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Pfizer CEO Albert Bourla

Pfizer's Transition: From "Revenues Now" To Pipeline Development

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Pfizer Inc. is reorienting its business development strategy from bringing in "revenues now" to building out the pipeline, CEO Albert Bourla said during the company's first quarter sales and earnings call April 30. The chief executive has been outspoken about his desire to avoid mega-deals since taking over as CEO 1 Jan from Ian Read and offered a few more details on the company's business development strategy, which includes continued interest in gene therapy.

"Before we were targeting revenues now or soon … because this is what we needed at the time," Bourla said. "Now our growth trajectory, I think, organically is going to be robust post-2020, so what we are looking for is to enhance even further our pipeline."

The company is bracing for a challenging year in 2019 and through the first half of 2020 because it is poised to lose its number-two seller, Lyrica (pregabalin), to generic competition in June. The company has guided investors to expect roughly flat revenues in 2019 versus 2018 before cycling through the loss in 2020. *(Also see "Pfizer: Time To Face The Lyrica Pain" - Scrip, 29 Jan, 2019.)*. Then, Pfizer believes it is poised for a period of growth driven by drugs like Ibrance (palbociclib), Xeljanz (tofacitinib), Xtandi (enzalutamide) and new launches like tafamidis for the treatment of transthyretin amyloid cardiomyopathy, which is pending at the US FDA, and a new 20-valent pneumococcal vaccine in development.

Chief Business Officer John Young, who oversees business development, said the focus will be on early- to mid-stage opportunities where the clinical risk is higher but the opportunity for creating value is greater.

"Assets that are in the range of a few billion, we consider to be bolt-on acquisitions and to really complement our pipeline," Young added.

Under the prior strategy, Pfizer brought in products like Xtandi through the $14bn acquisition of **Medivation Inc.** in 2016. The company added the late-stage non-steroidal phosphodiesterase-4 inhibitor crisaborole for atopic dermatitis with the acquisition of **Anacor Pharmaceuticals Inc.** for $5.2bn in 2016, now on the market as Eucrisa. Pfizer also bought **AstraZeneca PLC**'s commercial and late-stage antibiotics portfolio for $550m up front and a delayed $175m payment plus sales milestones.

Xtandi contributed $168m to Pfizer's top-line in the first quarter, representing its share of sales from the alliance with **Astellas Pharma Inc.** The sales came in softer than some analysts expected, but Pfizer said it remains optimistic about the product's growth coming from expanded indications. Eucrisa revenues have been notably disappointing, however. The topical product generated only $22m in the first quarter, a decline of 12%, which the company attributed to higher rebating. Pfizer forecast peak sales of $2bn for crisaborole at the time of the acquisition. In contrast, Pfizer's

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Gilead separates CAR-T specialist business unit (p4)

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from the editor

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Most of the larger pharma companies have now reported their results for the first quarter of this year. *Scrip*'s writers have been poring over the figures and analysing management comments and conference calls to fast-track our readers to the key things you need to know. From Pfizer's first quarter under the leadership of Albert Bourla (see cover story) to Gilead's first month under the leadership of Roche émigré Daniel O'Day (see p4), we bring you strategy updates, product sales detail and geographical sales analysis.

This quarter saw several groups benefit from recent growth in China, although AstraZeneca cautioned that this is expected to moderate as the year goes on (see p8). Nevertheless, the potential of markets beyond the traditional core markets of the US and EU once again is in the ascendant for pharma. As Merck & Co CEO Ken Frazier put it, current product sales in markets like China have only "scratched the surface" of the opportunity that may be available (p7).

What is exciting many pharma companies is that whereas not so long ago China was most apt to be targeted with "established" (ie older, less costly and therefore less profitable) products, recent policy initiatives have favoured innovative treatments, opening the door to reimbursement for higher-priced novel therapies.

For further analysis of what we have learned from the Q1 earnings season, why not register for our webinar, which is being hosted on 14 May by Scrip writers Jessica Merrill, Mandy Jackson and Kevin Grogan? You can find further details of Informa webinars at pharmaintelligence.informa.com/events/webinars

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Lower-Cost Competitors Hit Amgen's Blockbusters

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Amgen Inc.'s legacy products saw significant declines in the first quarter in the face of generics and biosimilars, but the firm is confident newer products can eventually pick up the slack. However, sales of its new migraine therapy Aimovig (erenumab) declined from the fourth quarter.

Amgen said when it reported $23.7bn in full-year 2018 revenue that it expected 2019 revenue to be about $1bn-$2bn lower, within the range of $21.8bn to $22.9bn. The company narrowed its revenue guidance slightly to a range of $22bn-$22.9bn when it reported first quarter earnings on 30 April, but it remains to be seen how many additional lower cost versions of its drugs will launch this year and how much new products will make up for 2019's revenue decline.

First quarter total revenue of $5.56bn was essentially flat compared with the same period in 2018 and in line with expectations – just $2m below analyst consensus. However, first quarter sales declined to $5.29bn, which was down 1% year-over-year from $5.34bn and $38m below consensus.

Since Amgen expects revenue to decline by $800m-$1.7bn in 2019, that means sales still have several hundred million dollars or more to fall this year.

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most recent deal was an option to buy the privately-held French gene therapy developer **Vivet Therapeutics** for €45m up front. *(Also see "Pfizer Buys Option For Vivet In Latest Gene Therapy Tie-Up" - Scrip, 20 Mar, 2019.)* Pfizer has several gene therapy programs in clinical development, including for Duchenne muscular dystrophy and hemophilia A, and has been building out its manufacturing capabilities.

MORE GENE THERAPY DEALS

Bourla said gene therapy will continue to be an area of interest for Pfizer when it comes to business development.

"Gene therapy is an area of significant focus for us," he said. "As we look in the future, we plan to do both, to grow our platform organically through drugs that we are developing and inorganically through licensing and partnerships."

Because of Pfizer's investment in manufacturing, Bourla said he believes Pfizer will be a partner of choice for gene therapy developers. Gene therapy has been a big focus for business development across the industry this year, perhaps most notably with **Roche**'s $4.8bn acquisition of **Spark Therapeutics Inc.** announced in February.

Pfizer's first quarter revenues increased 2% to $13.1bn, with biopharmaceuticals revenue up 3% to $9.2bn, driven by strong double-digit growth of brands like Eliquis, Ibrance and Xeljanz and 8% growth from Prevnar 13. Net income increased 9% to $3.88bn, Pfizer reported. The company reaffirmed 2019 revenue guidance of $52bn-$54bn.

TANEZUMAB PROSPECTS DIM

The prospects for one potential near-term growth driver appear to be diminishing, however. Pfizer has been developing a high-risk, high-reward asset with **Eli Lilly & Co.**, the nerve growth factor inhibitor tanezumab for pain, but recently announced disappointing Phase III data in patients with moderate-to-severe osteoarthritis of the hip or knee. The high dose in the study hit two of three efficacy endpoints but the lower dose of tanezumab missed all three efficacy endpoints, an issue since the treatment is associated with serious safety issues, including disease worsening. *(Also see "Lilly/Pfizer's Tanezumab Safety Takes A Hit With Latest Phase III Results" - Scrip, 19 Apr, 2019.)*

Pfizer had little more to say on tanezumab beyond what the company's statement when the data was released. "We plan to review the totality of the data with regulatory authorities and will assess potential next steps for tanezumab," Young said. An update should be coming within months, he added. Lilly echoed similar comments during its first quarter call the same day. The future of tanezumab certainly seems in doubt, however.

On the other hand, Pfizer is preparing to launch tafamidis for the treatment of transthyretin amyloid cardiomyopathy. FDA action on the application is expected in July, and Pfizer has big ambitions for the product even though ATTR-CM is a rare disease that is frequently misdiagnosed as heart failure. The company anticipates a big education hurdle and a slow ramp at launch, while it builds the treatment market.

"Diagnosis is going to be key to growing this market," Biopharmaceuticals Group President Angela Hwang said. "This will all take time because we need to educate both physicians and patients on these red flag symptoms. We need to drive the utilization of scintigraphy, and we also need to advocate for the changes in treatment guidelines, which will help to drive both diagnosis and treatment."

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Gilead To Let Kite Fly Free; O'Day Says It Will Become Separate Business Unit

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Saying he wanted to "make some swift decisions here," new **Gilead Sciences Inc.** CEO Daniel O'Day told the company's first quarter 2019 earnings call on 2 May that **Kite Pharma Inc.** will become a separate business unit of the company with its own CEO, for whom a search effort is under way.

O'Day joined Gilead from Roche and took over as CEO on 1 March, succeeding John Milligan, who along with predecessor John Martin had overseen the company's direction since 1996. *(Also see "Gilead Lures Roche Pharma CEO O'Day As CEO; Genentech's CEO Will Replace Him " - Scrip, 10 Dec, 2018.)* As Gilead has worked gradually to diversify its focus from virology, its $11.9bn purchase of CAR-T specialist Kite in August 2017 was seen as primary in shaping the firm's future direction.

> "I think we have a leadership position, but I think we need to maintain that leadership position."

The acquisition was quickly followed by Yescarta's (axicabtagene ciloleucel) US FDA approval for third-line relapsed or refractory large B-cell lymphoma in October 2017, but the product's growth has been viewed as sluggish at times and Gilead endured setbacks with other assets from the Kite pipeline. *(Also see "Gilead/Kite Pricing For Yescarta Undercuts Novartis's CAR-T Kymriah" - Scrip, 18 Oct, 2017.)* For first quarter 2019, Gilead reported Yescarta sales of $96m, up 19% from $81m in the

fourth quarter of 2018 as well as up 140% year-over-year, but the cancer cell therapy business has been slow to develop.

O'Day said the decision – announced internally in late March – to make Kite a separate, autonomous unit is about focus.

"Once appointed, [the new Kite CEO] reports to me and will have full accountability for all aspects of cell therapy," he told the call. "I believe that providing Kite with this degree of autonomy will foster agility, innovation and entrepreneurialism. Cell therapy is a critical piece of the puzzle with regards to the long-term future of oncology and a critical element of Gilead's long-term strategy, helping us to build on a legacy of transformational medicines."

O'Day later acknowledged that while Kite has given Gilead a leadership position in cell therapy, much work is needed to stabilize that position. That was one of the main conclusions he drew from both internal discussions and talks with investors during his first two months on the job, he added.

"As I looked out and held discussions with the team, [I realized] that Kite itself in cell therapy oncology is [in] an ultra-competitive area. I think we have a leadership position, but I think we need to maintain that leadership position," the exec explained. "And for the results of focus, we decided to create Kite as an independent business unit that will wake up and go to sleep every day thinking about how to be leaders in oncology cell therapy."

