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Upjohn/Mylan: Will "Potential Moderate Growth" Lure Investors?

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The global generic drug industry is poised for a big shakeup with Pfizer Inc. and Mylan NV announcing plans for Mylan to merge with Pfizer's Upjohn off-patent branded and generic medicines business, establishing the top generic drug company in the world based on consolidated revenues. The companies announced the merger on 29 July, a deal that will combine two slow-growing businesses in the challenging generic drug market.

The combination will result in a new company with expected 2020 pro forma revenues of $19bn to $20bn, edging out the world's current leading generic drug company Teva Pharmaceutical Industries Ltd., based on consolidated sales, although both companies have a mixed portfolio of specialty brands, branded off-patent drugs and traditional generics. Teva also grew its way into the top spot through the 2016 acquisition of Allergan PLC's generic drug business for $40.5bn as the industry has sought consolidation to navigate challenging commercial dynamics. *(Also see "Teva Gets What It Wants – Allergan Generics, Not Mylan" - Pink Sheet, 3 Aug, 2015.)*

Importantly, Teva's big generics merger didn't work out entirely as hoped. Teva generated $18.85bn in 2018 and has forecast roughly flat to slightly higher sales in 2019, off of expected pro forma revenues for the two companies of $26bn in 2016. Whether or not Upjohn and Mylan can deliver a healthy, growing drug company out of two declining-revenue businesses remains to be seen.

Mylan's board of directors has been conducting a strategic review of the business for the last year and Pfizer has explored the possibility of breaking up its innovative and generics businesses for many years, since the patent expiration of Lipitor in 2011. *(Also see "Mylan To Explore Strategic Options, Claiming Investors Have Failed To Appreciate The Value " - Scrip, 8 Aug, 2018.)* The announcement isn't surprising in that regard, but it does pose questions about how the new company will deliver long-term growth.

The combined company will have a new name, to be announced upon closing, and will be led by Upjohn CEO Michael Goettler. Mylan's current chairman Robert Coury will serve as executive chairman of the new company and president Rajiv Malik will serve as president. Mylan's longtime CEO Heather Bresch will leave the company upon the close of the deal. The new management team will be recruiting a new CFO.

STRONG CASH FLOW AND A DIVIDEND

In laying out the case to investors in a same-day conference call, Goettler insisted the new company will have the "potential for modest growth over time." Management forecasts pro forma 2020 EBITDA of $7.5bn to $8bn, as well as synergies of $1bn to be realized by 2023. The big selling point will be strong cash flow of around $4bn per year and a dividend of at least 25% of free cash flow, he said.

"By combining Upjohn's iconic brands with Mylan's rich portfolio across all therapeutic areas, we have a diverse, a differentiated and a sustainable portfolio of prod-

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from the editor

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This week's M&A headline splash sees Pfizer finally finding a way of addressing the divergence of its product portfolios and splitting into two (see cover story).

The action will push the remaining innovative pharma company down the revenue generation rankings. In 2018 Pfizer was the biggest fish in the pharma pond when it came to pharmaceutical sales; stripping out the revenues from the Upjohn business being merged with Mylan would push it down into fourth place behind Novartis, Roche and Johnson & Johnson (see p5).

While combining Upjohn and Mylan will create cost-cutting opportunities, excitement for the growth prospects of that group is not hugely in evidence among analysts. But nor are they particularly happy about Pfizer itself, which will retain 57% ownership of the enlarged generics and established medicines group. Both Mylan and Pfizer stock declined after the transaction was announced.

Pfizer released its earnings on the same day as the spin-out announcement, prompting analysts at Morgan Stanley after mulling all the figures overnight to declare that "real news was weaker underlying earnings" for both the remaining innovative business and the Upjohn business being merged with Mylan. It remains to be seen if Pfizer investors can be appeased with a merger-related windfall dividend. In any event, new CEO Albert Bourla has wasted no time in sculpting the company to look a lot more like a modern biopharma organization with a focus on pipeline innovation.

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Amgen's Murdo Gordon On Generating Sales Growth In A Challenging Commercial Year

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Amgen Inc. is at a crossroads as sales of multiple legacy products face generics, biosimilars and other competitors, while new revenue generators haven't grown enough to fill blockbuster sales gaps. Executive vice president of global commercial operations Murdo Gordon joined the company last year and is tasked with keeping Repatha, Aimovig and Evenity on the path to growth, while preventing sales of Neulasta, Enbrel and Sensipar from traveling too far south.

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To read the rest of this story go to: https://bit.ly/2KbNR8b

Lyrica Generics Launch, But Pfizer Has Been Bracing For The Hit

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The first generic versions of Pfizer Inc.'s blockbuster pain medicine Lyrica (pregabalin) launched in the US after the US Food and Drug Administration approved several generics on 19 July. The loss of marketing exclusivity for Lyrica will be a substantial hit to Pfizer, which generated $4.62bn from sales of the drug in 2018. It was the company's second best-selling drug behind the pneumococcal vaccine Prevnar 13.

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To read the rest of this story go to: https://bit.ly/2GBnl7m

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ucts and pipeline assets," Goettler said.

Pfizer's Upjohn business has largely been used as a means to manage Pfizer's off-patent drugs, including brands like Lipitor (atorvastatin), Celebrex (celecoxib) and Viagra (sildenafil). The latest brand to join the portfolio is Lyrica (pregabalin), the first generics of which launched in July. It is a cash-generating, but revenue-declining business with a big presence in China and other Asia-Pacific countries. Upjohn does not include Pfizer's biosimilar drugs like Inflectra (infliximab-dyyb), biosimilar Remicade, and recently approved biosimilars of Herceptin (trastuzumab) and Avastin (bevacizumab).

Pfizer released Upjohn's second-quarter results and outlook for the rest of the year during its 29 July earnings call. Revenues were down 7% operationally, mostly due to a 20% decline in China "driven primarily by volume-based procurement reforms that were implemented in March 2019." *(Also see "Drug Price Waterloo: China's New Bidding Process Hits MNCs Hard" - Scrip, 11 Dec, 2018.)* The impact has been expected and was included in Pfizer's 2019 guidance, but the effect has been significant for Pfizer because the Chinese reforms impacted Lipitor and Norvasc (amlodipine).

For the first six months of the year, however, Upjohn's operational growth was 13% and revenues in China for the full year are expected to grow by low- to mid-single digits; volume has been growing even where Upjohn's products didn't win the tender, Pfizer reported.

Upjohn also saw a decline in the US, where generic competition for Viagra, wholesaled destocking of Lyrica ahead of multi-source generic competition, and "continued industry-wide pricing challenges" contributed to a 9% drop.

WHAT MYLAN BRINGS TO THE TABLE

Mylan's business includes branded and generic versions of EpiPen, a small molecule generic drug business, and a portfolio of injectable and complex generics and biosimilars, including Fulphila, a biosimilar of Neulasta (pegfilgrastim) and Wixela Inhub, a generic version of Advair (salmeterol/fluticasone). Mylan has a bigger geographic presence in North America and Europe.

