial's innovative design, developed with a consortium of pharmaceutical companies, the National Institutes of Health, regulatory agencies and academic leaders, yielded new insight which can inform future research into the disease, including the more common form that typically strikes after age 65.

The results of the trial, which was conducted at 24 sites in Australia, Canada, France, Spain, the UK and the US, has not come as a great surprise,

given that the Alzheimer's space is littered with failures, not least for the two anti-Abeta antibodies used in the study. Investors had pretty much written off the chances for both subcutaneous gantenerumab and intravenous solanezumab but interest in the amyloid hypothesis was renewed at the end of last year when Biogen Inc. announced a stunning about-face to pursue US Food and Drug Administration approval for its previously discontinued Abeta drug aducanumab. *(Also see "An About Face As Biogen Says It Will File Aducanumab In Alzheimer's " - Scrip, 22 Oct, 2019.)*

Despite the DIAN-TU miss, Roche remains bullish about the prospects for its drug. Chief medical officer Levi Garraway argued that given the "experimental nature" of the study, "we are unable to draw firm conclusions about the impact of gantenerumab in autosomal-dominant Alzheimer's," which only accounts for less than 1% of all cases of the disease.

He added that "this outcome does not reduce our confidence in the ongoing Phase III GRADUATE clinical program." That consists of two large global Phase III studies in the broader population of people with disease that is not directly caused by gene mutations, sporadic Alzheimer's, and they are due to read out in 2022.

Roche noted that every person who received gantenerumab in DIAN-TU-001 started on a lower dose and only started titrating to a five-fold higher target dose halfway through the trial. However, the GRADUATE studies "have been designed from the outset to maximize exposure to gantenerumab, bringing all patients to target dose with minimal or no dose interruption within the study period," the company added.

Analysts at Jefferies issued a note in 10 February saying that while DIAN-TU was a small trial "and initially used perhaps suboptimal doses," the trial "again suggests the ongoing gantenerumab Phase III studies are high risk." They added that although the Scarlet RoAD Phase III trial evaluating subcutaneous gantenerumab in prodromal Alzheimer's was stopped early for futility, "subsequent exploratory analyses suggested a dose-dependent effect on clinical and biomarker endpoints, indicating that higher dosing could be required for clinical efficacy. Data from open-label extension studies have lent support to this thesis." *(Also see "Open-Label Extensions The Key To Gantenerumab Success, Stresses Roche" - Scrip, 26 Apr, 2019.)*

As for Lilly, the firm said that it would not pursue a regulatory submission for solanezumab for autosomal dominant Alzheimer's, but stressed that the outcome of DIAN-TU would not impact the ongoing solanezumab Anti-Amyloid Treatment in Asymptomatic Alzheimer's (A4) study. That trial is in older individuals who have evidence of amyloid in their brains, but do not show symptoms of memory impairment. *(Also see "Lilly To Bring Forward Alzheimer's Readout " - Scrip, 19 Dec, 2019.)*

Analysts at Mizuho Securities noted that while Alzheimer's had been "an extremely difficult disease for successful drug development and we do not have any revenues for solanezumab in our Lilly model, we believe some investors had been cautiously optimistic on a positive outcome." However, "we were not optimistic on this trial given it was a relatively small trial and in a more severe form of the disease."

In addition, the broker also pointed out the higher dose was not implemented until mid-late 2017, after an earlier solanezumab trial failed, "and it turns out only about 25% of the dosing in the trial was done with the higher dose." Mizuho said that while the news was a disappointment, "we are encouraged by the multi-pronged approach Lilly is taking in Alzheimer's," citing donanemab, a humanized IgG1 monoclonal antibody targeting N3pG-amyloid beta for which Phase II data are expected late 2020 or early 2021, and zagotenemab a tau antibody, Phase II results for which should read out next year.

ANY IMPACT ON BIOGEN'S ADUCANUMAB FILING?