This decision won't exclude Kite's team from working with the rest of Gilead to complement its oncology efforts, O'Day continued. "But we need to make sure to be secure in their leadership in cell therapy, while we complement it with combination approaches and immuno-oncology or targeted therapies or other mechanisms," he said.

Jefferies analyst Michael Yee called Yescarta's first quarter performance solid in a same-day note and generally in-line with expectations as the CAR-T product now offers Gilead roughly a $400m annual run rate. This looks good especially in comparison with **Celgene Corp.**'s JCAR017, which is not even filed yet for approval at the FDA, he added.

Novartis AG's competing CAR-T product, Kymriah (tisagenlecleucel), approved to treat pediatric acute lymphoblastic leukemia and relapsed, refractory non-Hodgkin lymphoma, yielded sales of $45m during the first quarter.

Overall, O'Day told his first earnings call as Gilead's top executive that his immediate top priorities are to strengthen the R&D pipeline both internally and externally, ensure optimal commercial delivery of the company's current and near-market products and optimize the organization by "ensuring that we have the right people in the right roles and that they are well equipped for success."

Refusing to be drawn out on business development strategy despite multiple questions, O'Day said that between now and the end of 2019, he anticipates holding talks with his team and with Gilead's board to develop a longer-term strategy for the company. "I anticipate that later this year, I'll be in a position to begin sharing more with all of you," he said.

O'Day concluded his remarks by noting the recently announced retirement plans of long-time Chief Financial Officer Robin Washington. He said he had hoped to work with her longer, but appreciated her decision and also her willingness to stay on until 1 March 2020 to aid in his transition.

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Novartis Settles Short-Lived Suit Over Janssen's Psoriasis Drug Promo

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Novartis AG and **Janssen Pharmaceutical Cos.** psoriasis drugs will continue battling it out in the US market rather than court, as the two have settled Novartis' suit seeking to halt Janssen's promotional material comparing the safety of their products.

The settlement comes less than two months after a court denied Novartis' request for a temporary restraining order and preliminary injunction to prevent distribution of material describing the results of the head-to-head ECLIPSE study of Janssen's interleukin-23 inhibitor Tremfya (guselkumab) versus Novartis' interleukin-17A inhibitor Cosentyx (secukinumab).

Novartis claimed a brochure and slide summarizing the safety findings of the study omits adverse events and suggests Tremfya is safer. *(Also see "Novartis Can't Halt Janssen's Promo Comparing Their Psoriasis Drugs " - Pink Sheet, 5 Mar, 2019.)*

In a 25 April court filing, the two companies noted that the case was dismissed and that they would bear their own costs and attorneys' fees.

The companies declined to provide the terms of the resolution, saying only that they settled the case "to their mutual satisfaction."

The litigation reflects how intensely competitive the psoriasis market is. Cosentyx and Tremfya are among 12 psoriasis products approved in the US, with many more in the pipeline.

TNF-ALPHA INHIBITORS DOMINATE MARKET

Datamonitor Healthcare's March 2019 report, "Psoriasis Pricing, Reimbursement, and Access," notes that IL-23 inhibitors have strong efficacy potential over IL-17 inhibitors. But it said the superiority data will drive physician preference rather than formulary positioning. To date, Tremfya is the only drug to demonstrate superiority against Cosentyx. *(Also see "ECLIPSE: J&J's Tremfya Beats Novartis' Cosentyx For Long-Term Psoriasis Clearance" - Scrip, 12 Dec, 2018.)*

The report says that despite the availability of IL inhibitors with superior efficacy, TNF-alpha inhibitors will continue to dominate first-line treatment. They include **AbbVie Inc.**'s Humira (adalimumab), **Amgen Inc.**'s Enbrel (etanercept), Janssen's Remicade (infliximab), and **UCB Group**'s Cimzia (certolizumab pegol).

"US payers note that the savings generated from the contracts for TNF-alpha inhibitors surpass what is possible with ILs, due to the former's wide number of approved indications, while in Europe biosimilar adalimumab and etanercept present a cost-saving opportunity," the report states.

The report also includes a run down of the annual treatment costs of 12 psoriasis drugs in the US, Japan, and five major European Union markets (*see page 6*).

Cimzia is at the top of the list in the US, with an annual treatment cost of $122,513, followed by Tremfya, which has an annual treat-

Psoriasis Drug Pricing

The cost of psoriasis drugs in the US are dramatically higher compared to other major markets. Annual treatment costs for key drugs in seven major markets, 2019.

MANUFACTURER/DRUG	US	JAPAN	FRANCE	GERMANY	ITALY	SPAIN	UK
UCB Cimzia	$112,513	N/A	$9,035	$17,552	$7,210	$13,639	$22,057
Novartis Cosentyx	$67,326	$17,493	$13,078	$16,531	$7,430	$16,444	$18,763
Amgen Enbrel	$63,336	N/A	$9,265	$16,344	$28,943	$9,726	$11,029
AbbVie Humira	$67,263	$14,948	$8,172	$16,735	$7,573	$14,790	$8,696
Sun Pharma Illumya	$57,443	N/A	N/A	N/A	N/A	N/A	N/A
Celgene Otezla	$41,342	$6,530	$7,271	$12,603	$5,898	$5,817	$8,607
J&J Remicade	$28,466	$18,036	$6,609	$15,808	$7,586	$14,459	$12,123
Bausch Health Siliq	$45,500	$17,499	$12,750	$16,013	$9,150	N/A	$19,756
J&J Stelara	$47,677	$17,423	$10,238	$19,004	$7,446	N/A	$11,030
Eli Lilly Taltz	$67,101	$17,490	$11,809	$16,056	$7,957	$14,537	$17,336
J&J Tremfya	$70,586	$19,084	N/A	$19,682	$8,104	N/A	$17,345

Source: Datamonitor Psoriasis, Reimbursement and Access Report; ex-manufacturer prices calculated from formulary listings

ment cost of $70,586. Cosentyx is slightly less costly at $67,326. Novartis' top product, Cosentyx had net sales of $791m for the first quarter of 2019 while Tremfya had worldwide sales of $217m for the first quarter. J&J touted the success of Tremfya in its quarterly earnings call, noting that it has secured a 6.9% share of the psoriasis market in the US. The latest entry to the US market is AbbVie's IL-23 inhibitor Skyrizi (risankizumab-rzaa), which was approved by FDA on 23 April for moderate-to-severe psoriasis in adults. It is the third "pure" IL-23 inhibitor approved for psoriasis treatment in the US, following Tremfya and Sun Pharmaceutical's Ilumya (tildrakizumab-asmn). *(Also see "AbbVie's Humira Succession Plan Begins Taking Shape With Skyrizi US Approval" - Scrip, 24 Apr, 2019.)*

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Dupixent And Vaccines Dominate As Sanofi Profits Rise

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Sanofi's first-quarter financials have shown stronger sales and earnings growth than had been expected, while the US performance of anti-inflammatory Dupixent suggests it will comfortably reach blockbuster status by the end of 2019.

After pipeline overhaul, Sanofi prepares for growth

Dupixent (dupilumab), which is partnered with **Regeneron Pharmaceuticals Inc.**, generated sales of €329m (+186.9%), with the US making up €266m of that, driven by continued growth in adult atopic dermatitis and by a successful launch for asthma. Sanofi noted that "market access for Dupixent in asthma reached 90% of commercial lives within the first five months of launch" and will be boosted further after becoming commercially available for adolescent atopic dermatitis in mid-March in the US.

Other indications beckon for the drug which was granted a priority review in March by the US Food and Drug Administration in adults with chronic rhinosinusitis with nasal polyps. In the same month, the European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion for Dupixent as add-on maintenance treatment for severe asthma. Sanofi is looking at other indications for the IL-4/IL-13 inhibitor: a Phase IIb/III study evaluating Dupixent in chronic obstructive pulmonary disease (COPD) is in the process of being initiated.

The French major's multiple sclerosis pill Aubagio (teriflunomide) continues to sell well, up 11.9% to €437m, while its rare disease franchise of drugs for Pompe, Gaucher and Fabry diseases saw sales increase 10.1% to €766m. Sanofi's vaccines business is also thriving, up 20.1% to €873m.

Cablivi (caplacizumab), for the treatment of adults with acquired thrombotic thrombocytopenic purpura (aTTP), which Sanofi got hold of through its €3.9bn acquisition of Belgium's **Ablynx NV** last year, contributed €5m from the two countries where it had been launched thus far, Germany and France; Cablivi only hit the US market on 2 April this year, but Sanofi CEO Olivier Brandicourt said on a first-quarter earnings call that

physician reaction to the drug, as well as to the firm's recently launched PD-1/L1 inhibitor Libtayo (cemiplimab) for cutaneous squamous cell carcinoma, has also been positive; the drug has today (26 April) received a positive opinion from the CHMP.

CHINA BOOST

Geographically, in common with a number of other European pharma players, Sanofi has been benefiting from significant growth in China, with sales there rising 22.3% to €798m. However, Brandicourt cautioned that the end of the first quarter saw the implementation by the Chinese authorities of a volume-based procurement program in key cities, which is expected to result in lower growth rates, meaning the first-quarter figures will be stronger than results for the rest of 2019.

There were some disappointments, however. Eloctate (recombinant Factor VIII) for hemophilia A dipped 4.2% to €174m, well below consensus. It was hit by competition from **Roche**'s Hemlibra (emicizumab) and the latter's expanded approval in the US last fall for adults and children without factor VIII inhibitors. First-quarter diabetes sales fell 6.9% to €1.29bn, mainly owing to lower sales in the US of insulin glargine products Lantus and Toujeo, while the revenue rise for the cholesterol therapy Praluent (alirocumab), up 10.2% to $56m but down 26.9% in the US, was lower than consensus forecasts as higher US rebates continued to impact sales of the injectable PCSK9 inhibitor.

In terms of R&D updates, as well as the Dupixent COPD trial, Sanofi has begun a Phase IIb study evaluating SAR442168, a Bruton's kinase (BTK) inhibitor partnered with Principia for multiple sclerosis, and a Phase II trial looking at isatuximab in combination with chemotherapy in pediatric patients with relapsed refractory acute lymphoblastic leukemia or acute myeloid leukemia. SAR441169, a ROR gamma T antagonist, entered Phase I for the treatment of psoriasis.

The Paris-headquartered drug maker unveiled an R&D pipeline overhaul earlier this year and on the first-quarter earnings call, research chief John Reed said that while the review was not yet complete, he does not expect "major changes." He added that Sanofi would continue to be "very active" in seeking opportunities to supplement its portfolio.

