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The End Is Nigh For Mylan, But How Different Will The New Company Be?

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Mylan NV has a long history in the generic pharmaceutical market, maintaining its independence while plenty of other mid-sized specialty generic peers were absorbed into larger corporations. Now the Mylan story draws to an end with the company's planned merger with Pfizer Inc.'s off patent Upjohn business and the creation of a new company.

Mylan's evolution into one of the top generic drug companies in the world has been a roller coaster of highs and lows. For investors, the farewell is touched with some relief.

It's no big surprise that a new corporate name will be unveiled after Mylan is merged with Pfizer's off-patent Upjohn business in mid-2020, as the companies announced on 29 July. Between generic drug price fixing charges filed against Mylan by the Department of Justice, ongoing manufacturing setbacks at its plant in Morgantown, West Virginia, exposure to opioid litigation and the gloomy cloud cast over the Mylan name by its handling of EpiPen pricing, there are plenty of reasons why fresh branding may be better received by investors.

Mylan was founded in White Sulphur Springs, West Virginia in 1961 and went public in 1973. Over the last decade, Mylan grew into a top generic drug manufacturer and top 25 pharmaceutical player through M&A, even as it fended off what now looks to have been a very attractive acquisition attempt by rival Teva Pharmaceutical Industries Ltd. for $40bn in 2015.

GROWTH THROUGH M&A

Mylan acquired Merck KGaA's generic drug business for $6.7bn in 2007, a pivotal deal that also gave the company the eventual blockbuster EpiPen (epinephrine). A series of acquisitions from 2014 to 2017 built out the company as Mylan sought to diversify outside of the challenging US generics market, both geographically and through the portfolio mix.

The company acquired the non-US established products business of Abbott Laboratories Inc. in 2014 for $5.3bn, a deal orchestrated in part to move the company outside the US to take advantage of ex-US corporate tax incentives. Through that deal, Mylan redomiciled from Pennsylvania to the Netherlands.

Mylan acquired the Indian women's health company Famy Care Ltd. for $750m in 2015, the topicals/injectables firm Renaissance Pharma Inc. for $950m and the Swedish generic drug company Meda AB for $9.9bn in 2016. *(Also see "Mylan Turns To Meda In Sweden For Open Door Into Consumer Market" - Pink Sheet, 15 Feb, 2016.)* That year, it also partnered with Momenta to develop six biosimilars, strengthening its position in complex biologics gained through an earlier partnership with Biocon Ltd..

By 2016, Mylan generated $11.08bn in sales, but that growth stalled. In 2018, Mylan generated $11.43bn.

EPIPEN PRICING: A CLOUD THAT CAST A LONG SHADOW

The years-long price hikes on the life-saving allergy rescue medicine EpiPen were one problem, erupting into public out-

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Collaborates with Sensyne Health (p13)

from the editor

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Following on from last week's news of Pfizer merging its established products arm Upjohn with Mylan, we bring you further analysis of the businesses behind the headlines. For a review of Mylan and its challenges over recent years, as well as consideration of what is to come, see cover story; turn to p5-6 for thoughts on the future of Upjohn's recently opened global headquarters in Shanghai. Mylan's domicile is set to move from the Netherlands to Delaware, US, but *Scrip*'s China reporter Brian Yang asks if broader geographical shifts are in store.

Most big pharma companies have now reported their results for the second quarter. The latest US drug pricing proposals are piling pressure onto firms already challenged by price squeezes outside the world's biggest pharma market (see p10-12 and p17). Soaring sales of the PD-1 inhibitor Keytruda helped lift Merck & Co out of the drug pricing drag on sales. But when it comes to M&A of the significant scale we have seen with Pfizer/Mylan, Takeda/Shire, Bristol-Myers Squibb/Celgene and AbbVie/Allergan, big pharma execs generally held back from declaring a desire to do a mega-merger, emphasizing rather their interest in "bolt-ons". As for Takeda, it says it is progressing well with integrating Shire and reported a strong start to its fiscal year (p8 & p9).

At the other end of the biopharma spectrum, Mandy Jackson dives into venture capital financing, with an interview with Vida Ventures, which has drawn much of its senior talent from Kite Pharma and has just raised more biotech investment cash (p14-16).

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Honjo, Ono Remain At Loggerheads As Opdivo Dispute Simmers

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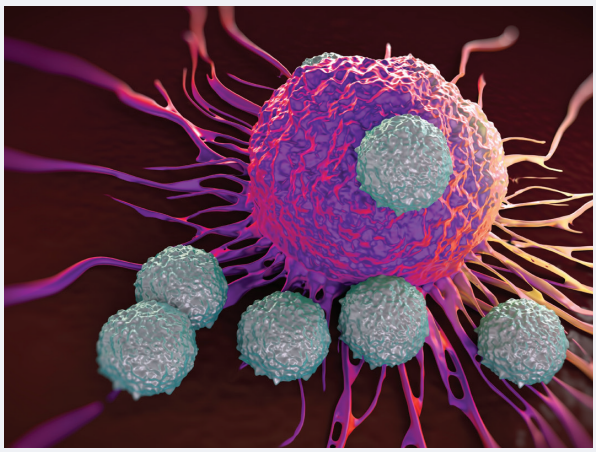

The Japanese academic discoverer of the PD-1 protein and the company that co-developed a blockbuster drug based on his work continue to be embroiled in a spat over patent royalties, with the protracted dispute seemingly coming to a head.

Tasuku Honjo, a distinguished professor at Kyoto University in Japan and Nobel Prize winner, is now said to be considering legal action against Ono Pharmaceutical Co. Ltd. should no other settlement be reached in the next few weeks.

For its part, the company says it is continuing discussions in good faith in the meantime for a possible out-of-court settlement, while also considering its responsibility to shareholders.

Honjo, now 77, discovered the T-cell surface protein PD-1 in 1992 and subsequently conducted years of research to elucidate its function and potential as an effective oncology target.

For this work, he shared the 2018 Nobel Prize in Physiology or Medicine with James Allison, the inventor of the CTLA-4 checkpoint inhibitor ipilimumab (Bristol-Myers Squibb Co.'s Yervoy).

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rage and resulting in a Congressional inquiry in 2016. The company had raised the price from $100 to more than $600 since acquiring the medicine, resulting in an untenable situation for patients, who were shouldering steep out-of-pocket costs.

The big pricing blunder stoked public ire over the high cost of drugs, contributing to broader scrutiny on the whole industry and backlash for Mylan specifically, from the public, pharmaceutical peers, legislators and investors.

The company's stock price sank and Mylan ended up agreeing to pay $465m in Medicaid rebates for EpiPen in October 2016 to avoid an investigation by the Department of Justice. It also launched a patient assistance program to cover half of the cost of EpiPen and rolled out an authorized generic.

CEO Heather Bresch went out on a PR crisis management blitz, framing the EpiPen scandal as a learning opportunity for the industry. In an appearance at the Forbes Healthcare Summit in 2016, Bresch called the EpiPen scandal a catalyst for the industry to better understand the challenges high deductible copays present to patients. But Mylan never fully regained its footing and the company's stock continued to decline, despite Mylan achieving several positive milestones with its complex generic and biosimilar portfolio.

Mylan was the first company to launch a generic version of Copaxone (glatiramer) 40mg, the first to launch biosmilar Neulasta (pegfilgrastim) and the first to launch a generic version of Advair (fluticasone/salmeterol). The company launched its first biosimilar, Fulphila, a Neulasta copy, in 2018. All three efforts were accomplishments in which Mylan beat rivals to the punch.

Nonetheless, the company's stock closed at $18.46 on 26 July, the day before reports of the planned merger were first reported in the *Wall Street Journal*. It had fallen more than 60% from where it was trading in August 2016, when the EpiPen scandal broke.

Last August, the company's board of directors launched a strategic review, claiming that investors had failed to appreciate the value. *(Also see "Mylan To Explore Strategic Options, Claiming Investors Have Failed To Appreciate The Value " - Scrip, 8 Aug, 2018.)*

Mylan CEO Heather Bresch

A CHANGE IN CORPORATE GOVERNANCE?

Mylan investors will likely welcome the exit that has been presented in the combination with Upjohn. The fact that Teva attempted to buy Mylan for $82 per share in 2015 and was rebuked by the corporate leadership may be hard to swallow, however. Teva pivoted at the time to acquire Allergan PLC's generic drug business for $40.5bn instead, a deal that has presented its own challenges for Teva.

One of the issues for Mylan investors has been the company's insular and longstanding leadership. Chairman Robert Coury has been the architect behind the company for going on two decades. He was CEO from September 2002 until January 2012, when he became executive chairman and Bresch was appointed CEO. Rajiv Malik has also served as president of Mylan since 2012.

Bresch was notably the first woman CEO of a Fortune 500 pharmaceutical company when she was appointed to the role and remains one of the industry's only female CEOs. But she has been a controversial figure and drew criticism for her handling of EpiPen.

With Mylan's inversion deal with Abbott in 2014, the company reincorporated in the Netherlands, further sheltering the leadership from certain investor actions. Now with the Pfizer deal, the new company will be redomiciled in the US, in Delaware, which management said will make the company more attractive to investors.

The new company will be led by a new CEO, Upjohn president Michael Goettler, but Coury will remain executive chairman of the new company and Malik will serve as president. Bresch is leaving, along with CFO Ken Parkes. The board of directors will have eight members designated by Mylan and three members designated by Pfizer, leaving some industry observers to question how significant a change the new leadership structure will be.

While investors approved of Mylan's efforts to redomicile in 2015, to appreciate the tax benefits, analysts say it also sheltered management. Mylan, for example, relied on an obscure Dutch legal structure – known as Dutch stitchting – to fend off the takeover attempt by Teva in 2015.

In the call outlining the deal on 29 July, Coury committed to more transparency with analysts and investors. "We're going to sit with you and we're going to come up with the right way to profile this very unique company," he said.

"If I tell you I'm going to do something, it's done, so let me be clear: I would never come back to the United States if we weren't ready to turn this company back over to shareholders," he added. "You can't get any more shareholder-friendly than Delaware."

The new company will need to build back trust with investors. Bernstein Research analyst Ronny Gal, in a research note, pointed out that Coury did not entirely answer the questions he asked on corporate governance during the investor call.

"He didn't answer questions on the issue directly – on shareholder versus stakeholder structure, ring-fencing the board and high compensation," he said. "Even within Delaware, there is a range of governance structure, and we are yet to learn if [the new company] is structurally responsive to shareholders," Gal warned.

Leerink analyst Ami Fadia, in a 29 July note, also highlighted changes to corporate governance as a potential positive of the merger. The new company "may get a clean slate start with investors with its change in domicile in the US, new management team members and commitment to transparency," Fadia said.

The official end of Mylan appears to be close at hand. The question is how different the new company will turn out to be.