Now the focus will return to Biogen and partner Eisai Co. Ltd.'s aducanumab. Observers will be keen to see whether the DIAN-TU blow to the amyloid hypothesis will have much of an influence on how the FDA responds to the submission of the conflicting clinical trial data on the controversial drug that is set to land on the agency's desk in the near future. *(Also see "Biogen Is Putting Its Money Where Its Mouth Is – Behind The Launch Of Aducanumab " - Scrip, 30 Jan, 2020.)*

Evercore ISI analyst Umer Raffat does not think there will be any effect. He said in an investor note on 10 February that the readout "does not change our opinion of Biogen's aducanumab approval odds," adding that while the aducanumab data "has major issues…I do think FDA approval is likely."

William Blair analyst Matt Phipps issued a note saying that while the DIAN-TU results are discouraging for the amyloid hypothesis, "at this point we believe the effect on aducanumab will be minimal given the regulatory review will come down to the FDA's interpretation of the subgroup analysis from the ENGAGE and EMERGE trials and any political pressures that come into play during the review process."

He added, "Biogen will argue aducanumab has shown a different clinical profile than solanezumab and gantenerumab across all studies to date, and therefore no comparisons can be made. We do believe solanezumab has a much different binding profile and mechanism of action, and therefore has little read-through to aducanumab, but gantenerumab, if dosed properly, has potential to result in similar target engagement in the cerebrospinal fluid."

Over at Baird, analyst Brian Skorney pulled no punches. In a 10 February note, he said, "We now need more than two hands to count the number of times a beta-amyloid antibody has failed to slow Alzheimer's progression in Phase III, as the DIAN-TU study failed to benefit from a more homogeneous patient population despite the administration of much higher than previously tested doses over longer durations than ever explored." He noted that the EMERGE trial "is the only result with an argument of positivity and we would dispute it is even that."

The negative results seen for solaneuzumab and gantenerumab, as well as Roche and AC Immune SA's crenezumab and Pfizer Inc. and Johnson & Johnson's bapineuzumab nearly eight years ago "are just more reason to believe EMERGE's faux-positivity is just random noise," Skorney concluded. *(Also see "AC Immune/Roche Drop Crenezumab After Phase III CREAD Alzheimer's Failure" - Scrip, 30 Jan, 2019.)*

Published online 10 February 2020

Fennec Nears Market For Chemo-Induced Hearing Loss In Children

KEVIN GROGAN kevin.grogan@informa.com

Fennec Pharmaceuticals Inc. has completed submissions on both sides of the Atlantic for Pedmark, a drug to prevent hearing loss in pediatric cancer patients caused by chemotherapy.

The Research Triangle Park, NC-based group has completed its rolling submission to the US Food and Drug Administration and a filing with the European Medicines Agency for Pedmark, a unique formulation of sodium thiosulfate, to counter the ototoxicity induced by cisplatin chemotherapy in cancer patients up to the age of 18. Cisplatin is a very effective treatment but around two thirds of children treated with the drug are left with some hearing loss; while cisplatin is rapidly removed from the body following treatment, it is retained in and damages the cochlea.

Many children on platinum-based chemo need hearing aids after

The submissions are based on two Phase III trials. In the most recent, the SIOPEL-6 study published in the *New England Journal of Medicine* in June 2018, 109 children with hepatoblastoma were treated with cisplatin and then, six hours later, with either Pedmark or placebo. Of the children treated with cisplatin alone, 63% suffered hearing loss, compared with 33% of children given the combination, a 48% risk reduction.

Armed with data from an earlier 2016 trial, the Children Oncology Group ACCL0431 study, and following discussions with the FDA in December 2018, Fennec initiated a rolling new drug application. However the US submission hit a bump in March 2019 when the company announced that its filings were delayed due to bringing a new substance manufacturer onboard.

Fennec believes its application should now satisfy the FDA which has a 60-day review period to decide whether the Pedmark NDA is acceptable for filing. It has already been granted orphan drug, breakthrough therapy and fast track designations from the agency so is expected to get a priority review and a prescription drug user fee act (PDUFA) action date in the third quarter of 2020.

CEO Rosty Raykov said the completion of these regulatory submissions to the FDA and EMA (which has approved a pediatric investigation plan) "are the culmination of many years of hard work." He added that "we are well underway with commercialization readiness activities to support the potential launch of Pedmark and our transition to becoming a commercial-stage organization."