Analyst reaction to the results was positive on the whole. Morgan Stanley issued a note saying that while "the weak performance on a couple of products will raise questions – Praluent and Eloctate," the strong showing of vaccines and Dupixent, plus better cost control that led to a better than expected business earnings per share growth of 9.4%, "are a clear positive." Regarding the pipeline, it noted that while the Principia-partnered product was "two years behind the competition in this class [namely Merck KGaA's BTK inhibitor evobrutinib], …the proposed differentiation is that the drug can cross the blood-brain barrier, potentially driving higher efficacy."

Jefferies analyst Peter Welford issued a note saying that he was optimistic about "the focus growth driver Dupixent, which offsets greater caution on Lantus. We believe the pipeline offers intriguing optionality, overlooked by many, and see steady future margin expansion."

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Merck & Co's Frazier: International Business Is Only Scratching The Surface

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Merck & Co. Inc.'s sales in China grew by 58% to $275m in the 2019 first quarter, or by 67% excluding the negative impact from foreign exchange. That double-digit growth, led by newly launched products, prompted chairman and CEO Ken Frazier to highlight the beneficial effects of non-US markets on the company's business.

"Our international business, which represented nearly 60% of our sales this quarter, has strong momentum, and we believe we have only scratched the surface, in terms of the opportunity we are now seeing in key markets, including China, where we are seeing significant growth," Frazier commented. "We foresee a stream of additional approvals from our current portfolio of products across markets globally, and we will look to maximize those opportunities, powered by our commercial team's proven ability to execute," he added.

Merck reported an impressive start to 2019 financially, with CFO Robert Davis calling it "one of the company's strongest quarters in its recent history."

Merck reported an impressive start to 2019 financially, with CFO Robert Davis calling it "one of the company's strongest quarters in its recent history." Merck's sales increased by 8% to $10.8bn in the first quarter of 2019, or by 11% excluding the negative impact of foreign exchange rates, compared with the first quarter of 2018, with the double-digit growth led by oncology, vaccines, and select hospital and specialty care products.

"In China, we are seeing strong sales of Keytruda (pembrolizumab), following its approval last year in metastatic melanoma, and we are very excited about our recent approval in China for Keytruda in first-line lung cancer," Davis said. Chief Commercial Officer Frank Clyburn explained that Merck intended to bring additional Keytruda indications to the China market and was piv-

oting towards innovative rather than established products in that market.

During the first quarter, the strong demand for the HPV vaccine Gardasil/Gardasil 9 continued, with sales of more than $800m in the quarter, representing growth of more than 31%, with particularly strong uptake in China, Davis said. Sales in Merck's hospital products business segment were led by the recently launched neuromuscular blockade reversal agent Bridion (sugammadex), whose sales grew by 30% to $255m.

He also noted that sales of Lynparza (olaparib, marketed with partner **AstraZeneca PLC**) doubled during the first quarter, driven by further uptake in ovarian cancer following the outcome of the SOLO-1 study.

The growth in oncology products led to one of the first questions asked on the analysts' earnings call on 30 April being about whether Frazier now considered Merck to be pivoting away from being a primary care company post-Januvia, a traditional strength of Merck, to become a specialty company.

The suggestion was rejected by Frazier, who argued Merck was focused on following the science and taking advantage of the best opportunities that brings. "Currently, growth is being driven by oncology, but if you look at our pipeline, we have pneumococcal vaccines, for example, which are essentially primary care-type products, so we haven't committed ourselves to one particular area of medicine," Frazier commented. The Merck exec also said following the science was one of the key drivers behind the company's business development plans, where bolt-on deals were currently the most attractive. However, with stock markets staging a recovery since the beginning of this year, potential targets have become more fully valued, Frazier noted.

GUIDANCE RAISED

Merck & Co raised its 2019 full-year GAAP EPS range to between $4.04 and $4.14 and narrowed and raised its 2019 full-year non-GAAP EPS range to between $4.67 and $4.79, including a small positive impact from foreign exchange, when presenting its 2019 first-quarter results.

Sales were led by blockbuster Keytruda, which now represents 23.5% of Merck's pharmaceutical sales, and whose sales rose by 55% to $2.27bn in the quarter, driven by higher first-line use in non-small cell lung cancer (NSCLC), both as monotherapy and by the roll-out of its use in combination with chemotherapy.

Although impressive, analysts suggested that Keytruda sales were below expectations in the first quarter, a view not held by CCO Clyburn. "We are seeing very good continued underlying demand for Keytruda, despite inventory movement quarter on quarter, and in particular we are seeing strong underlying demand in the lung cancer indications both in squamous and in non-squamous NSCLC. Indeed, in squamous lung cancers we are seeing our market shares exceed 75% for new patients, so we have become the standard of care in that subset of patients," Clyburn said.

He also said Merck was very excited about the opportunity for Keytruda beyond lung cancer, including in renal cell carcinoma, where there is a very strong opportunity for growth, and in head and neck cancer, where Merck is excited about the opportunity in earlier lines of therapy. "We also see significant opportunity for the roll out of additional indications in Japan, China and Europe," he added.

Questioned about companies in China that have checkpoint inhibitors in last-stage clinical trials, Clyburn noted that the oncology market is data-driven, and the "wall" of data that Merck has on Keytruda will differentiate it from potential competitors.

Among non-oncology products, sales of the antidiabetic Januvia/Janumet (sitagliptin) declined by 5% to $1.35bn in the 2019 first quarter, Merck reported. A US PDUFA date of 3 June 2019 has been given for the priority review of a supplemental NDA for Zerbaxa (ceftolozane/tazobactam) for the treatment of adults with nosocomial pneumonia, including ventilator-associated pneumonia caused by certain susceptible Gram-negative micro-organisms. Europe's regulators are also reviewing the same additional indication. Also in the middle of 2019, a priority review of relebactam combined with imipenem/cilastatin for Gram-negative infections with limited or no alternative therapies has a PDUFA review date of 16 July. During the first quarter, Europe's regulators accepted an MAA for the Ebola-Zaire vaccine candidate, V920.

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AstraZeneca CEO: Explosive Q1 China Growth Will Ease In 2H, Then Reignite

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AstraZeneca PLC's CEO said the 28% sales growth generated by the group in China during the first quarter of 2019 would decline later in the year, thanks to price trends.

But Pascal Soriot added that he remained bullish about market access prospects there for the UK pharma's innovative medicines and for continued strong revenue gains in China going forward. The French CEO was speaking on 26 April when presenting AstraZeneca's first-quarter update – which, as expected, showed solid growth buoyed by cancer drug sales and reduced pressure from patent losses, allowing the UK drug maker to confirm its 2019 product sales guidance of high single-digit growth, as revenue from recently launched therapies continued to expand. *(Also see "Q1 Drug Sales, Pipeline, 2019 Catalysts Top Themes For AstraZeneca Update" - Scrip, 23 Apr, 2019.)*

The update contained AstraZeneca's third successive quarter of rising sales, and reflected a strong showing in emerging markets, especially China, with posted growth of 22% and 28%, respectively.

That heady advance in China during the year's first three months will, however, ease later in the year.

"The growth that we've seen in China in this quarter is suddenly going to be lower in the second half of this year, because we will be impacted by tendering there," Soriot told reporters.

"We won the Iressa [lung cancer] tender, which was really the only tender won by an innovative international company .... But we lost a Crestor tender, and we will thus be impacted there," Soriot explained, referring to the company's cholesterol reducing drug.

On 25 October 2018, China's National Health Commission (NHC) released its latest National Essential Medicines List (NEML), the first update to the list in three years.

To win its bid, though, AstraZeneca agreed to lower the price of lung cancer product Iressa (gefitinib) by 76%.

"So we will definitely see a lower growth rate in the second half of this year in China," the CEO said.

"We still believe we can deliver very strong, double-digit growth, and see growth of 15% to 20% on a forward moving basis, but not the 25% to 30% growth that we experienced recently," he added.

IRESSA PROSPECTS

Soriot saw Iressa eventually riding strong demand in Asia, and in China in particular, which should buoy the drug's prospects there.

"EGFR mutations are probably seen in 15% to 20% of lung cancers in the West - but in Asia it's up to 40%, sometimes 45%," the CEO said.

"Almost half of all lung cancer patients have an EGFR mutation in China. Combine this with the size of the population and the fact that patients until now didn't get access to Iressa or any of the EGFR (epidermal growth factor) agents because they were too expensive," he said.

"The growth that we've seen in China in this quarter is suddenly going to be lower in the second half of this year, because we will be impacted by tendering there." - AstraZeneca CEO Pascal Soriot

"And as we give patients there access to a first-line treatment, we also establish a need for second-line use of Tagrisso, which is also reimbursed, but only for second line."

Next-generation EGFR inhibitor Tagrisso (osimertinib) was added on China's national reimbursement drug list as a second-line treatment for lung cancer as of the start of 2019. AstraZeneca said it expected a regulatory decision to come in the second quarter for Tagrisso 's use as a first-line treatment in China, too.

AS CHINA EVOLVES

Soriot said he saw the issue of pricing becoming more of an issue in China, as the country transitioned towards more of a western-style approach to medicine provision.

"We've seen better access to new medicines, better reimbursement ... On the other hand we also see a focus on getting lower prices for generics," he told reporters.

But China is increasingly focusing on innovation, he added.

"We've seen acceleration of review and approval of new, innovative medicines ... We've seen funding being deployed to reimbursing and facilitating access to new, innovative medicines like Tagrisso and Farxiga (dapagliflozin) which, quite frankly, not long ago, nobody would have thought would be reimbursed."

"Everything we've seen happening over the last year or two in China goes in the right direction," Soriot concluded.

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Teva's Ajovy Claims 28% To 30% New Prescription Share In Competitive CGRP Race

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Teva Pharmaceutical Industries Ltd. said its calcitonin gene-related peptide (CGRP) inhibitor Ajovy (fremanezumab) for migraine prevention has captured a roughly 28% to 30% share of new prescriptions in the competitive market following the initial launch, and that it expects that level of market share to persist.

Investors were eager to hear more about the early launch of Ajovy and another new drug, Austedo (deutetrabenazine), during the company's first quarter earnings call on 2 May. The two drugs are expected to be important future growth drivers for Teva as sales of the company's big seller Copaxone (glatiramer) decline.