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Love From Shanghai: Upjohn Started Here But Will It Stay Post-Mylan?

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Upjohn/Mylan Merger could shift focus from China To US

After the news of Pfizer Inc.'s plan to merge its established products subsidiary Upjohn with generics major Mylan Pharmaceuticals Inc. to create the world's biggest generics group by revenues, many are wondering if the move means Upjohn will retreat from its newly opened global headquarters in Shanghai.

During the opening ceremony for the Chinese facility, Pfizer Upjohn president Michael Goettler told *Scrip* that the main reason to choose Shanghai, the hub of China's pharma industry, was to be close to major customers and respond rapidly to local needs.

To that end, the generics subsidiary is developing in China a portfolio of 20 Pfizer established products, ranging from cardiovasculars Norvasc (amlodipine) and Lipitor (atorvastatin) to pain treatments Cerebrex (celecoxib) and Lyrica (pregabalin) and erectile dysfunction drug Viagra (sildenafil).

The move to Shanghai was also a bold one. Out of a total of 12,000 Upjohn employees, 5,000 will be based in China including at the Shanghai base, a formulation and manufacturing plant in the northeast city of Dalian, and sales and marketing networks across the country. *(Also see "Pfizer Unveils Upjohn Global HQ In China Amid Unprecedented Pricing Pressures" - Scrip, 3 Jun, 2019.)*

Upjohn was created after Pfizer consolidated its business into three main divisions and spun off off-patent products to the Upjohn unit. Biosimilars were excluded however and retained within Pfizer's innovative Biopharma arm.

SHIFTING FOCUS?

Now, with Mylan added to the equation and new leadership in place, and the combined entity being incorporated in Delaware, US, the focus for Upjohn might shift away from China and back to the US, industry observers say.

Like Pfizer, Mylan has an extensive marketing and sales network in the US, but unlike its new partner does not have a large footprint in China, where generic competition is heating up and pricing pressure mounting. Mylan saw its first-quarter revenues slide by 7% to $2.5bn and operating profit nosedive by 85% to $24m.

Meanwhile, Pfizer said in its recent second-quarter results that Upjohn's China revenues plunged by 20% due to volume-based procurement reforms implemented this March. Full-year revenues in the country should rise by the low to mid single digits, the company noted.

Although Mylan has partnered with Indian makers for multiple products, the company has only a limited direct presence in China. During a conference in Beijing in 2012, CEO Heather Bresch said the company was considering market opportunities while actively looking for partnerships. *(Also see "U.S. FDA Sees Progress Working Within China, And More Help Is On The Way" - Scrip, 21 Jun, 2012.)*

In comparison, Pfizer overall is among the top pharma firms in China, with sales exceeding $2.50bn in 2018 and with some of the country's top-selling cardiovasculars in the form of Norvasc and Lipitor.

"Combining Pfizer Upjohn with Mylan will give birth to a generics giant with potential to rival Teva, the largest generics maker in the world, because both Pfizer and Mylan have large volumes of prescriptions in US, the largest pharma market, the scale of the combined entity can't be underestimated," noted Chinese angel investor Jin Wang in a social media post.

The merged Upjohn/Mylan operation expects to generate 45% of its revenues from China and emerging markets.

POTENTIAL DIVESTMENT

Whether or not the focus of the combined group will shift to the US or remain in China, the generics sector in the latter market has one particularly large overhang - pricing pressures.

As alluded to by Pfizer in its results, the massive "4+7" centralized government procurement scheme has been rolling out in 11 major urban markets since the end of 2018, and the prices of winning products have fallen on average by over 50%. Nearly all multinationals except AstraZeneca PLC and Bristol-Myers Squibb Co. have managed to win one bid for each of their products.

The second round of bidding is due to take place and international firms are hoping to catch a break.

The steep price cuts needed to win bids have prompted several foreign firms to divest selected established products to local companies, focusing instead on higher-

margin innovative drugs. The latest to do so was GlaxoSmithKline PLC, which sold local rights to a major hepatitis treatment to Fosun International Ltd., while in April Lilly Research Laboratories out-licensed Vancocin (vancomycin) and cefaclor to Eddingpharm International Holdings Ltd. *(Also see "GSK Divests China Suzhou Site, Antiviral Rights To Fosun" - Scrip, 11 Jul, 2019.)*

Upjohn might also join the pack and divest a suite of products to local companies in China, although it said in May that it intended to penetrate the country's "broad market" segment comprising lower-tier county hospitals.

TRADE WAR OPPORTUNITIES?

Similarly in the US, generics are increasingly becoming commodities, forcing many makers to focus on higher-priced biosimilars or to exit the market.

Pfizer made the decision to move Upjohn to Shanghai in 2018, amid increasing costs and the need to attract more local talent. But since then, China and the US have engaged in a lengthy trade war without immediate obvious forward paths. Although medicines are not subject to the higher tariffs levied on many other products, companies are worrying that the dispute will have a negative impact on business operations.

Indian drug makers including Cipla Ltd. meanwhile are moving to enter the China market in force. Pricing issues aside, these companies are hoping to capitalize on China's policy tailwinds, including moves to encourage generics to meet increasing local demand for quality and affordable anticancer and infectious disease treatments.

China and the US, or both, will certainly be a top issue for the new Upjohn/Mylan leadership, which is now under Michael Goettler as CEO and Mylan's Robert Coury as executive chairman. Mylan CEO Bresch will retire when the deal closes.

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Want To Fly In China's New Normal? Learn From Merck

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Many are trying to figure out the formula to win in China's new pharma market environment, where new products are being launched faster than ever before but price pressure is mounting and there may be no reimbursement in sight.

For Merck & Co. Inc. (known as MSD outside North America), the right strategy seems to be a combination of market penetration, pricing and excellence in execution.

First, you need a portfolio that consists of products with large clinical needs, namely oncology drugs and antivirals. Merck has its blockbuster PD-1 checkpoint inhibitor Keytruda (pembrolizumab), which is selling over CNY100m ($14.5m) in China and expanding its indications from melanoma to non-small cell lung cancer.

The additional potential indication of gastrointestinal cancer will give it a further boost, and the ex-US opportunity is potentially bigger than on Merck's home turf, executives told investors during the company's second-quarter earnings call.

"I'm not going to give a specific number but we clearly do see the ex-US opportunity as very significant. And in fact this quarter alone we sold $1.1bn outside the US. It [Keytruda] grew 73%. So we see both ex-US and US Keytruda opportunities. But clearly, China is the one I would highlight as significant potential growth for us going forward," chief commercial officer Frank Clyburn said during the 29 July call.

Human papillomavirus vaccine Gardasil is another example. The local demand for the product is so strong that it has caught management by surprise, and it "has had a significant uptake in China."

Other good-selling products for the US firm in China included diabetes drug Januvia (sitagliptin), which has been included in the country's National Reimbursement Drug List (NRDL), and recently launched anticancer therapy Lynparza (olaparib) in collaboration with AstraZeneca PLC and Lenvima (lenvatinib) with Eisai Co. Ltd.

"So it's a broad-base innovative portfolio that is driving that 50% growth and we believe that will continue in China," said the executive. Overall, China market sales reached $725m in the quarter, growing 51%.

MARKET PENETRATION STRATEGY

A new product launch involves many aspects that needs concentrated effort across multiple functions, from medical affairs to marketing, from sales to market access. Market penetration is key to ensure any products score an opening goal in China, noted a recent report from Boston Consulting Group.

Among the factors are physician and patient education, sales channels and digital detailing, noted the report, "Upgrading Product Launch Strategy For New Drugs." *(Also see "Ready To Ride Next Growth Wave In China? Remember Five Keys" - Scrip, 20 Jun, 2019.)*

For Keytruda, facing one US peer and three Chinese domestic competitors with lower pricing, Merck said it all came down to good penetration. "There clearly are local players that are entering the market at a lower price. They are penetrating into some segments of the market. However, we're continuing to see very good penetration and very good growth in China," stressed Clyburn.

Access programs and sales networks are also parts of the strategy, which plays an essential role in China's largely self-pay market. "We have patient assistance programs and we have a very strong commercial presence in China. So I feel really good that we'll be able to compete with the local players going forward."

COVERAGE, INDICATION EXPANSION

The opportunities in China for major new cancer treatments like Keytruda present significant growth potential, noted the US drug maker. Not only in terms of disease incidence but also possible coverage by the NRDL, which is slated to include new drugs and for which negotiations are under way.

Merck hopes to get Keytruda included in the list soon, a process which involves rounds of expert consultations and price negotiations. "The NRDL, we are waiting to see if we'll be invited to actually participate for next year, It is an important poten-

tial listing. It does expand the population in China significantly. There's 500,000 to 600,000 lung cancer patients in China. There's probably 300,000 of those that are a part of our labeled indication [first-line non-small cell lung cancer]," Clyburn noted.

China's private payment system, however, cannot be underestimated. "There are clearly patients that are in the self-pay market where we compete today that can afford Keytruda."

Indication expansion is the next step to sustain the immuno-oncology therapy's further expansion in China, the executive stressed. "We have seen very strong growth given the recent launch in first-line lung and continued uptake in melanoma.

"We'd also like to highlight we expect to expand our label in China. China is going to be important for us not only for 2020, but 2020 and beyond, and we are seeing good self-pay market uptake in China as well," he noted.

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Italfarmaco Options Inhaled Teicoplanin For MRSA Lung Infections

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Milan, Italy-headquartered Italfarmaco SPA is adding to its rare disease/specialty R&D pipeline by taking an exclusive option to develop and commercialize globally Neupharma Srl's inhaled formulation of the antibiotic, teicoplanin, currently entering Phase I studies for the treatment of methicillin-resistant *Staphylococcus aureus* (MRSA) infections in cystic fibrosis patients.

Teicoplanin, which is targeted at Gram-positive bacterial infections, has been available for injectable or oral use for many years, as Sanofi's Targocid; an inhaled formulation "has the potential to improve the safety, pharmacokinetics and efficacy profile associated with intravenous teicoplanin," said Italfarmaco's director of R&D portfolio development, Antonio Nardi, in the 1 August announcement of the option agreement.

Mid-sized privately-held European pharmaceutical companies like Italfarmaco, with a broad range of commercial activities in specialty, branded generics and generic products, as well as fine chemicals and active pharmaceutical ingredients (APIs), have to some extent zeroed-in on the development of novel orphan and severe disease therapies as a way of accessing new markets – Italfarmaco already has the HDAC inhibitor, givinostat, in Phase III for the treatment of Duchenne's muscular dystrophy, and is expected to start Phase III studies with that molecule in polycythemia veria in the near future.

In a binding term sheet agreement, which is expected to become definitive in the second half of 2019, Italfarmaco will pay an undisclosed upfront, development milestones and tiered royalties to Imola, Italy-based Neupharma, for a total consideration in the "double digit" millions, excluding royalties. There is currently no defined standard of care for MRSA infections in cystic fibrosis, Nardi noted.