News of the submissions has gone down well with the investment community. Analysts at Wedbush issued a note on 11 February saying, "We would expect a quick turnaround to NDA acceptance [as the] FDA was only waiting on manufacturing and stability testing data."

They added that "we fully expect approval around August, and an initial, limited-scale commercial launch early September." Wedbush believes that the key catalyst for Fennec remains the eventual label for Pedmark "and whether it is broad (including all localized pediatric cancers treated with cisplatin-based chemotherapy) or narrow (only a subset of tumors treated in the clinical trials)."

Analysts at Laidlaw & Co described Pedmark as "a highly de-risked asset on the regulatory side. This, coupled with the significant unmet medical need and the lack of competition, comprise three pillars of its key value proposition." In the US and Europe, it is estimated annually that over 10,000 children may receive platinum-based chemo and many of them require lifelong hearing aids; only "expensive, technically difficult and sub-optimal cochlear implants have been shown to provide some benefit," Fennec noted.

For Europe, Laidlaw estimated the potential approval and product launch could occur around the second half of 2021 depending on how discussions for potential partnering are going. In the US, Fennec will launch Pedmark by itself, "given the small number of reps needed and relatively concentrated target physicians."

In September, Fennec appointed Shubh Goel as chief commercial officer, saying she was "a proven leader with nearly 20 years of global commercial experience successfully building and executing the launch of several oncology products." She joined from Odonate Therapeutics LLC and previously served in multiple leadership positions at Celgene Corp., where she oversaw the US launch of Abraxane (nab-paclitaxel) in pancreatic cancer.

The timing of the submission in the US has been key for Fennec's financial future. In February it entered into an agreement with Bridge Bank which agreed to loan $12.5m to the company but the loan was contingent on Pedmark getting FDA approval by no later than 30 September this year.

Getting priority review from the agency should mean that Fennec will meet that deadline. The firm ended the third quarter of 2019 with $15.2m in cash and no debt.

Published online 12 February 2020

Keytruda Closing In On First-Line Metastatic Triple-Negative Breast Cancer

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A closely watched clinical study involving Merck & Co. Inc.'s anti-PD-1 therapy Keytruda (pembrolizumab) has reported promising results at an interim analysis, in combination with chemotherapy as a first-line therapy for metastatic triple-negative breast cancer.

The pivotal Phase III KEYNOTE-355 study met one of its dual primary endpoints, improving progression-free survival in metastatic triple-negative breast cancer in patients whose tumors express PD-L1 with a combined positive score (CPS) of >10.

The results follow positive early data from KEYNOTE-522 involving the use of pembrolizumab in addition to chemotherapy in the neoadjuvant/adjuvant setting in early triple-negative breast cancer patients reported last year. However, also reporting last year was a negative study of pembrolizumab when used as a second- or third-line monotherapy in such patients.

Pembrolizumab has considerable ground to make up with Roche's checkpoint inhibitor, Tecentriq (atezolizumab), which was approved last year in the US and EU for use in combination with nab-paclitaxel for the treatment of triple-negative breast cancer, based on the results of the IMpassion130 study.

Pembrolizumab has considerable ground to make up with Roche's checkpoint inhibitor, Tecentriq.

Nonetheless, the results go some way to dispel the disappointment earlier this year from mixed top-line final Phase III results from KEYNOTE-604 in small cell lung cancer (SCLC).

CLINICALLY MEANINGFUL

In KEYNOTE-355, pembrolizumab was used in combination with either nab-paclitaxel, paclitaxel or gemcitabine/carboplatin, and was associated with a statistically significant and clinically meaningful improvement in PFS compared with chemotherapy alone, Merck reported, although the company did not go into further details.

Following an open-label part one of the study evaluating tolerability in 30 patients, part two of KEYNOTE-355 enrolled 847 patients who received either pembrolizumab 200mg iv, or placebo, on day one of each 21-day cycle of therapy with either nab-paclitaxel, paclitaxel, or gemcitabine/carboplatin. Triple-negative breast cancer tumors test negative for estrogen receptors, progesterone receptors and human epidermal growth factor-2 (HER2), and the condition is diagnosed in around 15-20% of breast cancer patients.

The study will now continue to evaluate the other dual primary endpoint, overall survival.