The launch of Ajovy in particular is being closely watched because of the big market opportunity in migraine prevention, but also because Ajovy is in the unique position of launching at the same time as two rival CGRP inhibitors – **Amgen Inc./Novartis AG**'s Aimovig (erenumab) and **Eli Lilly & Co.**'s Emgality (galcanezumab). It is still unclear if one of the three products might shake out on top, but payers are playing hard ball when it comes to market access by pitting the drugs against one another.

Ajovy generated $20m in first quarter sales, beating analyst consensus estimates, while Aimovig generated $59m, lower than consensus estimates and a sequential decline versus fourth quarter 2018. Emgality generated $14.2m in the first quarter.

Aimovig had an early jumpstart as the first-to-market product. Amgen reported that Aimovig has a 40% share of the market, leaving Teva and Lilly to split the rest. *(Also see "Lower-Cost Competitors Hit Amgen's Blockbusters" - Scrip, 30 Apr, 2019.)* Aimovig was approved by the US FDA in May 2018, but FDA approvals for Ajovy and Emgality followed closely behind in September. *(Also see "Migraine Market Gets Competitive With Second, Third CGRP Inhibitor Launches" - Scrip, 9 Nov, 2018.)*

It's not at all certain the early advantage will stick, as Teva CEO Kare Schultz indicated during the quarterly call. "The number one to launch normally holds a good grip on the market. That is not the case right now," he said.

The early launch of all three drugs has been particularly hard to evaluate, because the drug makers have been giving product away to patients for free while coverage is worked out. It's also an effort to build up usage to secure high volumes to help with market access. Now more patients are transitioning to covered drug, but the companies are offering steep rebates, which has impacted the net selling price.

Exec VP-North America, Commercial, Brendan O'Grady indicated that drug makers are offering rebates north of 40% on the products.

Teva has forecast Ajovy will generate $150m in 2019, and Schultz reaffirmed that target. "We are very happy with this 28%-30% we are holding right now, and I think that's the kind of level you should expect that we will be holding going forward."

AJOVY AUTO-INJECTOR ON THE WAY

Ajovy is different from Aimovig and Emgality in some respects. It can be dosed quarterly or monthly, while the other two are both dosed monthly, and it is administered in a pre-filled syringe while the other two are administered in an auto-injector.

> "We are very happy with this 28%-30% we are holding right now, and I think that's the kind of level you should expect that we will be holding going forward."

"While that isn't a big issue in a once-a-month injection, I think it's a bit of a drag in the new-to-brand share," O'Grady said. Teva is working to develop an auto-injector, which it hopes will be on the market later this year.

Austedo, approved for tardive dyskinesia and chorea associated with Huntington's disease, generated $74m in the first quarter and is on track to generate a target of $350m in 2019. Austedo is competing against **Neurocrine Biosciences Inc.**'s Ingrezza (valbenazine), which has the market lead in tardive dykinesia and generated $136m in the first quarter.

It remains a challenging year for Teva as pressure in the generic drug market persists, the Copaxone brand continues to decline under generic competition and the company pays down its debt. The company has guided investors to view 2019 as a trough year before returning to growth in 2020. *(Also see "A Trough Year For Teva, With A Turning Point Targeted For 2020" - Scrip, 13 Feb, 2019.)*

Copaxone sales came under even more pressure than expected in the first quarter, but Schultz said he remains confident Teva's earnings will return to growth in 2020. However, swing factors could impact when revenues return to growth, he said.

The silver lining to lower Copaxone sales is getting over the cliff faster. "If Copaxone comes in lower than we expected for this year, it's actually a benefit for next year, because there's less to lose," Schultz pointed out.

Copaxone sales in the first quarter declined 56% to $208 million in North America, where the bulk of sales are generated. In Europe, sales declined 26% to $114m. The company had forecast Copaxone would generate $1.5bn in 2019.

As a result of declining Copaxone revenues and a decline in the US generic business, Teva's first quarter revenues decreased 15% to $4.3bn. North American generics revenues declined 11% in the quarter to $966m, but the company insists the market is stabilizing. Teva reported a net loss of $97m.

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Can Sanofi Catch Up With Amgen Now That Praluent Has CV Risk-Reduction Claim?

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With cardiovascular risk-reduction language added to the product's US label, **Sanofi** and partner **Regeneron Pharmaceuticals Inc.** hope Praluent is now better positioned to compete with rival PCSK9 inhibitor **Amgen Inc.**'s Repatha, which nabbed an outcomes claim in December 2017. Further, the two companies may now hold an edge over the better-selling Repatha as the label update also includes data suggesting an all-cause mortality benefit.

The US FDA cleared the label expansion on 26 April, the same day Sanofi reported that Praluent (alirocumab) yielded disappointing sales of $64m during the first quarter of 2019.

The PCSK9 class came to market in 2015 with high expectations, but sales for the drugs have disappointed due to payer pushback related to initial pricing of approximately $14,000 a year. More recently, payers have eased restrictions based on outcomes data and lower prices.

Amgen got a leg up in the competition when its Repatha (evolocumab) obtained a CV risk-reduction label claim from the US FDA in late 2017, based on its outcomes trial, FOURIER, which found that the drug was associated with a 15% reduction in risk for a composite endpoint of cardiovascular outcomes.

Amgen has enjoyed a nice uptick in Repatha business following its CV outcomes claim. Repatha yielded full-year sales of $550m (up 72%) during 2018, significantly higher than the roughly $280m (€250m) brought in by Praluent. In March, the big biotech said it is launching a new CVOT study called VESALIUS-CV that offers the potential to increase the drug's addressable treatment population by roughly 4.5 million in the US.

Sanofi/Regeneron followed with the ODYSSEY Outcomes trial results in 2018. *(Also see "PCSK9 Inhibitor Labeling Parity Is Within Reach As Praluent And Repatha Strive To Make Commercial Case" - Pink Sheet, 20 Aug, 2018.)* It now remains to be seen whether Praluent can get the same boost in sales.

The ODYSSEY Outcomes study demonstrated in 18,924 patients who experienced acute coronary syndrome within a year of enrollment and were randomized equally to Praluent or placebo on top of statin therapy that Praluent produced a 15% reduced risk for major cardiovascular events (p=0.0003). The study's primary endpoint measured time to first heart attack, stroke, death from coronary disease or unstable angina requiring hospitalization.

The new indication is based on those data, but the updated label also includes other data from ODYSSEY Outcomes that Sanofi/Regeneron can cite, including an all-cause mortality benefit.

The study also demonstrated a 15% reduced risk of all-cause mortality (p=0.026), which could prove a notable differentiation for Praluent compared to Repatha, which does not have a mortality benefit in its label. The trial also showed a 27% reduced risk of stroke, a 14% reduced risk of non-fatal heart attack and a 39% reduced risk of unstable angina requiring hospitalization. "Because statistical testing of these endpoints was performed outside of the [trial's prespecified] hierarchy, the results are not considered statistically significant," the company explained. The all-cause mortality data is included in a table of the outcomes results, with the caveat that it is not statistically significant.

Patients in the outcomes study were assessed for a median of 2.8 years, some up to five years. Roughly 90% of those enrolled were on high-intensity statin therapy prior to randomization. Adverse event rates were similar between the treatment and placebo groups, the companies said, except for injection-site reactions, which occurred in 3.8% of those who received Praluent and 2.1% who received placebo.

PRALUENT'S PRESENT AND FUTURE PERFORMANCE

Total sales of Praluent came to €56m (about $64m) during the quarter, up 10.2% overall, but US sales declined 26.9%. The impact of rebates to reduce the price more than offset the healthy growth in prescriptions for the cholesterol-reducing drug.

Sanofi executive VP of primary care Dieter Winand noted on the firm's 26 April earnings call that Praluent tallied 53% growth in US total prescriptions during the first quarter, but that the impact of that volume growth was diminished by rebating, such as the formulary placement agreement it and Regeneron signed with **Express Scripts Holding Co.** last May. *(Also see "Let's Make A Deal: Sanofi/Regeneron Extend A Hand On Praluent, Express Scripts Takes It" - Scrip, 1 May, 2018.)* The companies followed Amgen's lead in February by slashing the list price of Praluent by 60% to $5,850 per year, at par with Repatha's pricing. *(Also see "Sanofi/Regeneron Cut Praluent List Price As PBMs Look To Maintain Rebate Status Quo" - Scrip, 12 Feb, 2019.)* In tandem with that, Praluent obtained an updated Medicare new drug code (NDC) in February.

Winand said those moves were made in recognition that "it was very important that we maintain very broad access to realize the full potential of the product going forward." He cited the new cholesterol-reduction treatment guidelines released by the American Heart Association and the American College of Cardiology last November – which said the PCSK9 class offered minimal therapeutic value compared to its pricing – as putting additional pressure on Praluent.

"The outlook for Praluent in the US is more volume growth going forward, offset by continued price pressure to maintain the access," the exec said, "while in Europe, we have seen very good growth in Europe with a 53% increase via Praluent. We expect that to continue going forward."

In an 26 April note, BMO Capital Markets analyst Matthew Luchini pointed out that Praluent first quarter sales were well below consensus estimates of $89m. Noting the impact of pricing pressure in the US, the analyst said, "we continue to expect label expansion in the US for reducing CV events in the second quarter of 2019 to inject growth into the drug."

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AbbVie Spotlights Its Early-Stage R&D Pipeline

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Early clinical-stage candidate therapies for glioblastoma multiforme, myelofibrosis, immune-oncologic indications and neurological diseases were highlighted by Michael Severino, **AbbVie Inc.**'s vice-chair and president, during the company's first-quarter earnings call last week.

AbbVie needs to bring a flow of new products to market to replace revenues likely to be eroded in the future by biosimilar versions of its best-selling product, Humira (adalimumab), and Severino noted that, as well as investing in its late-stage pipeline, AbbVie was paying a "large amount of attention and invested to make sure that we have a broad and promising early- to mid-stage pipeline as well."

Severino on 25 April highlighted an EGFR targeted antibody-drug conjugate, Depatux-M (depatuxizumab mafodotin, formerly ABT-414) which, although it is a late-stage program, had not previously attracted a lot of attention. Depatux-M had shown interesting mid-stage data in second-line patients with glioblastoma multiforme and was now in a Phase III study as a frontline agent in glioblastoma, with overall survival as the primary endpoint, Severino reported.

NAVITOCLAX

A molecule which inhibits both BCL-2 and BCL-XL, navitoclax, was in an ongoing Phase II study for the treatment of myelofibrosis in patients resistant or refractory to Jakafi (**Incyte Corp.**'s ruxolitinib).

"Even early on, we're seeing some very interesting responses," Severino said during a call with analysts. AbbVie also has a program targeting apoptosis and TRAIL, which had shown promise in solid tumors.