According to Informa Pharma's R&D database, Biomedtracker, a handful of other companies are evaluating investigational products for MRSA, including Savara Inc., which has a vancomycin-containing inhaler, Aerovanc, in a Phase III clinical study, AVAIL. The US's Aridis Pharmaceuticals Inc. has a monoclonal antibody, AR-301, in Phase III for *S aureus*-associated ventilator-associated pneumonia. The UK's Destiny Pharma is evaluating a product, XF-73, for MRSA in post-surgery patients.

But there have been failures too, including Pfizer Inc.'s multi-antigen *S aureus* vaccine candidate, PF-06290510, whose Phase IIb study was discontinued at the end of last year because of low efficacy.

Neupharma is a small company which specializes in the development and marketing of health products for cystic fibrosis, including nutritional products and medical devices, and nebulizer solutions containing colistimethate sodium and tobramycin for chronic *Pseudomonas aeruginosa* lung infections.

The company said it believes Italfarmaco has the right resources and development expertise to develop further the inhaled teicoplanin product, whose use for MRSA in cystic fibrosis has been granted orphan drug status in the US and EU. Intravenous teicoplanin is currently used to treat MRSA infections in cystic fibrosis patients, although administration is inconvenient and associated with side effects and limited lung penetration, the companies noted.

One of the most recent product launches by Italfarmaco, in March, was a biosimilar version of the low-molecular weight heparin, enoxaparin sodium, marketed as GhemaXan in Italy.

Italfarmaco has sales revenues of around €700m annually, and its products include Tiglutik (riluzole) for amyotrophic lateral sclerosis. Earlier in 2019, the company launched Votubia (everolimus) tablets in Italy, for the treatment of brain tumors and seizures associated with tuberous sclerosis complex.

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Takeda Keen To Show Shire Integration On Track

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After seven months of combined operations, Takeda Pharmaceutical Co. Ltd. remains upbeat on the Shire PLC integration, maintaining this "is progressing very well" and the pursuit of synergies is on track.

Speaking at the Japanese firm's fiscal first-quarter results briefing in Tokyo, chief financial officer Costa Saroukos pointed to some of the steps the combined group has been taking to deliver its targets.

Source: Ian Haydock

Tracking against these is being monitored monthly internally and is also embedded in managers' incentives, while investors are also keeping out a close eye.

On the personnel side, he noted that the talent selection process for specific positions has now been completed for 79% of employees, while an early post-merger internal survey in March showed 78% of staff believed the combined company would better serve patients' needs.

Jobs have not been unaffected however. While he stopped short of providing actual numbers, the CFO said that "full-time equivalent reductions are progressing as planned," including across the US sales force this April.

Decisions on 81% of commercial office locations across 66 countries have now been made, while integration of centralized IT and administrative systems is ongoing.

SHARES REACT

The progress update came as Takeda raised its revenue and core operating profit guidance for the full year, driven mainly by divestments and a lack of expected US generic competition to multiple myeloma drug Velcade (bortezomib).

The company's shares were buoyed by the news, trading up around 6% on the morning of 1 August in Tokyo after the results were announced after market close on 31 July. The early upward revision in the profit outlook apparently caught many investors by pleasant surprise. "We believe the stock will react by a larger degree than the guidance hike, given how investor expectations on earnings had rapidly slipped over the past 3-4 weeks," MorganStanley MUFG analysts correctly predicted in a 31 July note on the results.

'CLEAR VIEW' ON DIVESTMENTS

There continues to be much investor focus on the enlarged Takeda's next major divestment as it concentrates on newer products in its chosen core therapeutic areas – gastrointestinal, oncology, neuroscience, rare diseases and plasma-derived therapies.

Little new here was forthcoming in the briefing however, with Saroukos confirming only that the company is continuing to pursue opportunities for divestments totaling up to $10bn in non-core assets, and that "negotiations are ongoing."

But he stressed that Takeda has "a good clear view" on how this target will be achieved. "The piece that we don't have clarity on is the exact timing on the execution and completion of those deals or divestitures." There are literally "hundreds" of non-core products that the company is looking at. "We can't go into much dialog on which specific products" at this time, he added, but talks are continuing.

Products in the "other" list include two gout drugs, Uloric (febuxostat) - for which three generics were approved in the US in late July - and Colcrys (colchicine).

Takeda booked JPY36.7bn ($336m) in integration costs related to Shire in the quarter, and as part of ongoing cost reduction efforts held a summit in Boston in June with 40 of its largest suppliers globally.

This identified around $200m in synergies and secured a similar figure in cash flow through the extension of payment terms, the CFO noted.

R&D MOSTLY ON TRACK

In a brief update on the pipeline as part of the Q&A session, R&D president Andrew Plump commented that, "for the most part, we're on track."

The company currently has 19 new molecular entities in Phase II/III, and the focus is on pursuit of high innovation across the focus therapeutic areas, rather than on trying to fill any "gaps" within each field.

"We look at our pipeline in totality, not at each therapeutic area as an end-to-end business." He pointed to the ongoing Phase II trial with the NAE inhibitor pevonedistat (TAK-924) for myelodysplastic syndrome, for which discussions with the US FDA are continuing for this to be accepted as a pivotal study. Takeda expects a sufficient number of events this year for the already fully enrolled study.

Analysts have also been interested in the EGFR/HER2 inhibitor TAK-788, which is in a pivotal Phase II study in non-small cell lung cancer with exon 20 insertion mutations.

Data from this are expected next year, and company "is still on target" to start a Phase III study in the front-line setting in the first half of this fiscal year.

However, the proof-of-concept readout for the anti-CD38 attenukine molecule TAK-573 in relapsed/refractory multiple myeloma is "likely to be pushed into [fiscal] H2 this year" from the fiscal first half, Plump told the meeting.

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Takeda Raises Guidance On Divestments, Improved Velcade Outlook

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In its first full fiscal quarter since completing the acquisition of Shire PLC in early January, Takeda Pharmaceutical Co. Ltd. has raised its guidance for the rest of the year, pointing to the positive impact of delayed US generic competition to Velcade and the divestment of ex-Shire eye drug Xiidra.

But Japan's largest pharma company has given no further indications of what other assets or products may be sold off to pay down its remaining net debt load of JPY5,048.9bn ($46.51bn) from the $62bn acquisition, saying only that "negotiations are ongoing for further potential divestments."

As of the end of the quarter, the group net debt to adjusted EBITDA ratio stood at 4.4x, and the strategic target is to bring this down to 2x within three to five years following the close of the Shire acquisition.

The company maintained it is "relentlessly executing" on this goal and remains on track to meet its (already raised) cost synergy target of $2bn by the end of fiscal 2021 (ending March 2022).

The divestment of Xiidra (lifitegrast) to Novartis AG was completed on 1 July for $3.4bn up front plus up to $1.9bn in milestones.

'FLAT TO SLIGHTLY INCREASING'

Takeda said it now expects underlying revenue growth to be "flat to slightly increasing" in the full year ending next 31 March, versus its earlier expectation of "flat to slightly declining." (The firm no longer gives specific numerical targets.)

Among other key indicators, underlying core operating profit (previously core earnings) margin is now seen in the mid to high 20% range, compared with mid-20% range earlier. Actual reported core operating profit guidance has been moved up to JPY910.0bn, from the JPY883.0bn expected earlier, and marking a 98% increase from last year's actual figure.

On a reported basis, while the revenue forecast remains unchanged at JPY3,300.0bn ($30.07bn; +57%) for the year, the operating loss figure has been revised to -JPY166.0bn (rather than -JPY193bn) and net profit to -JPY367.7bn (-JPY383.0bn).

In the fiscal first quarter ended 30 June, reported and core revenues were both up 89% to JPY849.1bn, but fell by around 1% on an underlying pro-forma basis. Operating profit was at JPY9.9bn reported (-90%) and JPY283.0bn core (+142%), and net at -JPY20.7bn reported (not meaningful for previous year) and JPY198.4bn core (+103%).

ENTYVIO SOLID BUT RARE DISEASES WEAK

Takeda's portfolio of 14 core global growth brands had aggregate revenue of JPY270.2bn in the period (+22%), "mostly offsetting" negative factors such as generic erosion and competition. But while blockbuster Entyvio (vedolizumab) for inflammatory bowel disease along with the neuroscience and oncology sectors continued to grow, the (mostly ex-Shire) rare disease portfolio declined 10%.

> Takeda has given no further indication of what other assets or products may be sold off to pay down its remaining net debt load.

This was attributed to competition, price pressure, stocking effects and lower sales of older lines for hereditary angioedema.

Even so, chief financial officer Costas Saroukos characterized the three months as "a very strong start" and highlighted the strong margins and cash flow deriving from cost controls (which are running ahead of target).

Entyvio, for ulcerative colitis and Crohn's disease, is benefiting from increased use in biologic-naïve patients and sold JPY83.9bn (+27%) globally in the period.

Besides this, the other key factor behind the revised guidance was a further delay in the expected US generic competition for multiple myeloma drug Velcade (bortezomib). While the advent of a non-therapeutically equivalent version (in IV and SC formulations) had been anticipated as possibly coming in July, "Takeda no longer assumes any additional US competitor within FY2019," the company said. The proteasome inhibitor had global revenues (mainly in the US) of JPY31.7bn (+1%) in the first quarter.

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Q2 Review: Big Pharmas Weigh In On M&A, Pricing Reform

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Stakeholders have had a lot to react to as the biopharmaceutical industry rolls out second quarter sales and earnings figures, with the announcement that Pfizer Inc. will be splitting off its Upjohn division to merge with Mylan NV fanning already high flames around business development. Likewise, the US Senate Finance Committee's drug pricing bill has prompted analyst queries for reaction from most of the major players.

Industry has been consistent, claiming the proposal generates significant savings that would go to the government, not patients. Underscoring the importance of the US market, many companies have disclosed significant impact from negative pricing pressure globally – and that the changing US environment will remove an offset to lower prices abroad.

Drug makers have also been stressing that volume growth is driving their performance and highlighting the organic potential in their pipelines, another sign of the times as the recent wave of M&A has investors keen to detect what deal could be brewing next.

The pending mergers of Bristol-Myers Squibb Co./Celgene Corp. and AbbVie Inc./Allergan PLC have prompted questioning across the board about companies' business development priorities. While most CEOs are sticking to the playbook of never-say-never when it comes to mega-deals, preferring smaller bolt-on transactions, the pressures of pricing headwinds and achieving volume in competitive spaces could result in more big combinations as industry strives for growth.

MERCK STANDS STRONG, LOOKING TO AVOID DISRUPTION

Merck & Co. Inc. outperformed expectations in the second quarter, including besting projections for its immuno-oncology superstar Keytruda (pembrolizumab) with sales of $2.6bn – up 63% year-over-year as it builds share in first-line lung cancer and adds new indications. Overall revenue totaled $11.8bn (7% above consensus) and earnings-per-share was $1.30 (12% above consensus), with management raising both revenue and EPS guidance by 3%.