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Global Catastrophe Or Passing Nuisance? Pharma's Coronavirus Views

IAN HAYDOCK ian.haydock@informa.com

The main issue with the ongoing coronavirus outbreak is that even global health experts remain unclear on how things are going to play out in terms of disease spread and severity. Given all the unknowns over whether the now officially named SARS-CoV-2 virus will go fully global or fizzle out, pharma companies are also having a hard time predicting the precise future impact.

Specific comments on how the outbreak, originating from the Chinese city of Wuhan, are affecting and may hit business were thus completely absent at many company results briefings, where the issue was also not a major focus of analysts in Q&A sessions. Of those firms that did face questioning or which chose to address the issue, the responses were mixed.

CHINESE EXPOSURE

Perhaps surprisingly, the most vocal were the European majors, some of which now have substantial business exposure in the Chinese market. If there is one overriding message though, it is that the focus is on adapting to ensure business as usual as far as possible, while planning for contingencies.

With the help of *Scrip* global editorial team members Kevin Grogan, Sten Stovall, Andrew McConaghie, Vibha Ravi, Anju Ghangurde, Alex Shimmings and Jung Won Shin, who have scoured briefings and spoken directly to companies, here is a collation of corporate coronavirus sentiment as the COVID-19 disease spread continues to evolve.

EUROPEAN FIRMS STRESS CONTINUITY

UK-based AstraZeneca PLC, which now relies on the China market for around a fifth of its global sales, said in its 14 February call that it still expects to outperform in emerging markets including China, despite the impact of the outbreak.

Ruud Dobber, executive vice-president of the Biopharmaceuticals Business, said that despite the impact of the coronavirus in China, "we generally anticipate to continue outperforming the long-term trends with every sales growth in the emerging markets to be as high as low double-digit percentage per year." He pointed in particular to the "resilience of the [company's] leadership oncology" in China.

Commenting more specifically on China, Leon Wang, EVP for Emerging Markets including China, added: "I think the situation outside Wuhan, Hubei province is improving. I think we cannot speculate how long would this epidemic last. I think it will still be the next few months."

As for the impact on the company, his view was that, "Right now, the impact is mainly our sales people cannot easily visit the hospitals and access the health care professionals because doctors, especially some of the specialty, are focusing on fighting the epidemic. So I think all these disruptions are quite temporary.

"And patients now really, instead of visiting hospitals, they go to the pharmacy to refill prescriptions, and also they go online to consult their doctors and also to get their prescription refills."

Given recent positive developments for the company in terms of reimbursement inclusion, approvals and its strength in rural community hospitals, digital promotion and online pharmacy collaboration, the China subsidiary is aiming to minimize business disruption while ensuring employee safety. "So even during the epidemic…the logistics side, supply chain side, manufacturing, the head office people and a lot of functions are really working starting from the beginning of last week [6 February]," Wang noted.

The UK-based firm's China sales for the year surged by 29% to $4.88bn, accounting for 21% of the group total. CEO Pascal Soriot noted at the briefing that "we anticipate another year of strong growth" despite the coronavirus situation. "We anticipate total [global] revenue to increase by high-single digit to a low-double digit percentage."

> "Right now the impact is mainly our sales people cannot easily visit the hospitals" – Leon Wang

Sanofi CEO Paul Hudson's comments to investors on 6 February seemed applicable to companies in general. He said "It is difficult to predict what will happen over the next few weeks and I think it would be a bit naïve of us to say 'no disruption' or try and put a percentage around it.

"We feel well placed, we don't see business risk, but of course as it evolves, we're just going to have to recalibrate that. I don't think any company has a choice on that. So we'll update as we go along."

On 6 February, Lundbeck Inc.'s chief financial officer Anders Götzsche said: "Following the coronavirus outbreak, Lundbeck sees increased uncertainty on product distribution and sales in China for 2020. China is Lundbeck's second biggest market and the potential impact is difficult to quantify at this point of time."

Revenues are around DKK1bn ($147m) a year in China, he noted. "We have seen no impact so far, but it's also fair to say that our employees, we take their safety first and therefore they're working from home like many other companies."