Mylan's revenues for the first six months of the year declined 3% to $5.35bn. The company reported a net loss of $193.5m for the first six months and is facing overhangs around generic price-fixing allegations and opioid litigation.

As generic drug pricing has come under pressure in the US, Mylan has tried to pivot to more complex generics and biosimilars and expanded geographically through acquisitions. *(Also see "Mylan's Growth Strategy: Diversification, Expansion And R&D Investment" - Scrip, 2 Mar, 2017.)* But it has faced manufacturing issues, and while it has successfully gotten complex products to market, those drugs have faced commercial challenges. *(Also see "Generic Drug Sector Struggles Even As The Need For Cheaper Drugs Grows" - Scrip, 10 Aug, 2018.)*

The company's stock was down 30% from its opening price at the beginning of the year to close at 26 July at $18.46, the day before reports of a merger began circulating. The stock was trading down nearly 50% of its value from a year ago.

The combined company will have a balanced geographic footprint that will allow it to absorb volatility in any one market, Goettler said. About 55% of the combined revenue will come from North America and Europe and 45% from Asia and emerging markets.

> Whether or not Upjohn and Mylan can deliver a healthy, growing drug company out of two declining-revenue businesses remains to be seen.

Only about 15% of revenues will come from the US generics market. Upjohn will bring more off-patent brands to Mylan's portfolio, resulting in a more diversified combined portfolio of branded generics, over-the-counter medicines and biosimilars.

"Combining Mylan with Upjohn gives us a unique opportunity to create something entirely different in a pharma company with a truly unique financial profile that does not correlate to any of the pharma industry peers," Goettler said.

RETURNING TO THE US

The merger will be structured under an all stock Reverse Morris Trust transaction in which Mylan shares will be converted into one share of the new company. Pfizer shareholders would own 57% of the combined new company and Mylan shareholders would own 43%. The merger, expected to close in mid-2020, would be subject to approval by Mylan shareholders, but not Pfizer shareholders. The boards of directors of both Mylan and Pfizer have unanimously approved the transaction.

The new company will be domiciled in the US and incorporated in Delaware. Mylan redomiciled its business outside of the US in UK through the acquisition of the non-US established products business owned by Abbott Laboratories Inc. for $5.3bn in 2015, partly a tax strategy. The company will operate global centers in Pittsburgh, Shanghai and Hyderabad, India.

The new company will likely need to build trust with investors, given the ups and downs that have come with Mylan and the generic drug industry more generally.

As Bernstein analyst Ronny Gal put it in a same-day note, "We are admittedly suspicious (blame it on covering Mylan for 15 turbulent years). We expect investors to be suspicious as well."

"However, we could be convinced," he added. "This will require a much more open reporting structure and investor communication than we've seen in the past. … Let's see how they handle the next year or so."

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At Pfizer, A Split A Decade In The Making

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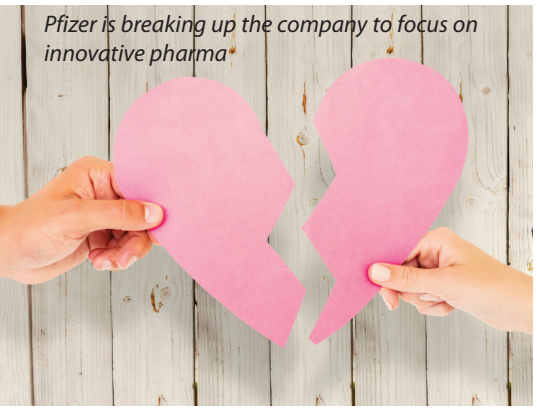
It was back in 2010, when Lipitor was edging close to losing its patent protection, that debate erupted among Pfizer Inc. investors over whether the pharma giant could unlock trapped value by splitting up the company into an innovative, R&D-focused company and a cash-generating established products business. The businesses were reorganized, the decision was considered, delayed, considered again, scrapped in 2016, and now nine years later, it is poised to happen.



Pfizer is breaking up the company to focus on innovative pharma

Pfizer announced on 29 July that it will split off its Upjohn off-patent branded and generics business and merge it with Mylan NV to establish a top generic drug company, with $19bn to $20bn in pro forma 2020 revenues. The result will be a diminished Pfizer, in size, but not innovative spirit. The new Pfizer will be much leaner and focused on innovative R&D. The company expects a 2020 annual revenue base of $40bn, shaving off about $10bn in revenues with the move.

Pfizer generated $53.65bn in revenues in 2018, although that also included $3.6bn in consumer health care revenues, which Pfizer is now spinning out into a joint venture with GlaxoSmithKline PLC. *(Also see "Pfizer Consumer Combo Deal Frees Capital For GSK Pharma Investment" - Scrip, 19 Dec, 2018.)* To understand how much Pfizer has already shrunk, consider that in 2011, the company generated $67.4bn. in revenues.

CEO Albert Bourla is certainly putting a big mark on reshaping the company, since taking over at the start of the year. Pfizer will relinquish its title as the number-one drug maker, based on pharmaceutical sales, to Novartis AG, and likely fall behind Roche and Johnson & Johnson as well.

After the consumer and off-patent businesses are divested, "Pfizer will be a smaller, more focused, science-based company with a singular focus on innovative pharma," Bourla told a same-day second-quarter earnings call, noting that the pipeline will be able to bring a more dramatic impact on Pfizer's growth trajectory. "Given our smaller size, we believe the growth will be more sustainable. We also will still have the financial flexibility to continue to invest in growth while returning capital to our investors. These are deliberate steps we are taking to make Pfizer a very different company and one that is even better equipped to fulfill our purpose: breakthroughs that change patients' lives."

PFIZER'S GROWTH PROSPECTS

The company had forecast a five-year compound annual growth rate of mid-single digits, but it now expects the growth to begin earlier than it would have and is guiding for high mid-single-digit revenue growth – because the lag of the Upjohn business will be removed. Management had previously forecast flat revenues in 2019, taking into account the consumer health care spinout, with a return to growth targeted in 2020 after Pfizer cycles through the loss of Lyrica (pregabalin) to generics. *(Also see "Lyrica Generics Launch, But Pfizer Has Been Bracing For The Hit" - Scrip, 22 Jul, 2019.)*

Pfizer will be relying on its branded pharmaceutical pipeline to drive growth, brands like Ibrance (palbociclib), Xeljanz (tofacitinib), Xtandi (enzalutamide) and new cardiovascular rare disease drug Vyndaqel/Vyndamax (tafamidis). New drugs – and any new commercial acquisitions – will have a bigger opportunity to move the needle on the top line.

The Upjohn business is a cash-generating one, but off a declining revenue base. Revenues for the second quarter declined 7% operationally to $2.8bn, dragged down in particular by Chinese pricing reform – although Pfizer reported volume increases.