Vaccine sales have also been strong, and Merck recently released promising results on an HIV therapy – so the company is confident in its ability to grow on its own, CEO Ken Frazier told the 30 July call. *(Also see "Merck Positions MK-8591 As Backbone For HIV Treatment And Prophylaxis" - Scrip, 24 Jul, 2019.)* His stance is that large-scale M&A would be too disruptive for Merck, so it continues to look for bolt-on acquisitions that would not be overly complex to integrate – like the Q2 acquisitions of oncology firms Peloton Therapeutics Inc.*(Also see "Merck Buys Peloton On Eve Of IPO, Expands Kidney Cancer Portfolio" - Scrip, 21 May, 2019.)* and Tilos Therapeutics Inc.*(Also see "Deal Watch: Vertex Expands Gene-Editing Efforts With A Pair Of Deals" - Scrip, 10 Jun, 2019.)*.

On the pricing front, chief financial officer Rob Davis echoed a refrain put forth by other industry leaders, about wanting reforms that benefit patients at the pharmacy counter. But he commented that the business impact of negative pricing pressure isn't a new challenge – it's been common around the world, but offset by pricing power in the US.

"As we look going forward, we no longer see the benefit of those price increases in the US because of obviously the changing dynamics. And so, as you look in total we do continue to believe we're going to see declining price as we look forward, impacting our margins."

Because Keytruda is reimbursed under Medicare Part B, Merck has less exposure to potential catastrophic coverage reform than some other firms – although approximately 25% of business for its PARP inhibitor Lynparza, partnered with AstraZeneca PLC, goes through Part D. But chief commercial officer Frank Clyburn said, pointing out Keytruda is Part B, "we feel as though we're balanced across our oncology portfolio going forward."

GILEAD GETS BACK TO SEQUENTIAL GROWTH IN HIV

Led by combination pill Biktarvy, the HIV franchise continued as Gilead Sciences Inc.'s growth leader during the second quarter, this time posting not only year-over-year growth, but sequential growth as well. Gilead's HIV products yielded aggregate sales of $4.04bn during the second quarter, the company reported on 30 July, good for 10% year-over-year growth and 12% quarter-over-quarter growth.

During the first quarter, the franchise brought in $3.62bn, a 14% uptick from 2018, but down 11% sequentially. *(Also see "Biktarvy, PrEP Continue Driving Gilead's HIV Dominance" - Scrip, 3 May, 2019.)* Biktarvy (bictegravir/emtricitabine/tenofovir alafenamide) posted its first blockbuster quarter during the second quarter, with $1.12bn globally, including $1.02bn in the US.

CAR-T product Yescarta (axicabtagene ciloleucel) continued a solid ramp-up in Q2, totaling $120m worldwide (up 25% from Q1), including $99m of US sales. There are now 120 authorized treatment centers to administer the therapy across the US and Europe, with reimbursement finalized in the UK, Germany, France and Spain.

CEO Daniel O'Day noted during the earnings call that he is now five months on the job and indicated Gilead is just getting started in terms of deal-making, following a quarter that included a major collaboration with Galapagos NV as well as smaller partnerships and licensing agreements to add pipeline assets in virology, immuno-oncology and renal disease. *(Also see "$5bn Galapagos Deal Won't Be Last For Gilead, Says O'Day" - Scrip, 15 Jul, 2019.)*

O'Day shrugged off pricing concerns, noting that Gilead's business is driven by volume, but he pointed out some positive policy changes that help the company: he said retaining the Medicare Part D protected class rule is good for patients and for Gilead's portfolio, and he also was encouraged that different approaches are being considered for CAR-T therapies. *(Also see "A Complete Retreat: "Protected Classes" Stay Protected In US Medicare" - Pink Sheet, 21 May, 2019.)(Also see "New Payment Models For Curative Treatments Have CMS' Attention, Verma Says" - Pink Sheet, 23 May, 2019.)* Gilead will be an active participant in Part D reform, O'Day added, though Gilead's portfolio exposure is a low double-digit percentage.

BIOSIMILARS TAKE CENTER STAGE AT AMGEN

CEO Bob Bradway brushed aside the business development question during Amgen Inc.'s after-market 30 July earnings call, saying the company has a strong cash flow, strong balance sheet and "will continue to look at opportunities large and small," while it can also grow organically. The firm's total revenues decreased 3% to $5.9bn versus Q2 2018 and sales were down 2%, "reflecting increasing competition due to patent expirations." It reported that Prolia (denosumab), Repatha (evolocumab), Parsabiv (etelcalcitide) and Aimovig (erenumab-aooe) units grew double-digits or better.

While Amgen's established products are in a difficult period, the company provided a positive pipeline update on its KRAS inhibitor AMG510, including tumor responses in colorectal and appendiceal cancer patients. The firm announced it would initiate a registrational study by the end of the year. *(Also see "Amgen's KRAS Inhibitor AMG 510 Leans Toward Tumor-Dependent, Not Agnostic, Approach" - Scrip, 3 Jun, 2019.)*

Amgen's biosimilars portfolio are another bright spot. Biosimilar sales generated $82m in the second quarter – above consensus estimates of $66m – and the company just launched its Avastin biosimilar Mvasi and Herceptin biosimilar Kanjinti in the US. *(Also see "US Market For Therapeutic Cancer Biosimilars Will Be Tested By Mvasi, Kanjinti Launches" - Scrip, 19 Jul, 2019.)*

Asked about the viability of the US biosimilars market, Murdo Gordon, EVP of global commercial operations, said "the dynamics on pricing and competition are fluid, but less of a hurdle than they were," which is a trend he expects to continue. He noted that the European marketplace started slow and became a more attractive market for biosimilars. Amgen continue to push that its presence in the market is unique, given its 40-plus years of biologics production and its ability to provide physician and education services as well as reimbursement support.

LILLY CITES PRICING PRESSURE AS REASON FOR FLAT REVENUE

During a flat quarter, Eli Lilly & Co. cited 6% aggregate volume growth as showing strength behind its portfolio. Overall, Lilly reported 1% year-over-year growth to $5.64bn on 30 July, with US sales flat at $3.25bn and ex-US up 2% to $2.38bn.

Sales volume increased 5% domestically and 9% internationally in Q2 (with 26% growth in China), but was hindered in each case by lower realized prices. CEO David Ricks also pointed to the loss of exclusivity for Cialis/Adcirca (tadalafil) in the US, along with the pending withdrawal of the soft-tissue sarcoma drug Lartruvo (olaratumab).

> "The dynamics on pricing and competition are fluid, but less of a hurdle than they were."
> – Murdo Gordon

"Consistent with our 2019 financial guidance, US price declined 4% with nearly 3% driven by increased rebates in the Medicare Part D coverage gap," chief financial officer Joshua Smiley said; the issue has been a common concern for big pharma. *(Also see "Impact Of Higher Part D Donut Hole Discounts Beginning To Show: Xarelto Sales Down 19%" - Pink Sheet, 17 Jul, 2019.)* Smiley added that changes in Medicare gap funding coverage should continue to impact Lilly's revenue during Q3, but begin to be less of a factor in Q4. "We still anticipate mid-single-digit declines in the US price for the full year," he said.

Diabetes remains Lilly's key growth-driver, with type 2 diabetes stalwart Trulicity the firm's top-seller, up 32% to nearly $1.03bn, continuing a trend. *(Also see "Lilly's CVOT Success With Trulicity Causes Bullish Outlook For Diabetes Franchise" - Scrip, 6 Nov, 2018.)* Other big gainers included Jardiance (empagliflozin), up 58% to $232m, and Basaglar (insulin glargine), up 44% to $291m. But the greatest growth came from autoimmune biologic Taltz (ixekizumab), up 61% to $354m.

Lilly is still looking to build in oncology, and announced that breast cancer drug Verzenio (abemaciclib) showed a significant survival benefit in the MONARCH 2 study. That follows the survival advantage shown for Novartis AG's Kisqali (ribociclib) in MONALEESA-7 earlier this year, but both rival CDK4/6 inhibitors have a lot of catch up to Pfizer's Ibrance (palbociclib). *(Also see "Novartis' Kisqali Scores Big Win In Competitive CDK4/6 Space" - Scrip, 1 Jun, 2019.)*

In terms of business development, Ricks said that Lilly's focus remains on bolt-ons that would fit within its therapeutic areas.

SANOFI WINS WITH DUPIXENT, STUMBLES IN HEMOPHILIA, DIABETES

Sanofi's second quarter earnings call on 29 July was, as expected, a quiet affair ahead of incoming CEO Paul Hudson's imminent arrival. Hudson, most recently North American head of pharmaceuticals for Novartis AG, will succeed retiring Sanofi CEO Olivier Brandicourt, with a start date of 1 September. *(Also see "Hudson To Succeed Brandicourt As Sanofi CEO" - Scrip, 7 Jun, 2019.)*

The French pharma's second quarter was basically a tale of two therapies, as Dupixent ran laps around consensus projections while Eloctate stumbled to the extent that Sanofi announced a €1.84bn ($2bn) write-down of its 2018 buyout of Bioverativ Inc.

Dupixent (dupilumab), partnered with Regeneron Pharmaceuticals Inc., tallied €496m ($553m) on the quarter, up 168% year-over-year, as Sanofi pointed to increasing uptake for atopic dermatitis and asthma in the US. An indication for chronic rhinosinusitis with nasal polyposis was added to the IL-4/IL-13 inhibitor's US label one month earlier, providing a new avenue for further growth. *(Also see "Dupixent Gets Room To Grow With New Indication In Chronic Rhinosinusitis" - Scrip, 26 Jun, 2019.)*

Far less fruitful for Sanofi has been its $11.6bn purchase of Bioverativ, less than two years after its spinout from Biogen Inc. as a specialty firm centered on hemophilia and blood disorders. Sanofi announced the write-off for Eloctate (recombinant Factor VIII) "based on actual sales performance in the US and revision of sales projections." The hemophilia A therapy yielded sales of €171m, down 8%, although hemophilia B product Alprolix (recombinant Factor IX), acquired in the same deal, grew 23.5% to €105m on the quarter. Competition has been even greater than expected from Roche's Hemlibra, Brandicourt explained: "the magnitude of it has surprised almost everyone." *(Also see "Roche's Hemlibra Wins Expanded FDA Approval, Opening The Door To Broad Hemophilia A Opportunity" - Scrip, 4 Oct, 2018.)*

Another recent setback for Sanofi was the disappointing Phase III data for partner Lexicon Pharmaceuticals Inc.'s SGLT1/2 inhibitor Zynquista (sotagliflozin) for type 2 diabetes, which resulted in termination of the collaboration.