CEO Deborah Dunsire added that many Lundbeck brands "are promotionally sensitive and when our sales force is not in the field, we believe it will have some impact."

Another Denmark-based company, Novo Nordisk AS, had executive vice-president and head of International Operations Mike Doustdar say during a 5 February Q4 analyst call: "The main priority is to protect the health of our employees and the public. Until Monday [10 February] we are working from home and not visiting the physicians and the hospitals. Hospitals are geared on trying to solve the coronavirus and chronic disease treatment has become priority number two right now.

"We have to see how long this situation continues before we can put some impact on it. In terms of manufacturing and supply chain, we right now feel comfortable that we can continue doing that again as this extra week of vacation [after Lunar New Year] is over. So for the time being, it's business as usual, but we're watching it very carefully."

API SUPPLIES WORRY INDIAN FIRMS

Given that two-thirds by value of its total API imports come from China, the Indian pharma industry is facing a difficult situation if China's factories remain below full production for several months, despite having two to three months of inventory on hand.

Investors quizzed managements of several leading Indian firms on the worrying and long-standing dependence for APIs/intermediates on China in the wake of the SARS-CoV-2 outbreak. Most frontline Indian firms, which appear to have stocks to tide over the supply crunch for some time, are keeping close watch on the evolving situation.

Cipla Ltd.'s global CEO and managing director, Umang Vohra, said on the firm's Q3 earnings call on 5 February that a lot of the pharma value chain is linked to China not just for the company, but for the entire pharmaceutical industry.

"A lot of us in the pharmaceutical industry have some stock cover available. But I think if this coronavirus thing continues for more than a month or 45 days, that will begin to create a huge amount of issues for the pharma sector, for those supplies which are dependent on China," Vohra said. But he added that "not everything" is dependent on China.

Others also underscored the overall China link. Sun Pharmaceutical Industries Ltd.'s founder and managing director Dilip Shanghvi referred to the firm's high dependence on the country for intermediates for its API business. "In our formulation business, our dependence on China would be relatively lower. But to some extent many of the raw materials, which we may be buying in India may have dependence on the Chinese intermediate. So, we think we are buying from India, but there is a China link," Shanghvi said on Sun's third-quarter earnings call on 6 February.

But he added that Sun believes the geography in which the majority of the pharma manufacturing sites are located

(in China) are physically different from the centers where coronavirus is a bigger challenge. "So hopefully, we will not have any significant impact. But...we are not getting any reliable and dependable information. But we carry some 'significant inventory' for most of the raw material as well as intermediate that we consume," the executive explained in response to an analyst's question.

Sun's chief also noted that, in general, there are some raw materials where industry's dependence on China is almost 100% - for instance in the case of azithromycin it would likely be around 80-90% - and penicillins and cephalosporins too have a significant dependence on China.

Shanghvi maintained that the current spurt in prices of some finished goods as reported in the local press is not justified and "only speculated buying, which would have raised prices."

Among other Indian firms, Lupin Ltd. executives said in a 6 February results briefing that "We buy only a couple of APIs from China and certainly buy some intermediates specifically for antibiotics like cephalosporins. Based on our inventories and what we have in WIP [work-in-progress] we don't see a disruption in this quarter if the situation sorts out in the next few weeks."

Unfortunately, they added, "there is no visibility on shipments because obviously the country is in a state of lock-down. If the situation eases out in the next three to four weeks we will be able to manage without any significant disruption. If it is three to four months there will definitely be a disruption in some APIs specially for Rest of World geographies."

The company noted that Penicillin G is one of the key supplies potentially affected and that "everybody buys from China" and so there would not be the ability to respond to acute shortages very quickly. "Right now we're good on supplies but it can't continue indefinitely," the company cautioned.

Zydus Group's Cadila Healthcare Ltd. said on 5 February that: "On the API front we don't have a significant exposure to China because a lot of our APIs are backward-integrated or sourced from other markets so we don't see a major impact on APIs, but we are still evaluating the impact on the intermediates sourcing because they may get affected in the future. Inventory situation depends on the molecule, but we are covered from 60-90 days."

LOW EXPOSURE FOR JAPAN?