The business was reorganized at the beginning of the year under the Upjohn name. It's made up of off-patent legacy brands and generic medicines, and was previously organized under Established Medicines. The company moved its biosimilars into its Innovative Medicines portfolio at the same time, so Pfizer will retain its biosimilar drugs, including Inflectra (infliximab-dyyb), a version of Remicade, and recently-approved biosimilars of Avastin (bevacizumab) and Herceptin (trastuzumab). *(Also see "Pfizer On Reorganizing, M&A And Investing In Internal R&D " - Scrip, 1 Aug, 2018.)*

THE OFF-PATENT BUSINESS

The off-patent business has been reorganized several times over the last decade, as Pfizer toyed with how best to structure its disparate businesses. In a prior incarnation, it was called Essential Health.

In 2010, when Jeffrey Kindler was Pfizer's CEO, some analysts and investors began pushing the company to consider a split to unlock trapped value, following the mega-merger with Wyeth and as the loss of Lipitor (atorvastatin) approached. Ian Read made a review of a business break-up one of his top early priorities to evaluate when he took over as CEO in late 2010.

But management took a more conservative road in 2012, deciding to sell its Nutritionals business and spin out Animal Health into Zoetis, while keeping its Established Products and Consumer Healthcare businesses. Pfizer focused on developing a new operating model to break the innovative medicines and established products portfolios out from one another in the financial record keeping while it continued to evaluate an eventual split. *(Also see "Pfizer Reorganizes Internally, Closer To Decision On Splitting Business" - Pink Sheet, 5 Aug, 2013.)*

In 2016, after years of consideration, Pfizer announced that it would not move forward with a split, ending the breakup

speculation for a time. Both its innovative business and what was then called Essential Health were performing well, with strong double-digit growth, bolstered by acquisitions, including the addition of Hospira to the Essential Health unit.

The decision, when it finally came, didn't disappoint investors immensely because of the company's evolving financial trajectory, and because breaking up the business was viewed as a challenge.

It's still not clear now if the move will unlock value. As Wolfe Research's Tim Anderson said in a same-day note, "Breaking up is hard to do and in this instance, it is not immediately clear to us whether the move creates value or destroys it on a net basis, from a pure financial perspective." That view, he said, is based almost solely on the low price-to-earnings multiples that continue to exist in the specialty pharma space.

During the earnings call, Anderson also pushed on how Pfizer was losing much of its emerging markets business in the transaction.

Nonetheless, Anderson said in his note on the deal, "Pfizer management deserves credit for attempting to reshape the business in various ways."

"Growth at the residual company will be better and new revenue streams from the pipeline (or from future bolt-ons) will have a bigger impact than before, which is a positive," he said

As for the question of what's next, Pfizer does now have an additional $12bn coming in. Chief financial officer Frank D'Amelio told the earnings call that the intention is to pay down debt and then, with the added $11bn-$12bn in operating cash flow post-close, pay out a shareholder dividend. "And then the remainder we'll be looking at relative to share repurchases and to business development," he said.

Bourla stressed that the company was standing pat on its business development strategy. Pfizer will continue to be active, with an eye toward early- to mid-stage bolt-on opportunities. "Regarding large scale M&A, as we said, never say never. But right now the opportunity we have to advance our pipeline is unique, and I still do not see the need to do a large deal right now, because that can only create disruption."

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Novartis's Zolgensma Loses EU Accelerated Assessment

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EU reviews for Novartis AG/AveXis Inc.'s novel gene therapy Zolgensma is now going at a more sedate pace after the European Medicines Agency reverted its initial accelerated assessment to a standard review.

It is among seven products whose MAAs (marketing authorisation applications) were originally granted an accelerated assessment that are no longer undergoing speedy review, according to the latest monthly list of products being reviewed under Europe's centralized evaluation procedure at the EMA (see box on page 8), as reported by *Scrip*'s sister publication, *Pink Sheet*. *(Also see "EU Accelerated Assessment – Hard To Get, Hard To Keep" - Pink Sheet, 19 Jul, 2019.)*

The decelerated process will bring some relief for its chief competitor,Biogen Inc.'s Spinraza (nusinersen).

An accelerated review in the EU is reserved for products that are expected to be of major public health interest, particularly from the point of view of therapeutic innovation. The mechanism reduces the time it takes the EMA to evaluate an MAA from 210 days to 150 days (not counting clock stops when applicants have to provide additional information).

They are not easy to get: around half the requests companies make to the EMA for accelerated assessment are rejected. So far in 2019, just three out of the nine requests processed have been granted.

Zolgensma (onasemnogene abeparvovec) was granted accelerated assessment in July 2018 but had had it removed by July 2019.

Zolgensma was approved in the US following expedited review for all three types of spinal muscular atrophy (SMA) at the end of May and has the distinction of being the world's most expensive drug, priced at around $2m, albeit with that cost spread over five years. As such, its early market performance is being keenly watched, not least by Biogen, which is feeling the first heat of competition to its blockbuster Spinraza. During its second-quarter results presentation, Novartis insisted that its roll-out was on track and in line with expectations, but did not give specific sales or numbers of patients treated.

Biogen has had the SMA market to itself since Spinraza's first launch in the US in early 2017, which was swiftly followed in the EU. It quickly became a top seller. Biogen reported Spinraza sales of $488m in the second quarter, 15% up on the $423m booked in the second quarter of 2018, although it represented a 6% decline from the $518m realized during the first quarter of 2019. Despite the slip, Biogen stressed that Zolgensma poses a minimal threat because it is indicated only for SMA patients two years old and younger, while the most significant market opportunity is in adult patients. *(Also see "Biogen Growth Continues, But Analysts Worry About Near-Term R&D Prospects" - Scrip, 23 Jul, 2019.)*

While it remains to be seen how effective Novartis will be at persuading individual EU countries to agree to cover its high initial cost once Zolgensma does gain EU approval, the loss of accelerated assessment will take a little of the pressure off and Spinraza's EU sales will remain unimpinged for that bit longer.

In response, AveXis Inc. said that being on a standard approval timeline would "give the [EMA] the time they need to review the robust amount of data we are providing to answer their questions." It added that it continued to work closely with European regulators during their review of its product and that it was anticipating a potential approval in the second half of 2019.

Pink Sheet reported that a London-based executive board member of the nonprofit group SMA Europe, Kacper Rucinski, said the EMA had "quite a significant number of questions for AveXis." He added: "My understanding is that the EMA wants to very thoroughly review the data and the scope of approval."

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Zolgensma is the only one of the seven products to revert to a standard review to be receiving support under PRIME, the EMA's priority medicines scheme. Products in PRIME are expected to undergo accelerated assessment.

LAROTRECTINIB

Bayer AG/Loxo Oncology Inc.'s larotrectinib is another product to have lost accelerated assessment in the EU, in December 2018, after it was granted in July 2018. It finally received a positive opinion from the EMA's Committee for Medicinal Products for Human Use on 26 July 2019. It was first approved as Vitrakvi in the US in November 2018 for both adults and children with solid tumors that have a neurotrophic receptor tyrosine kinase (NTRK) gene fusion, making it the first so-called "tumor-agnostic" anticancer. *(Also see "FDA Nod For Loxo/Bayer Tissue Agnostic Drug Marks Paradigm Shift In Cancer " - Scrip, 27 Nov, 2018.)*

Despite the loss of accelerated assessment, it has enjoyed a review time advantage over Roche's similar product entrectinib, which earlier this year failed to get an accelerated assessment. Roche had filed entrectinib for use in two settings: the tumor-agnostic NTRK gene fusion indication and for a NSCLC-specific indication in ROS1-positive metastatic disease. Unlike larotrectinib, entrectinib inhibits not just NTRK but also ROS1 kinase, a protein predominantly found in lung cancer.