ABBV-151

In immune-oncology, AbbVie has ABBV-151 (formerly glycoprotein A repetitions predominant, or GARP) that modulated TGF-beta and Treg function and could influence the immunosuppressive environment of tumors.

And in rheumatoid arthritis, AbbVie was evaluating an antibody-drug conjugate that delivered a steroid directly to rheumatoid arthritis-associated immune effector cells, without systemic side effects, Severino remarked.

AbbVie needs to bring a flow of new products to market to replace revenues likely to be eroded in the future by biosimilar versions of its best-selling product, Humira.

In neuroscience, a TAL antibody was in Phase II, and two inflammation assets developed in partnership with **Alector Inc.** were now in the clinic.

Nearer-term, chairman and CEO Richard Gonzalez noted AbbVie had put special effort into developing new therapies for immune-mediated diseases, pointing to the just-US approved psoriasis therapy, Skyrizi (risankizumab-rzaa), which was in late-stage development in several follow-on indications, and the close-to-market rheumatoid arthritis therapy, the oral JAK1 inhibitor, upadacitinib.

UPADACITINIB

Severino reported that upadacitinib had shown strong results across a wide range of patients in AbbVie's clinical trial program, including patients early in the treatment paradigm who were naive to methotrexate, and patients heavily pretreated with biologics.

The candidate was the only JAK1 selective inhibitor to meet all primary and secondary endpoints across all registrational trials and had shown clear superiority to Humira in a head-to-head study, as well as clear structural benefits in two Phase III studies. Upadacitinib was also effective as monotherapy, which AbbVie believed was an important differentiator because many rheumatoid arthritis patients do not respond to or tolerate methotrexate.

VENCLEXTA

With marketed products, a supplemental NDA was awaiting approval in the US for the use of Venclexta (venetoclax) frontline in chronic lymphocytic leukemia, for which it had received priority review and breakthrough therapy designation. This would be an important new treatment option for patients, Severino said.

However, a partial hold was placed on the study of Venclexta in patients with multiple myeloma in the middle of March.

Although the Phase III BELLINI study met the primary endpoint of progression free survival, a higher proportion of deaths was seen in the Venclexta arm of the study than in the control arm. AbbVie was working with the FDA on analyzing the results, but believed there was a potential role for Venclexta in a subset of patients with a t(11;14) biomarker-defined myeloma, which accounted for around 20% of patients with multiple myeloma, Severino noted.

ELAGOLIX

Turning to women's health, Severino said that AbbVie was nearing completion of a pivotal program on elagolix in uterine fibroids; two pivotal studies have shown that elagolix, combined with low-dose hormone add-back therapy, significantly reduced heavy menstrual bleeding compared with placebo. A regulatory application was expected to be filed in the middle of this year.

Elagolix is already marketed by AbbVie in the US as Orilissa for the treatment of moderate to severe pain associated with endometriosis.

ABBV-951

In neuroscience, a Phase III trial was starting of ABBV-951 in advanced Parkinson's disease. ABBV-951 is a levodopa/carbidopa prodrug, which involves the continuous subcutaneous delivery in a less invasive manner.

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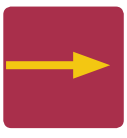

For analysis of AbbVie's financial performance in Q1 see: **https://bit.ly/2Wv9ZPN**

Open-Label Extensions The Key To Gantenerumab Success, Stresses Roche

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Roche remains hopeful that its anti-Alzheimer's antibody gantenerumab can prevail where so many other amyloid-beta-targeting antibodies have failed. Aside from the failure of its own crenezumab, the most recent clinical disappointment was that of **Biogen Inc./Eisai Co. Ltd.**'s aducanumab, in March. *(Also see "Why Biogen/Eisai's Aducanumab Failure Is Not The End Of Amyloid Hypothesis" - Scrip, 21 Mar, 2019.)*

"It is too early for us to draw concrete, scientific learnings from Biogen's announcement," Rachelle Doody, global head of neurodegeneration at Roche Pharmaceuticals, told *Scrip*. "It will be important to see the aducanumab data at an upcoming medical conference to better understand the reasons for the negative outcome of the futility analyses and potential learnings and implications for our programs."

Gantenerumab is one of only three assets in Phase III trials still following an amyloid-focused program. The other being ALZT-0P1, a small molecule designed to block amyloid beta aggregation and polymerization in the brain from **AZTherapeutics Inc.**, and **Biogen**/**Eisai**'s BAN2401, an anti-amyloid protofibril antibody which initiated its Phase III Clarity trial in March.

The list of prior anti-amyloid failures is well known, with disappointments also including **Eli Lilly & Co.**'s solanezumab and **Pfizer Inc./Johnson & Johnson**'s bapineuzumab.

Gantenerumab, which is partnered with **MorphoSys AG**, is a fully human anti-beta-amyloid monoclonal IgG1 antibody that binds aggregated forms of beta-amyloid, including neurotoxic oligomers, and removes amyloid plaques from the brain. *(Also see "Roche In New Phase III Bet On MorphoSys' Anti-Amyloid Agent" - Scrip, 7 Mar, 2017.)*

In Roche's previous Phase III program – SCarlet RoAD / Marguerite RoAD – lower doses of gantenerumab demonstrated exposure-dependent slowing of cognitive decline in fast progressors, as well as effects on downstream markers of neurodegeneration.

When asked how hopeful Roche was about the success of gantenerumab, Doody said the key to demonstrating positive results from ongoing pivotal trials was to incorporate the latest insights from the open-label extensions of the previous Phase III clinical trials SCarlet RoAD and Marguerite RoAD related to dosing, patient population and clinical trial design into its programs.

"These data have guided us to design the current GRADUATE Phase III program with a five-fold higher target dose administered subcutaneously; careful patient selection to enrich for progressors; and an optimized titration schedule to minimize ARIA [amyloid-related imaging abnormalities, associated with anti-amyloid treatment], allowing all patients regardless of APOE4 status to reach target dose and a 24-month study duration," Roche told *Scrip*.

Datamonitor Healthcare analyst Pamela Spicer said she was struck by Roche's response because "it's not spending a great deal of time differentiating its antibody from aducanumab, likely because of the similarities, but rather it is pointing to signals from its own data. Besides increasing the dose from previous trials, Roche may be more narrowly selecting a sub-set of patients, relative to the aducanumab Phase III program, that might improve its chances of success."

The long-term safety, tolerability and biological outcomes of higher doses of gantenerumab are also being evaluated in open-label extensions (OLE) of the previous Phase III clinical trials SCarlet RoAD and Marguerite RoAD.

DEVELOPMENT STRATEGY

Roche's gantenerumab endgame is to be able to provide Alzheimer's disease sufferers with a convenient subcutaneous treatment at home.

The GRADUATE 1 and GRADUATE 2 Phase III studies, which began recruiting in mid-2018, are investigating the efficacy and safety of gantenerumab in patients with early (prodromal to mild) AD over a 24-month period. These studies have been initiated in sites across the world and are currently enrolling.

"Learnings from the field have been incorporated into the GRADUATE program, treating early AD patients with confirmed amyloid positivity who are likely to progress at higher doses," Doody said. "Ad-

ditionally, we designed a titration scheme intended to optimize safety and reduce the incidence of ARIA, allowing all patients irrespective of their APOE4 status to be brought up to target dose. Our endpoint is assessed after 24 months of therapy to optimize detection of clinical benefit."

Gantenerumab is also being studied in familial AD in the DIAN-TU study, a Phase II/III randomized, double-blind, placebo-controlled multicenter study in individuals who have genetic mutations associated with AD.

Spicer recalled that shortly after the aducanumab failure Biogen's EVP of R&D, Mike Ehlers, spoke at an investor conference and pointed to the heterogeneity in the pathology of amyloid, stating that the results from ENGAGE and EMERGE (aducanumab's failed Phase III trials) were definitive for the patient population selected in those trials. "Selection of the right patient population is something that is frequently revisited after major amyloid failures and, here, Roche has mentioned that gantenerumab's current GRADUATE Phase III program is selecting for fast progressors," she said.

"I have looked at the inclusion criteria for these [ENGAGE and EMERGE] programs and there are some slight differences with gantenerumab's program allowing for the inclusion of patients with slightly lower cognition at the outset than aducanumab's (ex. MMSE > 22 vs aducanumab's 24-30 requirement and CDR-GS 0.5 or 1 allowed whereas aducanumab's inclusion required a score of 0.5)," she explained. "Although other anti-amyloid antibodies have failed they, along with gantenerumab, are still being evaluated in even earlier stages of the disease, like DIAN-TU study looking at individuals genetically at risk. Time will tell if these antibodies work in this patient population."Roche said it remained "committed" to the gantenerumab program.

ANTI-TAU PROGRESS

Roche's biotech arm **Genentech Inc.** also continues with the development of the anti-tau molecule RG-6100, an asset that emanated from crenezumab originator **AC Immune SA**, into its second Phase II clinical trial (LAURIET), which is currently enrolling patients with moderate Alzheimer's disease.

"The evidence for tau-targeting therapies is at a much earlier stage than beta-amyloid approaches and support for their role in AD is increasing," it said. The firm is also developing diagnostic solutions with the CSF beta-amyloid, tau Elecsys assays and its tau PET tracers.

Unlike amyloid pathology, which typically spreads throughout the brain prior to any symptoms and may plateau at relatively earlier stages of disease progression, tau pathology continues to accumulate even in later stages of the disease, including in moderate AD dementia, and the spread of tau pathology correlates with the progression of symptoms.

Roche dosed the first patient in its Phase II clinical trial (TAURIEL) in Q4 2017, which has completed its enrollment of patients with prodromal-to-mild AD. In Q1 2019, it also began enrolling patients in its second Phase II clinical trial (LAURIET) in patients with moderate AD.

While Doody would not be drawn on the differences between RG6100 and competing molecules from the likes of Biogen, Lilly, and **AbbVie Inc.**, she said that the chances of success for this candidate were optimized by the fact that it is being tested in a broad range of doses and a broad range of patients, and it is using a novel PET imaging agent, GTP1, to monitor activity.

There are currently 12 clinical stage antibodies targeting beta amyloid and seven clinical stage anti-tau antibodies, led by Eli Lilly, Biogen and AbbVie. There is interest preclinically, also. Most notably these include **Merck & Co. Inc.**, which recently signed a deal to license **Teijin Ltd.**'s preclinical antibody targeting tau protein, and Eisai, with the preclinical candidate E2814, the product of a University College London collaboration which is expected to enter the clinic this year. *(Also see "Eisai Adds To Alzheimer's Arsenal With Anti-Tau Drug " - Scrip, 11 Dec, 2018.)*

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AZ Inks Machine Learning Deal With BenevolentAI

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AstraZeneca PLC has advanced its efforts in the machine learning and artificial intelligence space by linking up with the UK's **BenevolentAI** in a pact it hopes will lead to new drugs for chronic kidney disease and idiopathic pulmonary fibrosis.