Despite having at the time of writing the second-highest number of cases of COVID-19 (the official name of the disease caused by SARS-CoV-2) globally – albeit mainly confined to a visiting quarantined cruise ship – pharma companies in Japan appeared generally unconcerned about potential business impact at the time of their early February quarterly briefings. (These were mostly third quarter, given the standard fiscal year end of 31 March.)

Generally, most pharma firms in the country have a relatively low exposure to China as a market, given that the main strategy historically has been to build strength in the US and Europe. For instance, Asia as a whole (mainly comprising China) accounts for only around 5% of post-Shire Takeda's global revenues.

Even so, Takeda Pharmaceutical Co. Ltd. faced questioning at its 4 February results briefing on the possible impact on its ex-Shire China plasma-derived therapy (PDT) business of local donors staying away from collection centers.

However, CEO Christophe Weber clarified that "We are not collecting plasma in China…so we will not be impacted by any diminished capacity."

The company is importing albumin into the country but Weber conceded that "we don't know what the impact on demand will be" from the outbreak. "We have a limited exposure in China for our PDT business," he stressed.

Among other firms, in its investor call on 31 January, Eisai Co. Ltd. remained generally bullish on its prospects in China, where its sales surged by 32% in the nine months, to JPY65.6bn (around $600m). It highlighted growth and launches and did not touch at all on business risks from the outbreak.

Answering a question on the Wuhan outbreak at its results briefing, Roche-owned Chugai Pharmaceutical Co. Ltd. confirmed at its 31 January annual results briefing it is "not developing treatments nor vaccines for the new coronavirus" but - like most companies - is taking steps to protect employees.

> "If this coronavirus thing continues for more than a month or 45 days, that will begin to create a huge amount of issues for the pharma sector" – Umang Vohra

SOUTH KOREA PLAYING SAFE

Hanmi Pharmaceutical Co. Ltd. told *Scrip* on 14 February that its Chinese subsidiary Beijing Hanmi is mainly producing essential drugs such as drugs for cough, cold and antibiotics, and is operating its factory under Chinese government's rules.

The company, in common with most, is thoroughly checking for any symptoms of coronavirus infection in its local employees and if anyone has these they should report and self-quarantine in principle. So far, no employees have entered self-quarantine, although marketing staff in China are doing their jobs mostly online from home.

Hanmi's holding firm Hanmi Science (whose CEO also heads the Korean biotech industry association) is currently discussing possible new drug development with association member companies but no details are available yet.

To date, close to 70,000 infections with SARS-CoV-2 have been confirmed in China and around 500 in 30 other countries globally, with around 1,000 deaths in total.

Published online 17 February 2020

Coronavirus Notebook: China Focuses On Antivirals As Death Toll Passes SARS: **https://bit.ly/39z0LIC**

Coronavirus Notebook: China Parachutes Top Physicians To Wuhan, Allows WHO Expert Visit: **https://bit.ly/2SxMLJw**

Stockwatch: Coronavirus Takes A Bite Out Of AstraZeneca's Guidance, GSK and AbbVie Get Spinning

ANDY SMITH

The first month of fourth-quarter 2019 earnings season was looking reasonably benign until AstraZeneca PLC owned up to the downside of strong emerging market sales that included China in its results. AstraZeneca is the first to warn that growth can be vulnerable when coronavirus depresses the Chinese economy.

While the first month of the fourth quarter of 2019 earnings season had a few more misses than hits, nothing cast a cloud over the pharmaceutical sector at the start. A case in point was Allergan Inc. reporting at the start of the fourth week. Allergan's impending $63bn acquisition by AbbVie Inc. made its financial results largely academic. Nevertheless, Allergan's revenues of $4.35bn rose by just under 7% in a year and easily beat analysts' consensus estimates of $4.10bn. Allergan's adjusted earnings per share (EPS) of $5.22 also trounced estimates of $4.61 and were helped by R&D expenses falling by 4.9%. The key revenue driver, Botox (onabotulinumtoxinA), grew 7.9% year-on-year generating $1.02bn in the fourth quarter.