The problem arose because the EMA was only prepared to fast-track entrectinib for the NTRK gene fusion indication and not for use in the ROS1 NSCLC setting. Under the EMA's rules, an accelerated assessment can only concern the entire scope of a single MAA. As the two indications were included in the same application, this meant the entire dossier was given a standard review.

The seven products that have reverted from accelerated assessment to standard review time:

- Shionogi & Co. Ltd.'s investigational antibiotic agent, cefiderocol.
- Stemline Therapeutics Inc.'s tagraxofusp (Elzonris) for blastic plasmacytoid dendritic cell neoplasm (BPDCN).
- AveXis/Novartis's onasemnogene abeparvovec/AVXS-101 (Zolgensma), for spinal muscular atrophy (SMA).
- Theratechnologies Inc./TaiMed Biologics Inc.'s ibalizumab (Trogarzo) for HIV.
- Daiichi Sankyo Europe GMBH's quizartinib (Vanflyta) for acute myeloid leukemia (AML) therapy.
- Karyopharm Therapeutics Inc.'s selinexor (Xpovio) for multiple myeloma.
- Bayer/Loxo Oncology's larotrectinib (Vitrakvi) for cancer.

(Also see "Roche's EU Accelerated Assessment Bid For Tumor Agnostic Entrectinib Backfires" - Scrip, 4 Mar, 2019.)

Meanwhile, Roche has beaten Bayer/Loxo to market in Japan. Last month, entrectinib was approved as Rozlytrek by the country's Ministry of Health, Labor and Welfare for the treatment of adult and pediatric patients with NTRK fusion gene-positive advanced or recurrent solid tumors, regardless of cancer type following an expedited priority review granted under Japan's orphan drug and "sakigake" schemes. *(Also see "Roche Beats Rivals To Japan Tumor-Agnostic Market With World-First Rozlytrek Nod" - Scrip, 19 Jun, 2019.)*

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With additional reporting by Maureen Kenny

BMS Ready To Pounce On Non-Chemo Opportunity In Lung Cancer With Checkmate-227 Data

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A split decision had been expected in Bristol-Myers Squibb Co.'s Checkmate-227 study testing Opdivo combination therapy in first-line, non-squamous non-small cell lung cancer, but the win for Opdivo with low-dose Yervoy was a surprise – and could possibly open up a needed edge in the NSCLC setting for BMS.

The Princeton, NJ-based pharma unveiled top-line data from the Phase III Checkmate-227 after the markets closed on 24 July, hours ahead of its second quarter earnings call the following morning. BMS reported a solid earnings quarter on 25 July, with several products besting consensus sales estimates, and had virtually nothing new to say about its pending but delayed merger with Celgene Corp. Nonetheless, the NSCLC combination data overwhelmed all other issues on the table during the investor call.

CEO Giovanni Caforio opened the firm's 25 July earnings call noting that "we plan to discuss these results with health authorities as soon as possible."

Checkmate-227 had been BMS's last best chance for first-line lung cancer. A shocking failure in the Checkmate-026 trial of Opdivo monotherapy in the first-line setting back in 2016, combined with subsequent successes for competitors – chiefly Merck & Co. Inc.'s Keytruda (pembrolizumab) – had led to Opdivo's loss of its lead position in the market. *(Also see "First-Line Chemo Combo Data Help Merck's Keytruda Power Past Opdivo" - Scrip, 29 Jul, 2018.)*

Part 1a of Checkmate-227, which tested the Opdivo (nivolumab)/Yervoy (ipilimumab) combo in 1,200 untreated NSCLC patients who tested positive for PD-L1 expression, had not been expected to show a benefit compared to chemotherapy, given previous disappointments with the CTLA-4 pairing. But BMS reported that the combo showed both an overall survival (OS) and progression-free survival (PFS) benefit. An exploratory arm testing the combo in 550 patients who did not express PD-L1 also indicated an OS benefit.

It's the company's second look at the trial – it first tried pooling data from Checkmate-227 and using the tumor-mutation burden (TMB) biomarker instead of PD-L1, but wound up pulling its filing.

BMS was expected to succeed, however, in Part 2 of Checkmate-227, where it was testing Opdivo plus a chemotherapy doublet against a control arm of double-agent chemo. Chemotherapy/PD-x combinations have worked for Merck and Roche.

However, the Opdivo-containing regimen in Checkmate-227 showed a median OS of nearly 19 months compared to nearly 16 months for the control, missing statistical significance.

During the investor call, head of oncology development Fouad Namouni said BMS needs to discuss the Part 1a data with regulatory authorities, but thinks it has meaningful data in the PD-L1-positive patients. "We have seen a clear benefit, clinically meaningful and statistically significant, of Yervoy plus Opdivo in the primary endpoint of the study, which is in PD-L1-positive [patients]," he said. "We have also seen a good survival benefit in the PD-L1-negative [cohort]. … I'm not going to comment on our interaction with health authorities as they would be happening in the next days and weeks, but I think we are seeing benefit across the board in terms of biomarkers, in terms of the totality of the data."

MAGNITUDE OF OS BENEFIT NOT YET DISCLOSED

Wolfe Research analyst Tim Anderson called the Part 1a data a win for BMS, but cautioned that seeing the magnitude of the OS benefit will be needed to assess the market opportunity for the chemo-sparing combo regimen. He added that there is greater unmet medical need in PD-L1-negative patients, where BMS has exploratory data, but not necessarily data it can file for approval. He added that earlier data with the combo suggested it worked regardless of the patient's PD-L1 status.

Further, safety data for the combo will be crucial. BMS said the combo showed safety and tolerability in line with earlier studies – the regimen tested in Checkmate-227 was 3mg/kg of Opdivo and the lower 1mg/kg dose of Yervoy, which has better safety and tolerability than the higher Yervoy dose that was first approved.

"The net is that Opdivo+Yervoy may finally be able to position itself as a chemo-free option in first-line non-squamous lung cancer," Anderson wrote on 24 July. "Even if results are weaker on side-by-side comparison to Merck's KEYNOTE-189 chemo/combo data, some patients will invariably seek to avoid chemotherapy and preference IO/IO. This is the 'win' from today's news, but quantifying it is difficult."

On 24 July, Morgan Stanley analyst David Risinger questioned the value of the Part 1a success, suggesting the Opdivo/Yervoy combo would need to show better efficacy than Keytruda monotherapy, which in the KEYNOTE-042 trial has shown median OS of 17 months compared to 12 months for chemo alone. He called Part 1a "a small glimmer of hope" for BMS, but like Anderson said he'd wait the fuller data the pharma says it will present at an upcoming oncology meeting.