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Biocon Expects US Success For Biosimilar Trastuzumab Despite Amgen Launch

PENELOPE MACRAE

Biocon Ltd.'s first-quarter net profit rocketed 72% and India's largest biologics group has forecast a strong full-year performance, insisting its US launch of biosimilar trastuzumab will be "very successful" despite the surprise early market debut of Amgen Inc.'s rival product.

Amgen's 19 July launch of Kajinti, a biosimilar of Roche's blockbuster HER2-positive breast cancer drug Herceptin, means Biocon and partner Mylan NV will be deprived of exclusivity benefits in the US when they market their biosimilar in the second half of 2019. Roche racked up $2.9bn in US Herceptin sales in 2018.

Biocon and Mylan had said they "anticipated potentially" being the first company to launch trastuzumab in the US and that they would enjoy six months of exclusivity. Mylan, along with Pfizer Inc., Merck & Co. Inc.-Samsung Bioepis Co. Ltd. and Teva Pharmaceutical Industries Ltd.-Celltrion Inc., signed a confidential pact with Roche not to market Herceptin biosimilars until mid- to late-2019. (Pfizer's Upjohn Laboratories and Mylan have just announced plans to merge. *(Also see "Upjohn/Mylan: Will "Potential Moderate Growth" Lure Investors?" - Scrip, 29 Jul, 2019.)*)

Amgen and partner Allergan PLC were the lone companies not to strike a delayed launch agreement, and Amgen launched Kanjinti after winning in July an ongoing litigation battle with Roche.

"I've no doubt when we enter the market with our biosimilar trastuzumab, it's going to be a very successful launch," Biocon founder and managing director Kiran Mazumdar Shaw said in an earnings conference call, after Biocon reported first-quarter net profit climbed to INR2.1bn ($30.5m) from INR1.19bn a year earlier, beating market expectations of around INR1.9bn.

Revenues jumped 25% to INR14.9bn in the three months to 30 June, driven by strong biologics and small molecule performances, while EBITDA surged 84% to INR4.37bn and EBITDA margins climbed to 31% from 26%.

BIOCON WILL 'SHAKE UP BIOSIMILAR SPACE'

Biocon's biologics division was the first-quarter earnings star, with revenues leaping 96% in the first half to INR4.9bn. "Biologics is really the segment to watch because this is what we've invested in and it's beginning to deliver," said Mazumdar Shaw. "Going forward, we expect this momentum to continue and the second half is expected to be even stronger" because of trastuzumab's launch, she said.

Biocon, which reckons it's at least five years ahead of other Indian firms' efforts to bring to market cheaper versions of some of biotechnology's biggest drugs, now has "an opportunity and an obligation to shake up the biosimilar space," said the MD, a self-made billionaire who aspires to make the company a "global biosimilar leader."

Shares of the Bengaluru-based firm, which have fallen close to 25% this year, climbed as much 9% on the back of the 26 July earnings report, helped by upbeat analyst comments, before erasing most of the gains amid ongoing Indian market weakness. The shares were down 2.25% at INR238.45 on 29 July, near their 52-week low.

Biocon's strategy has been to win global regulatory approvals for its biosimilars through tie-ups with multinationals, given that getting such products to market is so costly. Last June, Biocon and Mylan won US FDA approval for Fulphila, the first biosimilar version of Amgen's Neulasta (pegfilgrastim-jmbd), a G-CSF used to treat low blood cell counts in chemotherapy patients. In late 2017, the Biocon-Mylan combo got FDA approval for Ogivri, the trastuzumab biosimilar, which has been on sale in India since 2014.

During the first quarter, Canadian regu-

lators also approved Ogivri as the first trastuzumab biosimilar in the country, in 150mg and 440mg vials. Biocon also expanded its EU footprint with Ogivri's commercialization. Mylan continues to market Semglee, Biocon's biosimilar to insulin glargine, in the EU, and there were robust sales of trastuzumab and insulin glargine in key emerging markets.

Biocon also won regulatory approvals in other key emerging markets for the two biosimilars, "which augurs well for the future," Mazumdar Shaw said.

BIOCON, MYLAN 'WELL-POSITIONED' ON US TRASTUZUMAB LAUNCH

Biosimilar Herceptin is one of five biologics Mylan has been developing in partnership with Biocon. And despite what Mazumdar Shaw called Amgen's "unanticipated" launch, Shaw said Biocon is "very well-positioned when it comes to the quality of our product [trastuzumab], our cost of goods as well as our overhead structure with our competitiveness to serve the middle-income pyramid in particular."

Also, she noted, one hurdle for Amgen might be that it is "launching with the presentation of 420mg which isn't in the market today because Roche has completely converted the market to 150mg."

"Significant biosimilars adoption in both Europe and the US provides an opportunity for Biocon to increase penetration of its portfolio," Mazumdar Shaw said. Fulphila had strong first-quarter sales, snaring a 21% volume share of the US pegfilgrastim syringe market and "continues to be a great growth opportunity," the executive said.

"Biologics have been performing well in the last few quarters but the ramp-up is now being seen because we've seen a 9% sequential improvement in biologics performance," Mazumdar Shaw noted. She forecast "substantial full-year growth in biologics revenue" and said "the positive impact on margins resulting from this growth should be visible in fiscal year 2021…driven by new product introductions, market entries and increased penetration of products already launched by our partners in various markets."

The biologics segment reported first-quarter PBIT (profit before interest and tax) margins of 38%, up from 11% last year and 33% in the previous quarter, helped by a higher Fulphila contribution. Biocon said it's still planning to spin off its biosimilars segment and expects to complete a restructuring of legal entities in 2019, "after which we will consider the unlocking [of value] at the right time," Biocon said, but offered no specific timeline for any possible public offering.

The biologics division crossed the $200m revenue milestone last year, seen as key to an IPO. *(Also see "Biocon Biologics Reaches Landmark Sales Figure; IPO Beckons" - Scrip, 29 Apr, 2019.)*

INVESTING IN CAPACITY AND R&D

"We will continue to invest in expanding our manufacturing capacities to address volume growth...and also to support new biosimilar pipeline development and launches," Mazumdar Shaw said. Gross spending on R&D rose 78% year-on-year to INR790m. Commercial operations at Biocon's new molecule antibodies facility in Bengaluru are slated to begin late in late the 2020-21 fiscal year or early the following year.

In novel biologics, Biocon's partner Equillium Inc., which has licensed itolizumab for development in the US and Canada, is conducting a Phase Ib/II trial in patients with acute graft-versus-host disease (aGVHD) and a Phase Ib trial in patients with uncontrolled moderate-to-severe asthma with itolizumab (EQ001). It also plans to initiate a Phase Ib study for the treatment of lupus nephritis during the second half of calendar 2019.

The US FDA's pre-approval inspection of Biocon Malaysia's insulin glargine drug substance, drug product and device assembly facilities resulted in 12 observations across the three units, but Mazumdar Shaw reiterated she's "confident of addressing these expeditiously" and does not expect "any change to our partner Mylan's [US] commercialization plans for insulin glargine."

One division that didn't fare as well was branded formulations, as revenues fell 9% as business in the UAE continued to be hit by government-mandated re-pricing of branded generic products. Revenue from the Biocon's research services business under listed subsidiary Syngene International Ltd., climbed a modest 4% to INR4.21bn in the quarter.

For Biocon, long-term biosimilar investments "are delivering expected results" and the company foresees "strong overall growth in fiscal year 2020," Mazumdar Shaw said. "We're at an inflection point of our growth story" able to develop a "complex generic, a high-quality biosimilar or a cutting-edge novel therapeutic."

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Bayer CV Pact Gives AI-Focused Sensyne Health Its First Big Deal Since 2018 IPO

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In its first big commercial pact since listing last year, AI-focused healthcare technology group Sensyne Health PLC has signed an initial two-year collaboration agreement with Bayer AG to hasten the clinical development of new treatments for cardiovascular disease using the UK group's proprietary technology platform which processes patient data provided by NHS trusts.

The deal is Sensyne Health's first major drug development agreement since its IPO last August and has potential for expansion, its CEO, serial entrepreneur Paul Drayson, told analysts on 31 July when announcing the deal. Sensyne Health is listed on the AIM Market of the London Stock Exchange.

The former UK science minister said real world evidence from Sensyne Health's Clinical AI analysis of anonymized patient data

has the potential to generate new insights that could improve patient outcomes, support clinical staff and accelerate the discovery and development of new medicines to prevent and treat cardiovascular disease including heart failure and stroke.

"Here, we are working non-exclusively for Bayer to analyse data for the purpose of being able to help Bayer design clinical trials in the future for cardiovascular drugs which benefit from a better understanding of the subpopulation within the patient population suffering from stroke and heart failure, such that they can reduce the cost of clinical trials and improve the prospect of a successful clinical trial," Drayson said.

Currently Phase III clinical trials in cardiovascular disease have on average a 50% success rate. "And these are very large, very expensive trials, so this is very important for Bayer," he added.

The initial agreement will generate revenues for Sensyne Health of £5m across the two-year collaboration, and includes a £400,000 upfront payment to the Oxford-based company. Sensyne Health's partner NHS trusts will receive a 4% share of all revenues generated by Sensyne Health under this collaboration.

The AI specialist hopes the Bayer alliance will be successful and led to a longer term arrangement.

"A successful outcome from this initial Bayer collaboration would then see us move into the later stage clinical development of products, in collaboration. And we are in discussions with other clients about other projects in different areas but using similar techniques," Drayson said, but he declined to give details of the targets or assets that will be progressed under the pact.

The choice of cardiovascular disease as Sensyne Health's first big collaboration reflects the type and quality of data that has hitherto been made available to it by NHS trusts.

"The nature of cardiovascular disease and the prevalence of heart failure and stroke means that we have sufficient numbers of patients with those conditions in the datasets," he explained.

"A successful outcome from this initial Bayer collaboration would then see us move into the later stage clinical development of products in collaboration. And we are in discussions with other clients about other projects, in different areas, but using similar techniques." – Paul Drayson

"At our IPO we said we wanted to build a patient base of around five million. We are just above three million now. And because of the very large prevalence of stroke and heart failure we do have sufficient data with which to do this analysis."

He said expansion by the AI group into other therapeutic areas – such as chronic disease and cancer - would occur, but only once more anonymized patient data is provided by NHS trusts.

That seems to now be happening, however.

"We are certainly seeing an increase in the interest from NHS trusts wanting to work with us. We are currently in discussions with approximately 50 Trusts. And the general environment is increasingly positive towards this type of work."

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Ready To Make Bigger Biotech Investments, Vida Raises $600m For Second Fund

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Vida Ventures raised two times as much money for its second venture capital fund than it did for its first fund less than two years ago, but it will invest in the same number of companies with its new $600m pool of cash, according to senior managing partner Fred Cohen. The larger fund will allow Vida to make bigger investments in each opportunity and make sure that its companies can reach their next value inflection point even if the economy shifts into a negative cycle.