Allergan reports Botox sales in both cosmetic and therapeutic segments and AbbVie announced plans to move aesthetic Botox into a separate business after the merger during its results presentation the previous week. *(Also see "Countdown To The Allergan Merger, And More From AbbVie's Q4 Earnings" - Scrip, 7 Feb, 2020.)* A separate aesthetics business unit in a pure-play big pharmaceutical company like AbbVie may be an odd choice and perhaps the announcement was a prelude to yet another spin-off the like of which have spun out of the results announcements of Pfizer Inc., Merck & Co. Inc. and GlaxoSmithKline PLC this earning season. Allergan's results announcement did the company no harm as its stock price only finished down 0.9% for the week against the NYSE ARCA Pharmaceutical Index's (DRG) 1.6% fall.

Investors were probably spot on in being concerned about these costs.

GSK: NOT TOUGH ON SPIN-OUTS BUT TOUGH ON THE COSTS OF SPIN-OUTS

The results season overall seems to lend itself to an exercise in compare and contrast: pharmaceutical companies look to be competing to do some of the same things, while also making some opposite moves.

Allergan's 20% reduced R&D expense in 2019, for example, was mirrored by GSK's proposed 16% increase in 2020. A potential spin-out of AbbVie's yet-to-be-formed aesthetics business would be similar to GSK's proposed spin-off of its Consumer Healthcare joint venture. Unlike Allergan, GSK's £33.8bn revenues in 2019 were in line with analysts' estimates but its 4% increase in 2019 EPS to 123.9p missed consensus estimates of 125.0p. The maintenance of GSK's dividend did nothing to support the stock price in the face of the announcement of the two-year £2.4bn cost of splitting of the Consumer joint venture with Pfizer. It was almost certainly this hefty separation bill that led to GSK's stock price falling 4% that day.

The management consultants and investment banking fees incurred during the separation will not be cheap, nor will the costs of a new management team and board that sign off on those invoices so there may be an element of cumulative back-scratching there. But as those of us who worked in the predecessor company SmithKline know, there is virtually no overlap in manufacturing, R&D and commercialization infrastructures between Pharmaceutical and Consumer divisions so investors were probably spot on in being concerned about these costs. In a similar move to AbbVie, GSK also announced that its prescription dermatology business, Stiefel – which has always been a slightly odd bedfellow – was under "strategic review". The costs and timelines for this particular move have yet to be disclosed.

ASTRAZENECA'S GUIDANCE CATCHES CORONAVIRUS

The UK's two largest pharmaceutical companies GSK and AstraZeneca often report their financial results in the same week

TURN TO PAGE 23

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

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

PIPELINE WATCH, 7–13 FEBRUARY 2020

Event Type	Lead Company/Partner	Drug Name	Indication	Comments	Change To LOA (%)	LOA (%)
Phase III Updated Results	Protalix BioTherapeutics/Chiesi	pegunigalsidase alfa	Fabry's Disease	BRIDGE; Improved Kidney Function	0	63
Phase III Top-Line Results	Myovant Sciences Ltd.	relugolix combination	Uterine Fibroids	LIBERTY Ext; Met Primary Endpoint	0	79
Phase III Top-Line Results	Crescita Therapeutics, Inc.	MiCal 1	Psoriasis	Met Primary Endpoint	0	59
Phase III Top-Line Results	Merck & Co., Inc.	Keytruda (pembrolizumab)	Breast Cancer, Metastatic Triple-Negative	w/chemo, KEYNOTE-355; Met Primary Endpoint	0	45
Phase II/III Top-Line Results	Roche Holding AG	gantenerumab	Alzheimer's Disease, Inherited Early-Onset	DIAN TU-001; Missed Primary Endpoint	-3	39
Phase II/III Top-Line Results	Eli Lilly & Company	solanezumab	Alzheimer's Disease	DIAN TU; Missed Primary Endpoint	-1	16
Phase II/III Top-Line Results	Orphazyme A/S/CytRx	arimoclomol	Sporadic Inclusion Body Myositis	Encouraging Results	0	59
Phase III Trial Initiation	Laboratoris Sanifit S.L.	SNF472	Calciphylaxis In Kidney Disease	CALCIPHYX; Combined With Hemodialysis	34	47
Phase III Trial Initiation	Arcutis Biotherapeutics, Inc.	ARQ-151 (roflumilast) topical	Plaque Psoriasis	Open-Label Extension Study	-	-

Source = Biomedtracker; LOA = Biomedtracker's opinion on likelihood of approval.