Damien Conover of Morningstar said on 25 July that he'd expected both Part 1a and Part 2 of Checkmate-227 to succeed, but added that the "successful outcome for Opdivo plus Yervoy could allow for more differentiation." Overall, Conover projects that BMS will capture nearly 10% of the NSCLC market.

Wolfe's Anderson added that the Part2 miss might not be a substantial loss for BMS, considering the high bar Merck has set with its KEYNOTE-189 data. "Even if Part 2 had worked, which we thought it would, its commercial value was often debated – it was reasonable to guess that results would not be as strong as KEYNOTE-189 … and BMS would have been a late entrant into chemo combo with a regimen of its own," he wrote. "However, it would have netted the company at least [some] sales because Opdivo does already have critical mass as a product, and this would have been one more indication, enabling usage by Opdivo prescribers in one more setting."

Caforio noted that the Part 1a data comprise the third Phase III trial showing an OS benefit for Opdivo plus Yervoy in a cancer setting, along with melanoma and renal cell carcinoma. "I have full confidence in my commercial team's ability to execute in this competitive marketplace," he added. The mixed news in first-line NSCLC still is a better outcome than the OS miss for Opdivo compared to Bayer AG/Amgen Inc.'s Nexavar (sorafenib) in first-line hepatocellular carcinoma a month earlier. BMS still holds out hope for Opdivo plus Yervoy in second-line HCC as well as Opdivo monotherapy in the adjuvant setting.

ELIQUIS, IO FRANCHISE POST SOLID GROWTH

Overall the second quarter was a solid one for BMS, with 10% year-over-year sales growth to approximately $3.6bn. It finished the trading day 25 July up 5% to $45.41 per share.

Opdivo brought in $1.82bn worldwide during the quarter, up 12% from Q2 2018, while US sales rose 9% to $1.11bn. Yervoy increased 17% worldwide to $367m, with US revenue up 11% to $253m. However, Yervoy sales declined from first quarter 2019, which chief financial officer Charles Bancroft attributed to "unfavorable inventory compared to Q1 and slightly lower demand from non-promoted use of Opdivo/Yervoy, especially in small-cell lung cancer." BMS felt some impact from competition in first-line RCC, he added, but maintains a market share of 35%-40%, coming mainly in patients with intermediate-to-poor risk.

The anticoagulant Eliquis (apixaban) remains BMS' top-seller as well as its growth-leader. Global sales of $2.04bn during the quarter provided 24% year-over-year growth, while US sales increased 30% to $1.27bn. Bancroft warned, however, that the impact of Medicare Part D's donut hole will be felt more strongly during the third and fourth quarters – the impact in 2018 was about$550m and BMS expects a much larger impact this year, he said.

On the issue of the pending merger with Celgene, Bancroft said good progress is being made, with the deal expected to close in late 2019 or early 2020. The process for divesting Otezla (apremilast) is underway but a transaction will require sign-off from the US Federal Trade Commission, he noted. "We announced the planned divestiture late last month and are now preparing the sale process," the exec said. "We believe Otezla is an attractive asset and we have had significant interest from potential buyers."

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Novartis's Entresto PARAGON-HF Miss Puts Large Commercial Opportunity At Risk

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Entresto, Novartis AG's approved heart failure drug, has failed in a Phase III trial in an indication that promised to double the patient population for the product. The PARAGON-HF trial data have been keenly awaited as a key catalyst with the potential to lead to a big increase in sales and profitability of the dual-acting drug.

Entresto (sacubitril/valsartan), which is already approved to treat patients with heart failure with reduced ejection fraction (HFrEF), was being studied also for heart failure with preserved ejection fraction (HFpEF), an indication with a similar number of patients as HFrEF but with no approved treatment. However, the results of the 4,822-patient PARAGON-HF trial in HFpEF showed it narrowly missed the composite primary endpoint of reducing heart failure hospitalizations and cardiovascular death versus valsartan alone.

"Entresto's failure to show a benefit in this subgroup will significantly stunt its future revenue growth, as it limits use to patients with HFrEF, which is already a predominately genericized market," Datamonitor Healthcare analyst Hannah Cohen told *Scrip*. "Entresto only recently overcame recent barriers to uptake in the form of reimbursement delays and physicians' reluctance to shift from established treatment practices."

Hopes had been high for PARAGON-HF given the size of the unmet need and Entresto's previous positive results in HFpEF in the Phase II PARAMOUNT trial, which showed the medicine reduced NT-proBNP, a biomarker for cardiac strain, to a greater extent than valsartan alone at 12 weeks, as well as being associated with an improvement in New York Heart Association (NYHA) class at 36 weeks. NYHA classification of heart failure assigns patients to one of four groups based on their limitations during physical activity, measured by shortness of breath and chest pain. *(Also see "Heart failure hope for Novartis first-in-class neprilysin inhibitor" - Scrip, 26 Aug, 2012.)*

Entresto: a near miss in HFpEF

Analysts had predicted that approval of Entresto for the additional indication of reducing cardiovascular death and hospitalizations in patients with HFpEF could have added billions of dollars to its annual peak sales. Entresto sales were $778m in the first half of 2019, representing an increase (at constant currencies) of 83% on the first half of 2018. The drug has lately enjoyed a boost in sales, exceeding $1bn for the first time in 2018 following a faltering start after its launch in 2015, and positive results from PARAGON-HF had been expected to drive further growth.

PEAK SALES PARED

Peak annual sales of Entresto based on its HFrEF indication alone have been predicted to reach $3-4bn or more, with a label expansion to HFpEF potentially adding a further $2-2.5bn. That additional boost now looks to be at risk, even though Novartis says it plans to discuss next steps with regulators and clinical experts, suggesting it has not given up hope of winning expanded approval in HFpEF. Despite the missed endpoint in the PARAGON-HF study, Novartis said "the totality of the evidence from the trial" still suggested Entresto may have "clinically important benefits in HFpEF."

Novartis will present details of PARAGON-HF at the European Society of Cardiology (ESC) congress in Paris in late August/early September. It declined to provide any further information for the time being.

"It was not entirely unexpected that Entresto failed to meet the primary endpoint of reduction in CV death and HF hospitalizations in the Phase III PARAGON-HF trial in HFpEF patients, since there are a plethora of failures that encompass clinical trials in this patient population," commented Cohen. "Although it is currently unclear what clinically important benefits Entresto has in HFpEF, its narrow miss of statistical significance on the primary endpoint makes it highly unlikely that the FDA will support a label expansion in this indication." However, she noted that Novartis "may consider pursing Entresto in a subgroup of HFpEF patients, if any showed potential in the Phase III trial."

Credit Suisse analysts, meanwhile, flagged up the lost opportunity for improved profitability. "PARAGON was an important 2H19 catalyst for investors given the high unmet need in HF-PEF and existing commercial infrastructure for Entresto in HF-REF (reduced ejection fraction) which would have allowed a very high contribution margin on incremental sales," they wrote in a 29 July reaction note. "While management intends to engage with regulators, we would be surprised if Entresto was able to see an approved label indication based on a failed P3 study. However, if the data at ESC shows signs of meaningful efficacy then we would expect some off-label use in HF-PEF given no therapies have been shown to work to date."