Cohen co-founded Vida Ventures in 2017 with Arie Belldegrun, who was the CEO of Kite Pharma Inc. when the chimeric antigen receptor T-cell (CAR-T) therapy developer was sold that year to Gilead Sciences Inc. for $11.9bn. *Scrip* spoke with Cohen about Vida's beginnings and its plans for the future when the firm announced that it closed Vida Ventures II LLC on 1 Aug.

Vida I initially raised $255m from its founders and family offices with which the founders had connections in November 2017, but the inaugural fund grew to $295m by the time Vida Ventures officially announced its arrival on the biotechnology scene in April 2018. The unveiling was concurrent with its investment in the $300m series A venture capital round for Allogene Therapeutics Inc., which launched with a portfolio of allogeneic CAR-T candidates licensed from Pfizer Inc. and is helmed by former Kite executive David Chang, a Vida Ventures partner.

With Vida II, the firm is tripling its assets under management to more than $1bn and it is doubling the size of its team by recruiting three former Kite employees – Helen Kim, Rajul Jain and Heba Nowyhed – and entrepreneur Eric Trac.

Vida managing director Kim most recently was a partner at The Column Group, an investment firm, but previously was executive vice president of business development at Kite; Jain left his role leading the development organization at Kite, now op-

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erating as a Gilead subsidiary, to become a director at Vida; and the former Kite scientist and associate director Nowyhed was named a senior associate at Vida.

Trac worked at two VC firms prior to Vida, but recently earned a medical degree and a master of business administration at Stanford University; he earned his bachelor of science in chemical-biological engineering at the Massachusetts Institute of Technology (MIT), where he worked in the lab of frequent biotech start-up founder Robert Langer.

INVESTING IN BOSTON AREA, CALIFORNIA BIOTECHS

"We believe the bulk of the opportunities are in the Boston area and in California," Cohen said, which is why the expansion of Vida's team was especially focused on building its California presence. "We can serve a large part of the market by being in those locations."

As with Vida Ventures I, Cohen said, "we continue to believe that 15 companies is about the right number of companies to invest in. You want a concentrated portfolio so that your winners actually matter, but you don't want too much concentration so that stochastic risk works against you."

But instead of investing about $15m in each company, with the exception of some opportunities where Vida raised special purpose vehicles to make bigger commitments to certain companies, he noted that Vida II will put about $40m into each of its investments.

"What we observed during the Fund I investment was that with an average check size of $15m per company, we were a junior partner in any of the rounds that we participated in most of the time," Cohen said. "We believe that the average investment into a biotech company for a venture capital group that presumes they will lead investments is $40m."

Vida Ventures invested or committed about 75% of the money from its first fund by March of this year and decided then to raise its second fund so that it could make those bigger bets in its next set of opportunities. Its limited partners agreed that it was time to raise a new fund, because of the first fund's success to date.

Vida has invested in 14 companies and most recently co-led a $105m series A round for Kronos Bio Inc., whose CEO is former Gilead R&D head Norbert Bischofberger. To date, three of Vida's portfolio companies have gone public, including Allogene, while several others have successfully advanced their development programs. In addition, Merck & Co. Inc. agreed in May to pay $1.1bn up front for Vida portfolio company Peloton Therapeutics Inc.

"With that momentum behind us and with the general tailwinds that the biotechnology market has been enjoying of late, we went out and talked to our existing investors and some new investors," Cohen said. "At the same time, we as the general partners agreed that we would be a substantial part of the fund and we're over 25% of the capital in our new vehicle."

Vida II investors include members of the firm, investors in the first fund, endowments, foundations, family offices, funds-of-funds and various individuals from within and outside the US.

75% TO BE INVESTED IN THERAPEUTICS FIRMS

Three quarters of the companies receiving venture capital from Vida II will be in the therapeutics space, Cohen noted. In addition to drug developers, Vida I also invested in a contract research organization and an autism services opportunity.

Vida II's investments won't all be start-ups, but Vida Ventures will play an active role in starting about a quarter of the companies backed by the new fund, Cohen explained. He noted that about half of the companies will be opportunities that other firms played significant roles in and the remaining quarter of investments will be opportunistic. The latter category is "other areas where we thought we had insights that would allow us to be differentiated investors," Cohen explained.

"We've all started companies – Arie and Helen and I have started a number of different companies over the years and sometimes starting a company is the right answer," he said. "But what we try to ask is where is the value inflection and how long is it going to take to get it."

For instance, he pointed out that investors who backed biotech companies between 2000 and 2007 then ran into the economic downturn of 2008 and found that it would take quite a while to see a return, if any, on those investments.

"So if we see an opportunity that is interesting, but the capital that is being raised is not going to take you past the next value inflection, we will probably wait for the next round," Cohen said. "But if we see a great team and a great asset and we think we can shape the company, then we'll be the founders of that and we're happy to do that."

However, he added, "we also appreciate that founding companies is a lot of work" and noted that VC firms such as Third Rock Ventures and Flagship Pioneering specialize in company formation and have built the infrastructure to create start-ups.

"We don't have the capital to do that, so we've chosen not to do that exclusively, but that's not to say we won't do it," Cohen said.

AREAS OF INTEREST

In terms of therapeutic areas of interest to Vida Ventures, "there are a group of disorders where what everybody cares about is efficacy and they're willing to accept a certain amount of adverse events. Pancreatic cancer is a great example; if you cured a third of the patients with pancreatic cancer with some new drug, there are a whole lot of side effects people would be willing to tolerate," Cohen noted.

Therapeutic areas where the clinical opportunity can be adjudicated in a shorter amount of time with a smaller number of patients are what Vida is focused on, including monogenic orphan disorders, various cancers, and certain epilepsy syndromes or autoimmune syndromes.

"In contrast, there are another set of disorders where what people are really worried about is idiosyncratic toxicity or rare toxicity that is related to the mechanism of action – that might include metabolic disorders, including diabetes, or cardiovascular disorders," Cohen said. "If you look at many of the trials for new diabetes agents or new treatments in cardiovascular disease, the trials are at least 1,000 patients [and] we think that trials of that size and that timeline are outside of the pocketbook of venture capital and the de-risking step occurs largely in Phase III, so we tend to focus on those places where the capital that we have can create value."

Vida Ventures will back companies primarily in the US, but it is working on an ex-US start-up now and will continue to look at European companies.

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Roche's Pipeline Prospects Promise Steady Sailing To More Growth

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Optimism amongst analysts is growing over Roche's growth prospects and its ability to overcome looming threats from biosimilars and possible US pricing reforms, a trend that should be reinforced when the Swiss pharma presents a pipeline update in London on 16 September.

Roche's management used its half-yearly update on 25 July, which showed strong earnings growth, to underline prospects for its widening portfolio of new drugs and growing pipeline while playing down looming threats to US sales revenue from biosimilar pressure for its top three oncology therapies Herceptin (trastuzumab), Rituxan (rituximab), and Avastin (bevacizumab).

ANALYSTS' OPTIMISM GROWS

The overall reaction among analysts was that Roche is riding a wave that will overcome those challenges and carry it into a protracted period of earnings growth.

"We would expect market attention to gradually move from biosimilars to rejuvenation of the portfolio," analysts at Bryan Garnier said in a note to investors issued on 26 July.

"Roche shares continue to look undervalued as investors weigh near-term weakness such as biosimilar and potential US pricing reform headwinds, more than long-term strength offered by newer products and pipeline," Morningstar analysts said in a note published on 25 July.

Optimism among observers was reinforced by two recent cancer drug approvals, Polivy (polatuzumab vedotin-piiq) and Rozlytrek (entrectinib), prospects for two upcoming filings later in 2019 with neurology drugs risdiplam and satralizumab, and the pending acquisition of Spark Therapeutics Inc., which is still expected to close in the second half of 2019 despite being delayed by US and UK regulators. Roche this week said its tender offer for the gene therapy group had been extended again, this time from 31 July to 3 Sept, and left the prospect open that it could then be extended further.

LAUNCHES, NEW INDICATIONS AND PIPELINE

Roche's management says its pipeline is solid, advancing and helping support the group's large base.

CEO Severin Schwan told analysts that since sales from new drugs are expected to outweigh losses from older ones, there is no reason to anticipate declining profits in 2020, and even less so beyond this date since the peak from biosimilars is very much expected next year.

Pharma division head Bill Anderson underscored that trend, noting during the results analysts call that during every quarter, drugs launched over the past seven years had increased their weight in total Roche pharma sales.

In this year's second quarter, their weight moved further, up to 29% from 27% growth in the first quarter. They continue to grow fast, driven by Ocrevus (ocrelizumab), Perjeta (pertuzumab), Hemlibra (emicizumab) and increasingly by Tecentriq (atezolizumab), he added. "That gives us that confidence that we will continue to grow through the period of biosimilars and so, I think we're very well-prepared and excited to take on that future," Anderson said.

The therapeutic and commercial promise for Polivy was also emphasized. The therapy was granted accelerated approval in the US in June for the treatment of adults with relapsed or refractory diffuse large B-cell lymphoma (DLBCL).

"This molecule targets the CD79b protein on the surface of malignant B cells but it brings a very potent toxic payload along … We have been saying molecules like this can go where CAR-T doesn't because of patient eligibility, because of immediacy … You could look for much more from Polivy in the years ahead as we pursue first-line indications and go into other settings," Anderson said.

Meanwhile, Gazyva (obinutuzumab) was now being seriously evaluated in lupus nephritis, new territory for the therapy.

"We decided to do a Phase II study of Gazyva in lupus nephritis and those of you who have been around the biotech industry for many years know lupus nephritis has really been a graveyard for molecules," said Anderson. Roche had previously run large Phase III programs with Rituxan and then with Ocrevus in treating lupus nephritis, but those showed no benefit.

"Gazyva has the same target as Ocrevus and the same target as Rituxan, but has a different type of cell-killing ability. And based on this, we decided to take Gazyva into a Phase II study in lupus. We announced recently that we had positive results. We'll be sharing those at a major medical meeting later this year, but we are encouraged that we may have the world's first lupus nephritis drug, and so more to come on that," Anderson said.

Strong growth was also flagged for Tecentriq. "The growth from Tecentriq is really widespread both geographically as well as by indication," Anderson said.

"We have seen sources of growth in things like first-line, non-small cell lung cancer. The big use here [for Tecentriq] is in patients with liver metastases… we're now getting about 25% of the total business from small cell lung cancer, 50% from non-small cell lung cancer and then 20% from bladder cancer and 5% from triple-negative breast cancer, which is the newest indication."

"So we'll be basically going around the world with both the testing and the therapy [Tecentriq]. And we're very pleased at the progress," he said. And sales from MS drug Ocrevus, "is continuing to impress patients, and their families and to impress physicians" with over 100,000 patients treated globally todate.