In an interview with *Scrip,* Mene Pangalos, head of R&D biopharmaceuticals at AstraZeneca, said that as part of an initiative for future growth known as AZ2025, the company has been looking at technologies that it thinks could improve productivity over the next five to 10 years and one of the areas is machine learning and AI "and how we can apply that across R&D." He believes that great strides have been made in using those technologies in imaging, diagnosis and speech recognition, but can they be implemented "to optimize our molecules, large and small? It takes many years to get a candidate into the clinic so could you write an algorithm that could speed that process up and do it more efficiently?"


Mene Pangalos

Pangalos claimed that AstraZeneca is making good progress on its own and has built up its data scientist teams both in Sweden and at its global R&D headquarters in Cambridge, UK. However, the company wanted to supplement those activities with a leader in the machine learning field, hence the long-term collaboration with BenevolentAI unveiled today (30 April).

London-headquartered BenevolentAI has created a target identification platform and biomedical knowledge graph, which is a network of scientific data on genes, proteins, diseases and compounds and the relationship between them. AI-based reasoning is then used to extrapolate previously unknown connections. *(Also see "BenevolentAI Scoops $115M For AI Drug Development" - Scrip, 19 Apr, 2018.)*

Pangalos said that "if you read in a paper that drug X inhibits target Y, that becomes a pairwise relationship that you can use and then create an algorithm to interrogate." Every data set has hundreds of thousands of relationships within it and it is by investigating those relationships and creating knowledge graphs that scientists will hopefully get novel insights.

Another advantage of these graphs and platforms is that "they're not biased in any way by scientist prejudice. It's basically taking all the data sets that we can find, not just ours, and creating these graphs that basically give you ideas of where to look," he added. It becomes "a living, breathing entity…and the more data we put into it, the stronger and more powerful it will hopefully become."

Pangalos said the key word in the BenevolentAI deal was collaboration . "One of the things I was averse to was just buying something off the shelf, a black box machine learning algorithm that we apply to our data, because the worry is that you have no understanding of what's underneath the hood. Garbage in, garbage out."

With BenevolentAI, "our experts in machine learning and AI will be working side by side with their scientists in Cambridge so that we understand the algorithms, understand what we're designing, what we're developing. They've built something that we think could be very useful, and importantly, they're enabling us to learn at the same time and build our own capability."

As for the specific indications the partners will be looking at, Pangalos said that with chronic kidney disease, AstraZeneca has been working closely with Columbia University and gained genetic insights into risk factors. As for IPF, the company has a treatment called saracatinib, which has completed Phase I development but has AI to thank for it being selected as a potentially useful approach to tackle the lung scarring disease.

SARACATINIB TO BE AI SUCCESS STORY?

Saracatinib is an inhibitor of src kinase which was initially being developed in the oncology setting, Pangalos said, but was repositioned in part as a result of work conducted by one of the leading lights in digital health and AI, Joel Dudley at Mount Sinai in New York. AstraZeneca has a long standing partnership with the professor, who analyzes complex data sets to match molecules to diseases. The decision to move saracatinib forward for IPF, for which it was recently granted orphan drug designation from the US Food and Drug Administration, "was an example of the power of machine learning and AI, in interrogating complex data sets and then coming up with hypotheses that you can test," Pangalos stated. Ultimately, "the question is, can machine learning and AI help us get insight into these vast amounts of data? I don't know what the answer is yet. I hope the answer is yes but by doing this partnership, we're going to learn a lot to help us understand how to interrogate these rich data sets and turn them into something that our scientists can use more easily, working together to create algorithms and improve our knowledge."

As to whether AI really will speed things up dramatically in terms of drug development, Pangalos remains cautious, noting that "there is a lot of hype about machine learning and while saracatinib is probably one of the best examples so far, if it works in IPF, I'll be convinced, but right now it's a hypothesis." He added that it could identify new pathways and targets that will ultimately yield new medicines but "I'm not going to say it will be very useful until I have got some evidence that it has actually generated something that we wouldn't have otherwise done on our own."

Despite that caution, Pangalos believes that a key stage in the future of drug discovery and development lies in bridging the gap between AI, data and biology. "There's going to be more and more data generated every year, as we think about the NHS, electronic health records and genomic data. Countries are starting to think about how to use their population data to make better decisions for better health outcomes for their societies and these are the skills that need to be developed over the coming years."

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Benefits Outweigh Risks As Europe Okays Sanofi's Zynquista, Despite Unresolved FDA CRL

JO SHORTHOUSE joanne.shorthouse@informa.com

European regulators have given the thumbs up for **Sanofi** and **Lexicon Pharmaceuticals Inc.**'s type 1 diabetes drug Zynquista (sotagliflozin) despite concerns across the pond regarding the dual SGLT1 and SGLT2 inhibitor.

It has been approved in Europe at daily doses of 200mg and 400mg, for use as an adjunct to insulin therapy to improve glycemic control in adults with a body mass index of 27 kg/m2 or higher.

The news is not unexpected as a 1 March positive opinion from the European Medicines Agency's Committee for Medicinal Products for Human Use supported approval of the drug based on evidence including data from the inTandem clinical trial program, which recruited approximately 3,000 adults with inadequately controlled type 1 diabetes.

The marketing authorization is based on evidence including data from the inTandem clinical trial

Zynquista is an oral dual inhibitor of two proteins responsible for glucose regulation, sodium-dependent glucose co-transporter types 1 and 2 (SGLT1 and SGLT2). While SGLT1 is responsible for glucose absorption in the gastrointestinal tract, and SGLT2 is responsible for glucose reabsorption by the kidney.

While the news is good for the drug makers in Europe, where Zynquista can now commence battle with **AstraZeneca PLC**'s recently approved Forxiga (dapagliflozin) and others for market share, the 22 March Food and Drug Administration Complete Response Letter leaves the partners with some questions to answer regarding the dual inhibitor's risk of diabetic ketoacidosis. Clinical trials had shown that the risk of patients developing DKA while taking sotagliflozin was 1.1% and 3.1% with the 200mg and 400mg doses, respectively, compared to 0.0% with placebo. *(Also see "Keeping Track: Thumbs Up For Zulresso And Sunosi, Thumbs Down For Zynquista And IV Meloxicam" - Pink Sheet, 24 Mar, 2019.)*

Zynquista was the subject of a split FDA panel meeting in January, when the Endocrinologic and Metabolic Drugs Advisory Committee voted 8-8 on the question of whether the drug's risks outweighed its benefits.

Commenting at the time of the CRL, Datamonitor Healthcare analyst Peter Chang said: "The complete response letter is not at all surprising given questions about safety of the class in type 1 diabetes, with an elevated risk of diabetic ketoacidosis, along with the resulting mixed FDA advisory committee vote. It is unclear what the companies will be able to do to resolve the issue - to show the benefit outweighs the risk at least in a certain group of identified patients."

It is thought that Sanofi and Lexicon plan to engage with the FDA to discuss the requirements for resubmission and potential next steps for the type 1 diabetes program, which are estimated to occur mid-year with a second half announcement concerning requirements for resolution of the CRL.

When asked about FDA talks, Sanofi told *Scrip* that it was "still working on the next steps with the FDA," adding that "the FDA's decision does not impact our plans outside the US. We will continue to move forward with launch plans in Europe."

Wedbush analysts have pushed the predicted US launch date for Zynquista from July 2019 to March 2021 to allow enough time to fulfill FDA requirements.

EUROPE SEES BENEFIT OUTWEIGHING RISK

While some physicians have argued that the risk of DKA negates any benefits of sotagliflozin, others are hopeful that improved treatment strategies can further reduce the risk of DKA and generally believe that the HbA1c reduction, weight loss, and reduced insulin dose associated with sotagliflozin outweigh this risk, stated a recent Datamonitor Report into the type 1 diabetes market.

Diabetes patients with higher BMIs have a greater risk of cardiovascular events so the weight-loss benefit and higher use of insulin makes the DKA risk more acceptable.

"Europe appears to appreciate the SGLT inhibitor mechanism more than the US for type 1 diabetes," said Wedbush analysts in a company report released 29 April, noting also the CHMP and EMA did not recommend any post-marketing studies.

Wedbush analysts project a potential EU launch in November 2019 and gross annual sales of about $235m in 2025.

When asked about launch plans, a Sanofi spokesman told *Scrip* that "timing of individual country launches are determined at a national level, and would follow discussions with the relevant national commissioning and reimbursement bodies."

Lexicon's premarket share price rose 10% on the back of the news, having dropped significantly, by 29%, on announcement of the CRL on 22 March.

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Cystic Fibrosis Triplet Could Unblock EU Reimbursement Impasse

STEN STOVALL sten.stovall@informa.com

Vertex Pharmaceuticals Inc. said it remained at loggerheads with HTAs in England and France over product pricing, notably its cystic fibrosis drug Orkambi (ivacaftor/lumacaftor), but voiced optimism that some form of reimbursement solution could come once the merits of its eventual triple combination cystic fibrosis regimen become clear.

These were the key themes voiced on 30 April when the Boston-based specialty pharma released its first-quarter update, which analysts said was "solid" and driven by strong sales of its newest product Symdeko/Symkevi (tezacaftor/ivacaftor) which was launched in February 2018 and whose performance helped Vertex to maintain its 2019 guidance.

The group, which has only been profitable for three years, today tops the market for treating cystic fibrosis, with three disease-modifying medicines approved for the rare genetic disorder: Orkambi, Kalydeco (ivacaftor) and Symdeko/Symkevi. Total sales in the first quarter of 2019 were $857m, with Kalydeco and Orkambi declining from $250m to $244m and from $354m to $293m, respectively, while Symdeko/Symkevi sales grew from $34m to $320m. Group net income grew from $210m to $269m.

Vertex confirmed its intent to choose between its two investigation assets, VX-445 and VX-659, for a third-quarter US filing and a late-2019 EU submission, based on final 24-week Phase III data, which is expected in the second quarter of this year. The investigational triple regimens contain two next-generation CFTR correctors in VX-659 and VX-445 in combination with Symdeko or tezacaftor/VX-561 (deuterium-modified ivacaftor).

Management noted during the analysts' call that the coming submission timeline would not be affected by the specific combination chosen.