"We expected it to be more difficult for Entresto to demonstrate efficacy in the preserved ejection fraction population because the patients' hearts are in better condition, making it harder to show a benefit. Novartis estimates that there are 1.7m patients with HFpEF in the EU and 2.5m such patients in the US," wrote Jefferies analysts in a 29 July note, in which they also said they would expect an HFpEF indication on its label to boost Entresto sales by $2.5bn at peak by patent expiry.

While in HFrEF the heart does not contract with enough force to pump out blood sufficiently, in HFpEF the heart contracts

normally but the ventricles do not relax properly during ventricular filling. Novartis has said that around half of the estimated 13 million heart failure patients worldwide suffer from HFpEF. Unfortunately, it has proven a more challenging target for drug development. "Overall the prospects for a successful treatment in HFpEF patients do not look good as the pathophysiology of the disease is poorly understood. HFpEF is considered a heterogeneous disease prompted by a burden of comorbidities, genetic predisposition and lifestyle factors. This makes identifying a novel mode of action that is effective in a broad range of HFpEF patients increasingly difficult," observed Cohen.

PARAGON-HF studied ambulatory patients with established HFpEF being treated for symptoms and comorbidities; around half had a history of heart failure hospitalizations.

Novartis continues to run two additional Phase III trials of Entresto in HFpEF. PARAGLIDE-HF is studying the drug compared with valsartan when initiated in hospitalized patients with acute decompensated heart failure who have been stabilized during hospitalization; endpoints are changes in NT-proBNP and safety and tolerability. PARALLAX is studying Entresto versus valsartan, or enalapril, or placebo; its endpoints are changes in NT-proBNP at week 12 and changes from baseline in 6-minute walk distance at week 24.

Entresto is an oral pill combining the angiotensin II receptor blocker (ARB) valsartan, marketed by Novartis as Diovan for heart failure in the US since 2002, and sacubitril, a prodrug that inhibits the enzyme neprilysin, which is responsible for the breakdown of several vasoactive peptides.

One positive to be drawn from the PARAGON-HF trial update was that no new safety or tolerability issues emerged, indicating that it will not have a negative impact on the product's ongoing use in HFrEF.

Other companies running advanced trials in HFpEF include Boehringer Ingelheim GmbH and Eli Lilly & Co., which recently won fast track status for their SGLT2 inhibitor Jardiance (empagliflozin), and AstraZeneca PLC, with another SGLT2 inhibitor Farxiga (dapagliflozin). The Phase III EMPEROR-Preserved trial of Jardiance is expected to read out in 2020, while results from the DELIVER trial of Farxiga are expected in 2021. Jardiance is being studied for time to first event (cardiovascular death or hospitalization for heart failure) versus placebo, while Farxiga is being studied studied for its ability to reduce cardiovascular death or worsening heart failure compared with placebo.

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AbbVie's Five Biggest Priorities, Apart From Allergan

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With not much new to say about its pending merger with Allergan PLC, AbbVie Inc.'s second quarter earnings call on 26 July centered on how Humira sales are being affected by biosimilar competition in Europe, the launch of psoriasis drug Skyrizi and the pharma's thoughts on Senate legislation to reduce drug prices within Medicare and Medicaid.

AbbVie also revealed that it is terminating a Phase II trial investigating anti-tau ABBV-8E12 in progressive supranuclear palsy (PSP), but said the antibody candidate's Phase II study in Alzheimer's disease will continue.

Overall, it was a flat earnings quarter for the Chicago-area firm, with net revenues of $8.26bn down 0.3% year-over-year excluding the impact of foreign exchange, but up 1.5% incorporating foreign exchange. During the first quarter of 2019, AbbVie brought in $7.83bn, down 1.3% from a year earlier, as the impact of Humira biosimilars began making a more noticeable impact.

1. HUMIRA GROWS DOMESTICALLY, BUT EX-US DOWNTURN WORSENS

Humira (adalimumab) posted global net sales of $4.87bn, down 6.1% year-over-year, during the second quarter. US sales were up 7.7% to $3.79bn, but ex-US sales tumbled 35.2% (31% including foreign exchange) to $1.08bn, which the company attributed to the impact of biosimilar competition in Europe and elsewhere. Chief financial officer Robert Michael called the ex-US sales erosion "in line with our expectations."

During the first quarter of 2019, Humira US sales rose 7.1% to $3.21bn, while ex-US revenues declined 23% to $1.23bn. A primary driver of the $63bn buyout of Allergan is to reduce AbbVie's dependence on Humira – the world's top-selling drug – before 2023, when several adalimumab biosimilars will enter the US market. Sandoz International GMBH's Hyrimoz, Amgen Inc.'s Amjevita and Boehringer Ingelheim GmbH's Cyltezo already have an FDA thumbs-up, while biosimilars from Pfizer Inc. and Samsung Bioepis Co. Ltd. are under FDA review.

During the 26 July earnings call, chairman and CEO Rick Gonzalez noted that AbbVie had completed the ninth and final intellectual property dispute pertaining to Humira biosimilars with BI. "This final settlement agreement reinforces our confidence that we will not see direct biosimilar competition in the US until 2023," he said.

2. ABBVIE ECHOES PEER CONCERNS ABOUT SENATE PRICING BILL

Similar to comments from other pharma execs in recent days, Gonzalez expressed support for the goal of reducing patient upfront costs for drug therapies while questioning whether the proposed Prescription Drug Pricing Reduction Act of 2019 is up to the task as currently drafted. The bill would reduce Medicare and Medicaid patients' out-of-pocket costs somewhat, he said, but he questioned whether it will be enough to make difference.

"We're obviously very supportive of anything that lowers patients' out-of-pocket costs," Gonzalez said. "I think one of the most significant challenges that we face in the US is that the way the [Medicare] Part D design was built originally, it didn't necessarily envision the level of specialized medicine that would develop over time, and the out-of-pocket cost for patients made many of those drugs unaffordable for the average senior. And so, any-

thing we can do to reduce that, I think, is a positive for the industry and it's certainly a positive for patients."

He also echoed peers' statements that the bill as presently constructed might be punitive toward innovative biopharmaceutical companies. In a note published on 24 July, Bernstein analyst Ronny Gal named AbbVie as one of six firms that would be affected most greatly by Part D restructuring based on their portfolio mix, along with Celgene Corp., Gilead Sciences Inc., Novartis AG, Biogen Inc. and Amgen.

"There are some aspects of the legislation that we believe are punitive, particularly [for] the innovation-driven companies," Gonzalez said. "And clearly, it does give benefit to some other companies that don't have specialty products that get into the catastrophic phase. And so, I don't know that that was the intent, that companies should pay lower than what they pay today. I doubt that was the intent. But that is the nature of the way it's structured today, and I think that's something that ought to be debated and discussed."