"We'll see continued growth from Ocrevus for many quarters to come," helped by the therapy's US label having recently been updated to include active SPMS (secondary progressive multiple sclerosis) and clinically-isolated syndromes, Anderson said.

Published online 2 August 2019.

Editor's Note: This article was updated on 2 Aug. to note that Gazyva was tested in a Phase II lupus study, not Ocrevus.

Almirall's Dermatology Pitch Takes Shape

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Analysts were impressed with Almirall SA's first-half sales, noting the strong launch of the oral acne antibiotic Seysara in the US. CEO Peter Guenter told *Scrip* the firm had "executed well on the new, more ambitious agenda" to focus on "meaningful and clinically relevant innovation" in dermatology.

Guenter, who took over as CEO in October 2017, has accelerated and sharpened the company's focus on dermatology, committing to pursue first-in-class and best-in-class therapies, whether through in-licensing or in its in-house R&D. (See sidebar for a timeline of Almirall's refocus on dermatology).

LAUNCH TRIO PERFORMS WELL

Seysara (sarecycline), which was launched in the US in January 2019 following approval by the Food and Drug Administration in October 2018, generated sales of €8m in the first half, against predictions of €2m by analysts at Credit Suisse and of €5.5m by those at Jefferies, who noted that "it is now the number one oral branded antibiotic for acne in the US, and importantly also gaining share from the broader non-branded market." Almirall acquired Seysara with the purchase of Allergan's US medical dermatology portfolio last year.

Another recent launch, the anti-interleukin-23 monoclonal antibody Ilumetri (tildrakizumab) licensed for Europe from Sun Pharmaceutical Industries Ltd., also booked first-half sales of €8m. The treatment for moderate to severe psoriasis was approved by the European Commission in September 2018 and is being rolled out across Europe.

Meanwhile, Skilarence, the oral dimethyl fumarate treatment for psoriasis, generated €16m in Europe.

Although still representing a relatively small portion of the group's first-half net sales of €430m, the newer products are expected to drive longer-term growth and improved profitability. Almirall is forecasting combined peak net sales of more than €250m for Skilarence and Ilumetri, for both of which it owns European rights. It anticipates peak net sales of $150-200m for Seysara in the US. But two late-stage in-licensed products are expected to bring even greater revenue contributions. Tirbanibulin, the Phase III actinic keratosis treatment also known as ALM14789 and KX2-391, should exceed revenues of

Almirall Timeline: Key Steps In Dermatology Refocus

November 2014
Sale of respiratory franchise to AstraZeneca
For $875m up front and up to $1.22bn in milestones.

November 2015
Stiefel derma deal
Acne and impetigo products licensed to be commercialized through Almirall's Aqua Pharmaceuticals in US.

January 2016
Acquisition of ThermiGen
US aesthetics business.

February 2016
Acquisition of Poli Group
Adding marketed and pipeline dermatology assets for €365m+.

July 2016
Acquisition of rights to tildrakizumab
European rights acquired to late-stage anti-IL23 MAb for psoriasis from Sun Pharma.

March 2017
Bhushan Hardas becomes head of R&D
Formerly head of Allergan's dermatology and medical aesthetics business.

June 2017
Skilarence approved in EU
Oral dimethyl fumarate approved for moderate to severe psoriasis.

July 2017
Profit warning
Following troubles in US, including pharmacies inappropriately using patient assistance programs.

October 2017
Peter Guenter becomes CEO
He was formerly chief of Sanofi's cardiovascular and diabetes business.

December 2017
Partnership with Athenex
For US and European development and commercialization of PhIII actinic keratosis treatment KX2-391.

August 2018
Acquisition of Allergan's US medical dermatology portfolio

For $550m in cash. Included acne antibiotic Seysara.

September 2018
Ilumetri approved in EU

Tildrakizumab for moderate to severe psoriasis.

October 2018
Seysara approved in US

FDA approved oral antibiotic for severe acne.

February 2019
Option agreement with Dermira

Almirall pays $30m to option European rights to anti-IL-13 MAb lebrikizumab in Phase IIb for atopic dermatitis.

March 2019
ThermiGen divested

Sold to Celling Biosciences.

June 2019
Lebrikizumab option exercised

Almirall pays $50m to take on lebrikizumab for AD following positive Phase IIb results.

€250m from the EU and US, following initial launch in early 2021, Almirall forecasts.

And lebrikizumab, recently licensed from Dermira Inc., should bring in around €450m in peak sales in the EU, it says. The anti-interleukin-13 antibody is scheduled to enter Phase III trials in moderate to severe atopic dermatitis by the end of 2019, following the recent success of a Phase IIb study. *(Also see "Dermira's Lebrikizumab Data Set Up Atopic Dermatitis Showdown With Dupixent" - Scrip, 18 Mar, 2019.)* But it will be chasing Sanofi/Regeneron Pharmaceuticals Inc.'s IL-4 and IL-13-targeting Dupixent (dupilumab), which was approved in the EU in this indication in 2017. Lebrikizumab is not expected to reach the market until around 2023.

Nevertheless, Guenter believes the degree of unmet need and the size of the treatable patient population will make "room for many players in that market." He cited market research indicating there will be 5.6 million patients living with moderate to severe atopic dermatitis in Europe by 2026, with around 4 million receiving treatment, roughly 0.5 million of whom will be treated with new systemic drugs.

"The good news – for us at least – is that the unmet medical need is extremely high: for the most severe patients the disruption of sleep and impact on quality of life is really dreadful," he said. "We believe there is a tremendous expansion that is going to take place in atopic dermatitis. We think that atopic dermatitis is to some extent where psoriasis was 10-15 years ago. The first biologics were introduced with the anti-TNFs, and today the systemic treatment of psoriasis, especially with biologics, has become an enormous market, and we think atopic dermatitis is going to follow to a certain extent what we have seen in the psoriasis market."

While cautioning against making cross-trial comparisons between those conducted for dupilumab and those for lebrikizumab, the CEO expressed enthusiasm for lebrikizumab's profile to date, noting in particular strong response rates on the pruritus score for the lebrikizumab 250mg every two weeks arm. Pruritus, or itch, is the key negative symptom of AD in terms of its effect on patient quality of life and co-morbidities, said chief scientific officer Bhushan Hardas on the company's 29 July results call with investors. He said lebrikizumab had the "potential to be best-in-disease therapy for atopic dermatitis" based on the Phase IIb trial and its high affinity to IL-13.

But with the other two active arms of the Phase IIb study investigating lebrikizumab every four weeks (125mg and 250mg), it would obviously be a real advantage for Almirall to be able to aim for less frequent dosing than twice-a-month Dupixent. It isn't yet clear if Almirall and partner Dermira have the confidence for that based on the results to date. The Phase III trial is now being designed "to set us apart from currently available treatments of atopic dermatitis," noted Hardas.

DEAL FIREPOWER

Even with this year's Dermira deal, Almirall "continues to have significant firepower" for further deal making, said Guenter. "We continue to hunt in two ways. We look for assets that answer the innovation agenda we set last year: we're not going to go after targets that are incremental innovation targets; we really want to make a difference in patients' lives. And if we see the possibility to buy an existing business or marketed asset that fits well with our medical dermatology agenda that also fits our geographic focus on the US and Europe, we will continue to look at those opportunities to further increase our critical mass."

Meanwhile, the CEO said that the company's internal R&D was progressing "and we think that by the end of this year or early next year we will be able to move the first candidates into first in man studies. And we're very excited there because on those products we will have full rights and we will not be burdened with milestones, royalty payments or geographic restrictions."

While declining to divulge specifics, he added that internal R&D was focused on "those diseases within medical dermatology where even in 5-10 years they will be attractive to us. We define attractiveness by the size of the market, the unmet medical need, the degree of competition and our credibility to be competitive."

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UCB Spotlights Bimekizumab And Other Later-Stage R&D Projects

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Belgium's mid-sized pharmaceutical company, UCB Group, has highlighted new understanding of the importance of axial spondyloarthritis and psoriatic arthritis, both of which are now believed to be more common than rheumatoid arthritis, as a factor in the development of its late-stage investigational selective IL-17A and IL-17F inhibitor, bimekizumab.

UCB is investing in its R&D pipeline

CEO Jean-Christophe Tellier reported that Phase III results involving bimekizumab are expected in the fourth quarter of this year, and a Phase III study of padsevonil, potentially the first anti-epileptic to target two receptors, has started in refractory patients.

Further, a proof-of-concept study has started with rozanolixizumab in chronic inflammatory demyelinating polyneuropathy (CIDP). Rozanolixizumab is already in Phase III in myasthenia gravis, with results expected in the first half of 2021, and a Phase III study in immune thrombocytopenia patients is expected to start in the fourth quarter of 2019, Tellier said in a 25 July call with analysts.

An anti-tau antibody, UCB-0107, is in a Phase I study in patients with progressive supranuclear palsy, Tellier added.

Bimekizumab currently features in eight late-stage studies by UCB, including three pivotal Phase III studies and a Phase IIIb study in psoriasis, two studies in psoriatic arthritis, one study in ankylosing spondylitis and one in non-radiographic axial spondyloarthritis, UCB executive vice-president and head of immunology patient value unit, Emmanuel Caeymaex said in the same call. "Four out of the eight studies have an active comparator arm, that includes the market leaders," he noted. With regards to the bimekizumab comparative studies in psoriasis, the comparators are AbbVie Inc.'s Humira (adalimumab) and Johnson & Johnson's Stelara (ustekinumab), with results expected in the fourth quarter, and Novartis AG's Cosentyx (secukinumab), with results expected in the second quarter of 2020. A Humira comparator is also being used in one of the psoriatic arthritis Phase III studies, from which results are expected in 2021.

The way moderate to severe psoriasis can evolve into potentially more daunting conditions was noted by the UCB executives. "If left untreated, moderate to severe psoriasis commonly leads to psoriatic arthritis and cardiovascular disease, but treatment rates are low and represents a market with significant market potential," remarked Caeymaex.

The market for psoriasis, psoriatic arthritis and axial spondylarthritis treatments is expected to grow to $37bn by 2027, Caeymaex noted, driven by IL-17 and IL-23 inhibitors. "In psoriasis, the IL-17s and IL-23s will gain the majority of dollar share as more patients gain access to systemic treatments, and as the treatment goals evolve towards sustained, totally clear skin and resolution of inflammation as a means to prevent co-morbidities," Caeymaex added.

> "There is no reason for us to believe that a numeric imbalance in cardiovascular events is linked to Evenity." – Jean-Christophe Tellier

RECENTLY LAUNCHED PRODUCTS

The product developed in partnership with Amgen Inc., Evenity (romosozumab), has been approved now in the US, Japan, South Korea, Canada and Australia, although in the EU it has received a negative opinion by the CHMP, and UCB has requested a re-examination, which should take four to six months.