Analysts noted that both regimens look similar on key efficacy and safety data.

"We remain on track to submit an NDA in the US in the third quarter, followed by an MAA in Europe later this year," Vertex CEO Jeffrey Leiden said. "We look forward to updating you on our plans and to sharing additional data for our chosen triple combination regimen later this quarter," he added.

EU HTA RESISTANCE A CONCERN

Management voiced frustration over the strong push-back it has had from payers in Europe, due to its pricing approach, particularly in France and England.

It tried to ease concern over the reimbursement impasse by saying that it was "back at the tables" talking with the National Health Service and NICE HTA in England, and French authorities.

Vertex's message to investors was that the recent hearing at the House of Commons Health and Social Care Committee into the availability of Orkambi on the NHS in England had allowed the company to re-engage in discussions with health technology assessment body NICE and NHS about CF treatment reimbursement.

> "Vertex could leverage its triple combo data and filing to increase the likelihood of additional portfolio reimbursement agreement in Europe." - BMO Capital

Its CEO said Vertex was "fully committed to getting access for those patients who've been waiting too long in England and those patients who are still waiting in France."

He couldn't offer a time-frame, however.

"I wish I could tell you exactly when we're going to reach a successful conclusion. Unfortunately, that's just not within our ability to predict; I can't point you to any specific milestones, because there really aren't any along the way that would be externally visible," Leiden said.

Management also noted that its recent opportunity to speak on behalf of the company at the Health Select Committee inquiry in England in March allowed the company to outline the significant benefit that its medicines offer to patients and defend the value that they are able to bring to the patient community.

Leiden and his management team hope to more easily secure reimbursement with the triple combination regimen, given a recent increase in patient advocacy and the substantially better benefit profile seen in the trials thus far.

"With a medicine which has that kind of level of benefit-risk profile, clearly, there are patients who are going to want those medicines, and I find it very hard to believe that there's going to be government sitting around to deny patients access to such an important medicine that can treat the underlying cause of their disease," Vertex's chief commercial officer Stuart Arbuckle told the analysts' presentation.

Some analysts also said the way to agreement could eventually be smoothed by Vertex's choice of triple combination regime for treating CF.

"We believe Vertex could leverage its triple combo data and filing to increase the likelihood of additional portfolio reimbursement agreement in Europe," BMO Capital said in a 1 May reaction note to investors.

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Biocon Biologics Reaches Landmark Sales Figure; IPO Beckons

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Biocon Ltd. continued its strong showing in the fourth quarter, buoyed by momentum in its biologics business and robust growth in its research services segment. The Indian firm also appears to have taken more definitive steps towards eventually unlocking value from the biologics business via a potential initial public offer (IPO), though it did not share specifics or timelines on such plans.

Biocon's biologics business grew 87% to INR4.51bn ($64.6m) in the fourth quarter, closing what chairperson and managing director Kiran Mazumdar-Shaw termed as a "landmark" year for the segment, which crossed the $200m revenue milestone in the financial year ended March 2019. *(Also see "Biosimilars Begin To 'Pay Off' For Biocon" - Scrip, 25 Jan, 2019.)*

"Our biosimilar strategy has begun to deliver with the start of monetization of our biosimilars pipeline in the developed markets of the US and EU. The launch of biosimilar pegfilgrastim (marketed as Fulphila by partner **Mylan NV**) in the US and the ramp-up of sales of our biosimilar trastuzumab in emerging markets were the main contributors to this growth," Mazumdar-Shaw said on the company's earnings call on 26 April. *(Also see "Key Wins In US By Indian Firms - Keep An Eye On These In 2019 " - Scrip, 19 Dec, 2018.)*

Mylan commenced commercial sales of Fulphila, a biosimilar version of **Amgen Inc.**'s Neulasta, in the US in July last year. The US company also launched Semglee (biosimilar insulin glargine) in the UK last November and Ogivri (biosimilar trastuzumab) in the fourth quarter in Europe. Biocon's biosimilar trastuzumab continues to gain traction in key markets of Latin America and AFMET [Africa, Middle East and Turkey] regions.

GROWTH MOMENTUM TO CONTINUE

For the fourth quarter ended March 2019, Biocon reported overall revenues of INR15.57bn (+26%), with net profits surging 64% to INR2.14bn. Revenues of the small molecules business were up 11%, while Biocon's research services arm, Syngene, reported revenues of over INR5bn with a net profit milestone of INR1bn in the fourth quarter on a standalone basis.

The Indian company expects growth momentum across its business segments to continue in fiscal 2020, led by higher biosimilars revenues.

ICICI Direct Research said that Biocon had invested "heavily" in the biologics space over the past two to three years and that progress had been "encouraging", with approvals and launches in the US, EU, Japan, Australia and emerging markets.

"We expect biologics to grow at ~50% CAGR [compound annual growth rate] to INR34.28bn in FY19-21E," ICICI said in a 26 April note.

The strong showing notwithstanding, Biocon fell short of its consolidated $1bn aspirational revenue guidance for fiscal 2019, dragged down by branded formulations, which faced "external and internal challenges." The branded formulations business, which includes sales in India and UAE, was hit due to headwinds in the UAE. The India business, however, was strong led by double-digit growth in metabolics, critical care, immunotherapy and market access divisions.

Biocon continues to inch towards plans to unlock value of its biologics business

INDEPENDENT FUNCTIONING OF BIOSIMILARS BUSINESS

Significantly, there also appears to be some uptick in activity towards eventually unlocking value from Biocon's biologics business – the Indian firm has in the past indicated that it could consider a potential initial public offering and listing.

Biocon indicated that fiscal 2020 will see a spurt in "investment in human capital" as it sets up "an organizational structure" to support the "independent functioning" of the company's biosimilars business under Biocon Biologics. Earlier this year Biocon appointed ex-Roche official Dr Christiane Hamacher as CEO of Biocon Biologics India Ltd, a subsidiary of Biocon, while Dr Gopal Krishna Dasika was appointed as the subsidiary's head of R&D.

Biocon also approved, at the company's 25 April board meeting, the transfer of equity shares held by the company in Biocon Biologics Limited, UK (BUK) to Biocon Biologics India Limited (BBIL). Both BUK and BBIL are wholly owned subsidiaries of Biocon and "continue to be the same post transfer of shares, subject to regulatory approvals, if any," a notice to the Bombay Stock Exchange said.

To an analyst's query on the rationale for the equity transfer, Biocon said that it is looking at consolidating its biosimilars business under Biocon Biologics India Limited.

"And one of the potential options for our money raising is the IPO, and we can consider raising IPO at this entity level," the company said on the investor call.

Biocon had previously announced plans to transfer the company's insulin formulations, biosimilars API and biosimilars formulation business as well as the insulin API business to its step-down

subsidiary, Biocon Biologics India Limited. *(Also see "Weak Q3 For Biocon, All Eyes On Biosimilars Approval Flow" - , 25 Jan, 2018.)*

BOSTON AMONG BUBBLING BIOTECH HUBS

Meanwhile, Mazumdar-Shaw also referred to the setting up a of a Boston-based subsidiary, Bicara Therapeutics, to support the company's immuno-oncology programs pursued as part of its novel drugs programs.

"We expect these investments to augur well in pursuing our ambition of enabling access to affordable biologic therapies to patients worldwide, whilst establishing Biocon as a leading global player in biologics," Mazumdar-Shaw said on the earnings call.

The Biocon chair said that the company was "very excited" with its immuno-oncology pipeline which has been in the form of fusion antibodies – part of a "very hot area" – and while this was being done at Biocon, the company felt the need to accelerate these programs. "And we felt it was best done in the US and Boston is one of the most bubbling kind of biotech hubs in the world which has been doing a lot of this kind of work and where you can get the best people, best of scientific advice to really accelerate these kind of programs. So, we felt that it was best to create the Boston-based subsidiary and now start developing these programs with that kind of base," Biocon's chair added.

In the area of novel therapies, Biocon's novel anti-CD6 monoclonal antibody, itolizumab, licensed to biotechnology firm **Equillium** in the US and Canada, has commenced Phase Ib/II trial in acute graft-versus-host disease (aGVHD). Equillium has been granted fast track and orphan drug designations for the molecule in both prevention and treatment of aGVHD by the US FDA.

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Takeda Executive Rejig In ICMEA Region As Shire Integration Shapes

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Takeda Pharmaceutical Co. Ltd., which completed its acquisition of **Shire PLC** in January this year, appears to be rejigging its leadership in some key international market groupings that include India, the CIS and Africa, among others, as it readies to move full throttle towards integrating operations with Shire.

Takeda has appointed Andrey Potapov as area head, ICMEA (India, CIS, the Middle East including Turkey, and Africa), while another key executive, Taka Horii, who led the NEMEA (Near East, Middle East and Africa) area, is moving to a new role as general manager for the Middle East.

Takeda, which underscored an attractive combined footprint aligned with market opportunity at the time of the Shire deal, expects to evolve its "operational focus" from the NEMEA region to ICMEA as the acquisition and integration of Shire progresses. The move is seen reducing complexity within the organization, while "increasing agility" and moving Takeda "closer to the patients it serves."

"Potapov will be instrumental in guiding the successful integration of Takeda and Shire under the Takeda brand, reinforcing the company's leadership position across its global footprint while strengthening its R&D-driven pharmaceutical operations," Takeda said.

Potapov will take charge at Takeda's Dubai hub and his new role follows an impressive stint as general manager of Takeda Russia and head of the CIS Area, where the executive drove "above market" profit growth for the past five years, backed by the successful launch of new pharmaceutical products there. A former auditor at Arthur Andersen, Potapov also comes with over 15 years' experience at Nycomed, which was acquired by Takeda in 2011.

Andrey Potapov

EXECUTIVES TO WORK CLOSELY

The executive changes are interesting given that Taka Horii was appointed area head for the NEMEA operations only last year. Taka Horii has held senior Takeda positions in several markets including as head of strategic planning at Takeda China and president and general manager, Taiwan, among others. The executive has been credited with having played a key role in Takeda's success in Asia over the past several years.

New ICMEA area head Potapov is expected to work closely with Taka Horii, to "maintain his success to date." The Japanese company also said that since Horii's appointment in 2018, the executive had helped define a "successful operating model" for the area, focusing on key business priorities such as portfolio optimization, specialty care product launches, and talent development.