3. ANTI-TAU CANDIDATE VIABLE FOR ALZHEIMER'S, BUT NOT PSP

AbbVie president Michael Severino told the call that based upon a futility analysis showing disappointing efficacy, the company is discontinuing a Phase II study of ABBV-8E12 in progressive supranuclear palsy (PSP), but continuing a Phase II study with the tau-targeting antibody in Alzheimer's. AbbVie licensed global rights to the antibody from C2N Diagnostics LLC in 2015.

"Alzheimer's disease and PSP differ in a number of important ways, including the genetic background in which they occur and the distribution and potentially the nature of tau pathology," Severino said. "Therefore, the ongoing Phase II study in Alzheimer's disease will continue as planned."

It remains to be seen whether this setback for ABBV-8E12 will read through to a similar R&D effort at Biogen, which is investigating a tau antibody licensed two years ago from Bristol-Myers Squibb Co. in the same two indications. Biogen already is catching flak from market analysts by continuing efforts to study amyloid-beta candidates in Alzheimer's, despite mounting failures and terminations at other companies.

4. SKYRIZI LAUNCH SOARING AT START

Internally, AbbVie's strategy for growth after Humira loses US patent protection includes the interleukin-23 inhibitor Skyrizi (risankizumab-rzaa), approved for psoriasis in April and launched in May, along with the Phase III upadacitinib, filed for approval at the FDA for rheumatoid arthritis with a 20 August action date.

In less than a full quarter on the market, Skyrizi posted sales of $48m during the second quarter. AbbVie pointed out that products launched since 2015 have brought in roughly $2.1bn so far, about 21% of the company's net sales during that period.

Through 11 weeks, roughly 1,700 physicians have prescribed Skyrizi, with about 3,750 patients treated so far, including those with bridging access from clinical trials, Gonzalez said. "Commercial access for Skyrizi is also tracking in line with our expectations," he noted. "As a result of the launch progress and the momentum, we are increasing our full-year guidance for Skyrizi and now expect full-year global sales of approximately $250m. The outlook for Skyrizi remains very strong and it represents a significant long-term opportunity for AbbVie with multibillion-dollar peak sales potential."

5. IMBRUVICA, VENCLEXTA RAMP-UP CONTINUES

Hematologic oncology continues as a growth area for AbbVie, as the company reported 38.7% growth for the two-drug franchise to $1.27bn during the quarter. Imbruvica (ibrutinib) posted worldwide sales of nearly $1.1bn, a 29.3% year-over-year increase, including US sales of $886m and profit-sharing revenue from ex-US sales of $213m on the quarter. Venclexta (venetoclax) yielded $169m in sales during the quarter, more than 100% year-over-year growth and 9% sequential growth from $151m in the first quarter.

Gonzalez said Imbruvica is seeing market-share growth across multiple chronic lymphocytic leukemia (CLL) settings, including a 35% market share in new frontline CLL patients, a 10 basis-point uptick from second quarter 2018.

"This strong momentum directly relates to the growing body of clinical evidence, label augmentation and recently updated treatment guidelines, which now position Imbruvica as the only preferred therapy in the frontline CLL market," the exec said. "Venclexta also continues to make very good progress in the broad relapsed/refractory CLL setting and has established a strong growth trajectory in the recently approved indications for first-line CLL and [acute myeloid leukemia]."

AND... ALLERGAN MERGER ON TRACK FOR EARLY 2020

The biggest priority for AbbVie is of course its pending mega-merger with Allergan. Gonzalez told the call that the deal remains on track for closing during the first quarter of 2020. The pharma has been conducting outreach with investors on the transaction and will continue to do so in the coming weeks, he said. Efforts to integrate the two companies continue as well, he added.

"The integration planning is already underway, and we are working to ensure a seamless transition on day one," Gonzalez said. "We've identified individuals within AbbVie that will lead the integration process, and there will be dedicated teams to ensure there is no disruption to our strong momentum. And finally, I'll be meeting with the Allergan employees in the coming weeks. I look forward to engaging with and ultimately welcoming this experienced and very talented organization into AbbVie."

An SVB Leerink note issued on 23 July evaluates AbbVie/Allergan favorably compared to two other recent biopharma mega-mergers: BMS/Celgene and Takeda Pharmaceutical Co. Ltd./Shire PLC. Noting that investors have responded negatively to all three M&A transactions, Leerink pointed out that while Takeda shares have declined 32% and BMS shares 16% in the aftermath of their deals, AbbVie's decline has only been around 10%.

"In our analysis of the benefits of the transactions, AbbVie-Allergan appears to be the most favorable with greater benefit from revenue diversification, more (and more predictable) synergies, and significant [loss of exclusivity] mitigation," the Leerink note states. "However, AbbVie-Allergan also entails significant incremental leverage for the combined company, which is the main source of investor anxiety about the transaction."

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AZ On The Rise In All Regions And Therapy Areas

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With its second quarter results showing growth across every region and all three of its core therapeutic areas, AstraZeneca PLC is now preparing for the next six months and what CEO Pascal Soriot said will be the busiest half year for the pipeline since he took the job in 2012.

He was speaking as the drugs major posted a 14% rise in sales for the quarter to $5.72bn, with turnover at its oncology unit leaping 51% to $2.17bn. Leading the charge was the EGFR inhibitor Tagrisso (osimertinib) for lung cancer, now AstraZeneca's biggest-selling medicine with revenues of $784m (+86%), way ahead of consensus forecasts.

In an interview with *Scrip*, oncology head Dave Fredrickson said that in the US, Tagrisso returned to sequential growth, "which is something that we were expecting to see but it's obviously good that there continues to be underlying demand." He added that in the US, "as we approach being the standard of care in the frontline setting, we are seeing that growth slow down."

TAGRISSO EX-US SALES ARE GALLOPING

However, while Tagrisso slows down across the Atlantic, "Japan's growth in the quarter was torrid and the emerging markets, especially in China, are really fueling outstanding growth rates," Fredrickson said. In Europe, "We are seeing growth happening in Germany, France, Italy with encouraging reimbursements which is allowing us to have a medicine that is performing remarkably on a global scale."

Geographically, total emerging markets sales grew 17% to $1.95bn, with China leaping 34% to $1,17bn. Turnover in the US sales increased 16% to $1.88bn, while Japan sales climbed 30% to $672m.

Group sales in Europe returned to growth, edging up 1%, and head of biopharmaceuticals, Ruud Dobber, told *Scrip* that AstraZeneca is getting over the patent loss on the blockbuster statin Crestor (rosuvastatin) that hit in 2018 and the beginning of 2019. "We are moving out of that period," he said, noting that Fasenra (benralizumab) for severe asthma, Tagrisso, the checkpoint inhibitor Imfinzi (durvalumab) and the PARP inhibitor for ovarian and breast cancer, Lynparza (olaparib) are softening the blow.

AstraZeneca is looking to consolidate Lynparza's market-leading position with a series of trials and Fredrickson highlighted the ovarian cancer PAOLA-1 study, which is looking at a combination of the drug with Roche's VEGF inhibitor Avastin (bevacizumab) in all-comers, not just *BRCA*-mutant patients. He said that Avastin was the best comparator because 50% of women across the globe receive it as a therapy in the frontline setting and in Europe, almost all of those getting it as induction are on Avastin as maintenance.