"There is no reason for us to believe that a numeric imbalance in cardiovascular events, seen in one of our studies, is linked to Evenity, which has shown a strong benefit in patients with fragility fractures," Tellier remarked.

"UCB is the lead company for Evenity in Europe, and that for us is a clear priority and we are doing everything we can in order to have a positive outcome of the reexamination," he added.

UCB has also gained approvals for Nayzilam (midazolam nasal spray) for acute repetitive seizures in the US this May. The product "completes our portfolio in epilepsy," Tellier added.

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J&J Drops Alligator's MAb ADC-1013 After Reviewing Combination Data

Sweden-based Alligator Bioscience AB put on a brave face when announcing Johnson & Johnson's Janssen Biotech Inc. unit had handed back rights to its experimental CD40 agonistic antibody, ADC-1013, and said it will now "rapidly advance" the tumor-directed immunotherapy candidate to Phase II trials while looking for a replacement partner.

Janssen had gained exclusive rights to develop and commercialise ADC-1013, also known as JNJ-64457107, under a deal signed in 2015.

Since then, Alligator and J&J have completed Phase I trials of intratumoral and intravenous formulations of the drug.

DATA DOUBTS

But Johnson & Johnson decided to return the rights to Alligator Bioscience's anti-CD40 oncology drug after reviewing its pipeline, the Swedish biotech's CEO Per Norlén told analysts on a 31 July conference call.

He said the intravenous formulation had shown limited efficacy when given as a monotherapy, achieving one partial response in 95 patients with advanced solid tumors.

The abstract presenting the data stated "future clinical development will require combination with either chemotherapy, or other immunotherapies such as antitumor vaccines or checkpoint inhibitors." And unpublished preclinical work done at J&J raised doubts about whether the combinations will work as hoped, he explained.

"They had performed a number of preclinical assessments. In some of these models, 1013 had not performed as in our models. That might have impacted on their strategic decision," Norlén said.

He added that there "is no bad data that I'm aware of" but that the results were evidently weak enough for J&J to decide its R&D budget was better spent on other assets. If the concerns that underpinned J&J's decision apply to CD40 drugs in general, a clutch of companies could be affected.

> "We still believe as strongly as ever in ADC-1013 and will now make all the necessary preparations to advance the product to Phase II." – Per Norlén

Companies including AbbVie Inc., Apexigen Inc. and Roche have moved CD40 drugs into clinical development in the belief that the target can help activate immune responses against tumors.

UNDAUNTED ALLIGATOR

Despite the data questioning whether ADC-1013 can deliver on that promise, Alligator plans to take the drug forward once it regains control.

"We still believe as strongly as ever in ADC-1013 and will now make all the necessary preparations to advance the product to Phase II clinical development and to initiate combination trials. In parallel, we will start seeking for an optimal partner for the development of this product," Norlén said.

SEEKS NEW PARTNER

Norlén is optimistic that the partnering talks and clinical development plans will progress quickly. On the partnering front, Norlén said there have been "quite a number of companies knocking on" his door, adding that "there's a lot of interest in accessing CD40 in combinations."

Alligator will need to find a partner with a potentially complementary drug to start the planned Phase II combination trial. There has been some interest in pairing CD40 drugs with chemotherapies and checkpoint inhibitors but Norlén sees particular promise in cancer vaccine combinations, noting that ADC-1013 "actually improves antigen presentation."

As it stands, Norlén expects to move ADC-1013 into Phase II within one year and to find a partner well before the completion of the study. Alligator has a initial synopsis for the study in place but still needs to generate a protocol and find a partner for the combination part of the midphase program.

Alligator will need to fund the work itself until it finds a partner willing to take on some or all of the financial burden. That could force Alligator to make some tough decisions over the coming months.

Alligator had SEK 358.2m ($37m) in the bank as of the end of June and a handful of R&D programs in need of money.

"We will have to make a review of our financial situation and see how we will progress but definitely 1013 will get full attention. We will obviously have to review our pipeline and prioritize our projects. We will focus on our clinical programs," Norlén said.

ADC-1013 will soon be one of three assets in Alligator's clinical pipeline. CTLA-4xOX40 bispecific ATOR-1015 is already in Phase I. 4-1BB antibody ATOR-1017 is set to join it in the near future.

Alligator has two other preclinical assets that could be negatively affected by the need to fund work on ADC-1013, however.

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

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

PIPELINE WATCH, 26 JULY–1 AUGUST 2019

PHASE II

Event Type	Lead Company/Partner	Drug Name	Indication	Comments	Change To LOA (%)	LOA (%)
Phase II Updated Results	Cidara Therapeutics, Inc.	rezafungin	Candidemia	STRIVE; Met Endpoints	1	63
Phase II Updated Results	Clearside Biomedical, Inc.	Xipere	Diabetic Macular Edema	TYBEE; Delivery Shown	0	24
Phase I/II Updated Results	Amicus Therapeutics, Inc.	AAV-CLN6 gene therapy	Neuronal Ceroid Lipofuscinosis	Positive Interim Results	3	27
Phase IIa Top-Line Results	InterveXion Therapeutics	IXT-m200	Substance Use Disorder	STAMPOUT; Positive Results	0	12
Phase II Top-Line Results	Aclaris Therapeutics, Inc.	ATI-501	Alopecia Areata	AUAT-201; Improved Hair Growth	5	29
Phase Ib/II Top-Line Results	Aravive Inc.	AVB-500	Ovarian Cancer	w/PLD or Pac; Encouraging Activity	0	10
Phase I/II Top-Line Results	Translate Bio	MRT5005	Cystic Fibrosis	RESTORE-CF; Mixed Results	1	19
Phase II Trial Initiation	BELLUS Health Inc.	BLU-5937	Chronic Cough	RELIEF; In Unexplained Cough	6	18
Phase II Trial Initiation	Infinity Pharma/Bristol-Myers Squibb	IPI-549	Bladder Cancer	MARIO-275 (w/nivolumab); Second-Line	10	10

PHASE III

Event Type	Lead Company/Partner	Drug Name	Indication	Comments	Change To LOA (%)	LOA (%)
Phase III Top-Line Results	Sanofi/Lexicon	Zynquista (sotagliflozin)	Diabetes Mellitus, Type II	Sota-Met, -CKD3, -CKD4; Some Benefits	-3	62
Phase III Top-Line Results	Merck & Co., Inc.	Keytruda (pembrolizumab) Plus Chemo	Breast Cancer, Triple-Negative	KEYNOTE-522; Met One Co-Primary Endpoint	2	43
Phase III Top-Line Results	Pfizer Inc./Eli Lilly	tanezumab	Chronic Low Back Pain	TANGO; Mixed Results	0	55
Phase III Top-Line Results	Atlantic Healthcare plc	Camligo (alicaforsen) enema	Ulcerative Colitis	Pouchitis; Missed Co-Primary Endpoints	-34	55
Phase III Trial Initiation	Biohaven Pharma	verdiperstat	Multiple System Atrophy	M-STAR (MSA); At 50 Sites	35	52
Phase II/III Trial Initiation	Momenta Pharmaceuticals, Inc.	nipocalimab	Warm Autoimmune Hemolytic Anemia	An Adaptive Study		30

Source: Biomedtracker | Informa, 2019

Indivior Submits Products For Approval Outside US

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Indivior PLC is working towards achieving marketing approvals for its buprenorphine containing products, Suboxone Film and its once-monthly injectable, Sublocade, in markets outside the US, a small piece of good news for the embattled addiction therapy company.

The once-monthly Sublocade (buprenorphine subcutaneous) injection is now approved in the US, Australia (approved on 17 July) and Malaysia, and the company is responding to questions from regulators on Sublocade marketing submissions in the EU, Israel and New Zealand. Marketing applications are also underway for Suboxone (buprenorphine/naloxone) Film in the EU (approvals expected in Q1 2020), Canada (submitted in June 2019, approval expected in Q1 2020), Israel and New Zealand.

Further, Indivior's second product in the launch phase in the US, Perseris (once-monthly risperidone injection), is being prepared for a marketing application in Canada, Indivior's chief scientific officer Christian Heidbreder told analysts in a 1 August call. And INDs are being prepared for its orexin 1 receptor antagonist, C4X3256, a potential non-opioid medication for opioid use disorder, and APV202701A, a selective dopamine D3 receptor antagonist for substance abuse disorder.

The firm is also focusing its R&D efforts on addressing treatment-related questions, such as duration of benefits after the end of treatment. Heidbreder noted that in preliminary data from the RECOVER study, involving patients evaluated 12 months after the last dose of Sublocade, there was a clear relationship between the treatment duration on Sublocade and the level of abstinence, as reported by patients and on a urine drug screen.

Another fillip seen in Indivior's first-half results, reported on 31 July, was that Suboxone Film sales in the US did not decline as quickly as expected after the advent of generic competition earlier this year.

This unexpected turn of events allowed the UK-headquartered Indivior in the middle of July to revise upwards its financial guidance for the year and also to add to its cash reserves which now total just under $1bn, which will be "very helpful as we face the uncertainties" of the coming year, said CEO Shaun Thaxter in the 2 August call. That said, generic erosion is expected to return to industry norms over the coming months and is likely to account for 80% of the buprenorphine/naloxone film market by the end of the year.

Indivior is facing legal action from the US Department of Justice involving alleged improper marketing of Suboxone Film and/or tablets in the US, against which on 19 July Indivior filed a motion to dismiss, but a seven-week trial is scheduled to begin on 11 May 2020. The DoJ is seeking to recover $3bn, but Indivior says it has a strong defense against the allegations.

Published online 2 August 2019

APPOINTMENTS

Executive	To Company	New Role	From Company	Previous Role	Effective Date
Anders Karlsson	Idogen AB	Chief Executive Officer	Allenex AB	Chief Executive Officer	19-Aug-19
Graham Dixon	Mithra Pharmaceuticals	Chief Scientific Officer	Zaluvida	Group Head, R&D	16-Jul-19
Catherine Stehman-Breen	Obsidian Therapeutics Inc	Chief Development Officer	Atlas Venture	Entrepreneur-In-Residence	25-Jul-19
Ryan Daws	Obsidian Therapeutics Inc	Chief Financial Officer and Head, Business Development	Robert W. Baird & Co	Managing Director	25-Jul-19
Nicholas Adams	ReNeuron Group plc	Vice President, Business Development and Alliance Management	Redx Pharma	Chief Business Officer	12-Jul-19
Kris Elverum	Rubius Therapeutics Inc	Senior Vice President, Business Development and Strategy	Turnstone Biologics	Senior Vice President, Corporate Development	25-Jul-19
Setareh Shamsili	Selvita SA	Chief Medical Officer	AxImmune	Chief Medical Officer	25-Jul-19

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