It's not immediately clear whether the executive changes will impact reporting lines in markets like India or the broader strategic thrust therein as the integration with Shire progresses. *(Also see "Takeda-Shire In India: Sleeping Giant?" - Scrip, 21 May, 2018.)*

Takeda, which has generally been keen to do more in emerging markets like India, has hitherto appeared somewhat tentative about a sharp ramp-up in the country, although the Shire deal has given it access to a portfolio of products largely in the

hematology segment. Takeda had set up an India arm, Takeda Pharmaceuticals India Pvt. Ltd, in 2011 and also has a Nycomed legacy joint venture, Zydus Takeda Healthcare Pvt. Ltd., with **Zydus Cadila**. The JV essentially manufactures generic active pharmaceutical ingredient (APIs) across various therapeutic segments exclusively for Takeda.

Another factor that may impact the contours of the Takeda-Shire combine in some emerging markets is the anticipated divestiture of non-core assets – Takeda had earlier provided an "illustrative case" of roughly $10bn post-tax in non-core divestments overall. *(Also see "Takeda Says Last Pre-Shire Quarter 'Robust', But Quiet On Divestments " - Scrip, 3 Feb, 2019.)* There has been speculation that certain product lines in emerging markets could be on the block, with some reports suggesting that parts of Nycomed's business could be shed.

Published online 29 April 2019

The Medicines Co. CEO Timney On Selling Inclisiran And Why Big Pharma Is Still Interested In CV Disease

JESSICA MERRILL jessica.merrill@informa.com

The Medicines Co.'s new CEO Mark Timney took over the helm in December to execute a straightforward business plan: shepherd the RNAi therapeutic inclisiran successfully through Phase III development and find a buyer for the cholesterol lowering medicine.

"There is no doubt in my mind to really fulfill its full potential, [inclisiran] is better off in the hands of a larger pharmaceutical company," he said in an interview with *Scrip*. The strategy is one that is fully aligned with the company's board of directors, including Chairman Alex Denner, the activist investor who recruited him to lead the effort. Denner's investment company, Sarissa Capital Management, has a solid track record selling biotechs.

Timney was tapped as CEO of TMC in December, succeeding Clive Meanwell, who led the company for two decades. The leadership change came about as TMC has shifted its business strategy over several years from a multi-product hospital specialist to a pure play drug developer focused on inclisiran. The company gained the product through a in-licensing deal with **Alnylam Pharmaceuticals** in 2013.

Timney was previously CEO of Purdue Pharma, where he emphasized business development, and he previously worked at Merck & Co. as president of global primary care, where he gained extensive commercial experience in cardiovascular disease with brands like *Zocor*, *Vytorin* and *Januvia*.

Those two experiences have prepared him for the task at hand, he said. But

Mark Timney

executing on what appears to be the straightforward strategy could be challenging. Cardiovascular disease hasn't exactly been a hot bed of drug development at big pharma for the last decade and the first new biologics to hit the market for high cholesterol – the PCSK9 inhibitors *Repatha* (evolocumab) and *Praluent* (alirocumab) – are facing steep commercial barriers. The drugs' makers, **Amgen Inc.** and **Sanofi/Regeneron Pharmaceuticals Inc.**, respectively, have had to reset their expectations and dramatically lower the prices of the drugs since they launched in 2015. *(Also see "Sanofi/Regeneron Cut Praluent List Price As PBMs Look To Maintain Rebate Status Quo" - Scrip, 12 Feb, 2019.)* It could be hard to find another large biopharma eager to wade into the PCSK9 space.

Like Repatha and Praluent, inclisiran lowers cholesterol by targeting PCSK9, but as an RNAi therapeutic, it works differently from the monoclonal antibodies. TMC believes those differences – which include dosing every six months versus every two weeks – set it apart.

Timney is convinced the persistent unmet need in cardiovascular disease is also keeping big pharma's interest piqued. Cardiovascular disease remains the leading cause of death in the US and the highest contributor to healthcare spend. He was persuaded to take the job after talking with opinion leaders and drug executives involved in the space.

"At first, I thought wow, cardiovascular medicine. That is going to be tough. It's not as easy as rare disease or oncology, but I was pleasantly surprised," he said.

"I spoke with a number of companies, some of which I knew were in the cardiovascular space and some of which I knew had been but had moved on, but it was very clear that there was still strong interest," Timney added. Among the drug makers he talked to were two currently committed to cardiovascular drugs, two that previously worked in the space and reconsidering their involvement and two companies that are involved with metabolic drugs but declared a strong interest in cardiovascular disease.

PHASE III DATA READOUT APPROACHES

The big catalyst for a deal likely hinges on the Phase III data for inclisiran, which is expected in the third quarter. The Phase III program includes four pivotal trials in patients with atherosclerotic vascular disease, ASCVD-risk equivalents, heterozygous familial hypercholesterolemia (FH) and homozygous FH. Data from three of

TURN TO PAGE 23

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

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

PIPELINE WATCH, 26 APRIL – 2 MAY 2019

Event Stage	Lead Company/Partner	Drug Name	Indication	Comments	Change To LOA (%)	LOA (%)
Phase III Published Results	Novo Nordisk A/S	Victoza (liraglutide)	Diabetes Type 2, In Children	Ellipse; NEJM, 28 April	0	100
Phase III Published Results	HUYA Bioscience International	tucidinostat (HBI-8000)	Breast Cancer	The Lancet Oncology, 26 April	0	6
Phase III Updated Results	Bausch Health Companies Inc.	Lotemax SM (loteprednol etabonate)	Ocular Pain After Surgery	842, 843, 875; Safe And Effective	0	100
Phase III Updated Results	ObsEva SA	nolasiban (OBE001)	IVF Procedures	IMPLANT2; Favorable Follow-Up	0	68
Phase III Updated Results	Allergan/Molecular Partners	abicipar pegol	Wet Age-Related Macular Degeneration	CEDAR, SEQUOIA; Met Primary Endpoint	0	61
Phase III Updated Results	GenSight Biologics S.A.	GS010	Leber's Hereditary Optic Neuropathy	REVERSE; Improved Vision	0	47
Phase III Updated Results	Sylentis, S.A. (PharmaMar)	tivanisiran (SYL1001), a siRNA	Dry Eye Syndrome	HELIX; Improved Symptoms	0	48
Phase III Top-Line Results	GlaxoSmithKline/Innoviva	Trelegy Ellipta (fluticasone, umeclidinium/vilanterol)	Uncontrolled Asthma	CAPTAIN; Met Primary Endpoint	0	68
Phase III Trial Initiation	I-Mab Biopharma/MorphoSys	MOR202	Multiple Myeloma	w/lenalidomide In Relapsed, Refractory Disease	0	0
Phase III Trial Initiation	Pluristem Therapeutics Inc.	PLX-PAD placenta cell therapy	Critical Limb Ischemia	An EMA Adaptive Pathways Pilot	0	45
Phase III Announcement	Samumed, LLC	lorecivivint (SM04690)	Knee Osteoarthritis	STRIDES 1, STRIDES X-ray; By Joint Injection	0	27

Source: Biomedtracker | Informa, 2019

CONTINUED FROM PAGE 21

the trials is expected in the third quarter and will support a regulatory filing in the US by the end of the year. A regulatory filing in Europe is targeted for the first quarter of 2020.

In Phase II, treatment with inclisiran lowered cholesterol by more than 50% in patients with ASCVD or ASCVD risk equivalents and elevated LDL-cholesterol despite taking maximum tolerated doses of LDL-C lowering therapies.

The company recently began enrolling patients in a large cardiovascular outcomes trial that is expected to read out in 2024.

It's hard to predict the timeline for a potential sale, Timney said, pointing out that understanding the safety and efficacy of inclisiran will be important. "The timing is always dependent on each company," he said. "Do you have a gap in the pipeline? Is this the right time to fill that gap? Has something happened in the pipeline where you need to fill?"

In the meantime, TMC is keeping a close watch on the Phase III program and will begin preparing for commercialization in the case that Plan A falls through. "We will be ready if we need to to ensure that we are fully prepared to launch," Timney said.

PRICING FLEXIBILITY

The biggest challenge for the marketed PCSK9 inhibitors has been around market access, given that the biologics cost thousands of dollars a year – even as the prices have come down – when statins are available generically for a fraction of the cost. Payers have put in place a lot of paper work and red tape for patients to gain access to the drugs and they often require substantial out-of-pocket costs. TMC sees inclisiran as having advantages in terms of cost, first because it is dosed just twice a year and secondly because the costs of manufacturing the RNAi therapeutic are cheaper than the process for biologics.

"The way that this is manufactured gives us a lot of flexibility in terms of cost of goods, so that allows us to think about pricing and the way we approach the market quite differently to what has been done in the past," Timney said. "Affordability is the approach we will take."

He said it's hard to compare the launches of Repatha and Praluent to the potential for inclisiran, which he said remains a blockbuster commercial opportunity. Repatha generated $550m in revenues in 2018 and Praluent generated $308.6m.

"Many people term [inclisiran] a PCSK9 and I think that's a little bit unfair. PCSK9 is the target but it behaves very differently than the MABs," he said. Inclisiran harnesses RNA interference to block the production of PCSK9 at its source, in the liver, and remove LDL-C from the bloodstream. "It is more like turning the tap off at its source," he added, and that's what contributes to the durable cholesterol lowering of the product.

The Phase III data read out will be a pivotal event for TMC and could determine what comes next for the company. The company has cash and equivalents of $199.7m at the end of the first quarter, enough to see it through the Phase III data read out and into 2020. After that, if inclisiran advances toward the market, TMC's timeline could fade out.

Published online 30 April 2019

APPOINTMENTS

Executive	To Company	New Role	From Company	Previous Role	Effective Date
Robert Pomrenke	Allovate LLC	Chief Executive Officer	B3 Precision Medical Technologies	Principal	1-Apr-19
Pradeep Bhadauria	Amneal Pharmaceuticals Inc	Chief Scientific Officer	Apotex Inc	Executive Vice President, Global Research and Development	2-Apr-19
Peter Greenleaf	Aurinia Pharmaceuticals Inc	Chief Executive Officer	Cerecor Inc	Chief Executive Officer	29-Apr-19
Michelle Zheng	Frontier Biotech	Senior Vice President, Pharmaceutical Sciences, Macromolecule Therapeutics	MabPlex	Chief Operating Officer	30-Apr-19
Alan J. Jacobs	Hemostemix Inc	President and Chief Medical Officer		Consultant	1-Apr-19
Clive Bertram	Petra Pharma Corp	Head, Corporate Development	Woodruff BioPharm	Director	2-Apr-19
David Vario	Tedor Pharma Inc	Vice President, Quality and Regulatory Affairs	Lantheus Medical Imaging	Senior Director, Quality Systems	3-Apr-19

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