CONTINUED FROM PAGE 21

but with AstraZeneca's fourth-quarter 2019 report coming just over a week after GSK's, AstraZeneca was probably hoping to miss the market fall-out that accompanied GSK's separation cost announcement. AstraZeneca's total revenue increased 4% to $6.66bn in the fourth-quarter of 2019 compared with the fourth-quarter of 2018, but missed analysts' estimates of $6.71bn. In addition, the 20% total revenue growth that was lauded as the turnaround point at the end of the third-quarter 2019, drastically dipped in the three months to December 2019. AstraZeneca's full-year core EPS of $3.50 was unchanged from 2018 but also missed analysts' estimates of $3.57. The externalization revenue that results from selling off cash-generative but older pharmaceutical assets was also less supportive than usual in the last quarter of 2019, falling 36% to $414m. *(Also see "AstraZeneca Returns To Growth, But Coronavirus Likely To Hit China Revenues" - Scrip, 14 Feb, 2020.)*

AstraZeneca has a class-leading oncology product in its PARP inhibitor Lynparza (olaparib) for ovarian cancer which not only reached blockbuster status for the first time in 2019, but also put into the shade GSK's Zejula (niraparib). Zejula was the main reason for GSK's $5.1bn acquisition of Tesaro Inc. but generated revenues of £66m in the quarter, barely up from £64m in the third quarter of 2019.

AstraZeneca's stock price was holding its own with the DRG index in the first four days of the week before its results announcement on the morning 14 February, but subsequently ended the week down 4%. The reason for this reversal was paradoxically the other star of AstraZeneca's results announcement – its 29% and 25% revenue growth in China in the year and fourth quarter, respectively.

China is AstraZeneca's fastest-growing region and comprises 60% of its emerging market sales, so when AstraZeneca warned that their guidance assumed an "unfavourable impact from China lasting a few months as a result of the coronavirus" the market naturally assumed a greater impact. Moreover, the big pharmaceutical companies that have already guided for the full year 2020, and those who have yet to report, will have no choice than to follow AstraZeneca's lead. Pharma firms are not the only multinational companies with significant exposure to China and if AstraZeneca's early warning turns out to last for more than for a few months, we may be in for a coronavirus-induced earnings recession in 2020.

Andy Smith gives an analyst and former investor's view on life science companies. He joined the independent research house Equity Development in October 2019 having previously been an analyst at Edison group and a Senior Principal in ICON PLC's Commercialization, Pricing and Market Access consulting practice. Smith has been the lead fund manager for four life science–specific funds, including 3i Bioscience, International Biotechnology and the AXA Framlington Biotech Fund, was awarded the techMark Technology Fund Manager of the year for 2007 and was a global product manager at SmithKline Beecham Pharmaceuticals.

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APPOINTMENTS

Executive	To Company	New Role	From Company	Previous Role	Effective Date
Kenji Hashimoto	Crescendo Biologics Ltd	Chief Medical Officer	Roche	Associate Clinical Director	3-Feb-20
Joel W. Beetsch	Eisai Inc	Vice President, Corporate Affairs	Celgene Corp	Vice President, Corporate Affairs/Patient Advocacy	3-Feb-20
Scott R. Steuart	Eisai Inc	Vice President, Market Access	Sanofi	Vice President, Specialty Pharmacy, Trade and Retail, Market Access	3-Feb-20
David Morris	Enterprise Therapeutics Ltd	Chief Medical Officer	Novartis Venture Fund	Managing Director	10-Feb-20
Theresa Heggie	Freeline Therapeutics	Chief Executive Officer and Director	Alnylam Pharmaceuticals	Head, CEMEA and Senior Vice President	4-Feb-20
Bruce Goldsmith	Passage Bio	Chief Executive Officer	Deerfield Management	Venture Partner	28-Jan-20
Rajiv Patni	Portola Pharmaceuticals Inc	Chief Medical Officer and Executive Vice President	Adamas Pharmaceuticals	Chief Medical Officer	3-Feb-20

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

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