AstraZeneca expects a first readout of the PAOLA-1 study later this year, and if it shows that there is a benefit to adding Lynparza on top of an Avastin backbone, Fredrickson believes that given physicians' familiarity with the Roche drug, there could be wide uptake of the combo. He added that the European Medicines Agency has accepted a filing for Lynparza in metastatic pancreatic cancer patients with BRCA mutations based on recent positive data from the Phase III POLO trial. *(Also see "GSK's Zejula Poised To Take On Lynparza In First-Line Ovarian Cancer " - Scrip, 15 Jul, 2019.)*

The results from PAOLA-1 will be keenly followed by GlaxoSmithKline PLC. The company is hoping that its PARP inhibitor Zejula (niraparib), acquired through the $5.1bn buy of Tesaro, could have an edge as a first-line maintenance therapy in ovarian cancer based on results from the recent positive Phase III PRIMA trial in the broad population. *(Also see "GSK's Zejula Poised To Take On Lynparza In First-Line Ovarian Cancer " - Scrip, 15 Jul, 2019.)*

Soriot noted that the second half of 2019 would be as busy as any he can remember in terms of newsflow, with one key event expected to be a US filing of the anemia therapy roxadustat, a closely-watched first-in-class oral inhibitor of hypoxia inducible factor-prolyl hydroxylase (HIF-PHI) which was approved in China in December 2018. However, confusion over top-line pooled cardiovascular Phase III safety data on roxadustat caused shares in AstraZeneca and partner FibroGen to slide in May, although analysts later said the negative reaction was overdone. *(Also see "AstraZeneca, FibroGen Plan New Roxadustat Filings, But CV Data Confuse Investors" - Scrip, 10 May, 2019.)*

AstraZeneca confirmed that roxadustat is on track for a filing in the coming months and noted that FibroGen is holding a meeting with the US Food and Drug Administration before the end of July. The drug is expected to be one of the next wave of blockbusters for AstraZeneca, Dobber told *Scrip*, along with Fasenra, the potassium binder Lokelma (sodium zirconium) and the BTK inhibitor Calquence (acalabrutinib); approved for mantle cell lymphoma and being evaluated in a number of blood cancers, the latter contributed $64m to AstraZeneca's coffers in Q2.

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AZ Heads Talk Pipeline And Partnerships

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Having presented a very strong set of second-quarter results with a number of new products close to blockbuster status already, AstraZeneca PLC has highlighted some pipeline programs that it hopes will become future growth drivers.

Mene Pangalos

Speaking to journalists to discuss the Q2 financials on 25 July, Mene Pangalos, head of biopharmaceuticals R&D at AstraZeneca, said the firm was "focused on making sure we continue to drive sustainable growth not just for the next five years, but for the next decade." One of the respiratory projects he highlighted was the Phase III asset PT027, a fixed dose combination of budesonide (an inhaled corticosteroid) and albuterol (a short-acting beta-2 agonist) "that we will hopefully be using as reliever therapy across the globe and which we know is highly effective in mild asthmatics for reducing exacerbation rates." A readout from the Phase III trial is expected in the second half of 2020.

Pangalos also spoke about cotadutide, a GLP-1/glucagon co-agonist which will be going into Phase II trials in the second half of this year for nonalcoholic steatohepatitis and possibly in the future for diabetes. He said the two programs were moving rapidly "and there's an abundance of Phase I and Phase II assets, not all of which will work but it gives us great breadth and depth in the pipeline."

José Baselga, who heads up oncology R&D at AstraZeneca, said the firm was committed to growing in hematology "and we have a number of compounds there that are quite exciting." He highlighted AZD5991, an MCL1 inhibitor, and AZD4573, a CDK9 inhibitor, which are both in Phase I, as well as AZD2811, an aurora kinase B inhibitor in Phase II for blood cancers as well as small cell lung cancer.

Baselga also mentioned a candidate that is potentially much closer to the market, trastuzumab deruxtecan to treat advanced HER2-positive breast cancer. In March, AstraZeneca paid $1.35bn upfront to Daiichi Sankyo Co. Ltd. for global rights to the antibody drug conjugate in a deal potentially worth up to $6.9bn and in May the firms presented positive data from the Phase II DESTINY-Breast01 trial; a Phase III study is ongoing. Rather than major M&A activity, deals such as the one with Daiichi Sankyo are the most likely way forward for AstraZeneca. In an interview with *Scrip*, oncology head Dave Fredrickson said "companies that have their hands on transformative medicines want to continue to play a role in the commercialization of them," and with the Daiichi Sankyo alliance and the pact with Merck & Co. Inc. on the PARP inhibitor Lynparza (olaparib), "we are building a capability in terms of how we work well together with other large partners and accomplish more together than we would be able to individually."

Head of biopharmaceuticals Ruud Dobber added that such partnerships were not only taking place in oncology. He cited AstraZeneca's partnership with Amgen Inc. on tezepelumab, which blocks thymic stromal lymphopoietin and "can potentially be a best-in class biologic for asthma and chronic obstructive pulmonary disease." *(Also see "Tezepelumab Deemed Breakthrough But Can Phase III Reproduce Data? " - Scrip, 7 Sep, 2018.)*

Dobber told *Scrip* that in terms of research projects, "the plate is full and there is no immediate need to look outside" although the company has business development groups "still sniffing around the world for assets and unique opportunities that will fit our strategy."

It also looks as though AstraZeneca's policy of asset disposals to fund future R&D is coming to an end. Dobber said it was becoming more difficult as most of the non-core assets had been divested, "though you could argue there are still a couple of them in our portfolio but we are quite bullish: if we are not getting the fair value for those assets, we're not going to dispose of them.

"If there's an attractive offer, and we evaluate them on a monthly basis, we will consider it but there is less of a need to do that because of the organic growth of the company and the new products which are taking off."

SORIOT ON BREXIT

With the media call coming the day after Boris Johnson was named as UK Prime Minister, it was not surprising that AstraZeneca CEO Pascal Soriot was asked about the risk of a no-deal Brexit. He said that "while we are hoping for an orderly transition like everybody else," the company had been preparing for a hard Brexit for three years.

"We have increased our stocks both in continental Europe and here in the UK, we have looked for alternative routes to supply our products in case of a hard Brexit and supply chains could well be disrupted," he said. AstraZeneca has also re-registered products in Europe and duplicated quality control tests in Sweden so it can still sell goods at European standards.

"We are ready, we've done everything we could so patients don't miss out on their medicines," Soriot concluded. "Whether we have a hard Brexit or an orderly transition, I will not venture to bet on this because I really don't know."

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GSK On Track For Six Regulatory Submissions In H2

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GlaxoSmithKline PLC has six new drug and indication expansion filings planned in the second half of 2019, the company said during its second quarter financial call on 23 July. Three of those filings are in oncology, including two new oncology drugs.

The company's chief scientific officer and R&D president Hal Barron highlighted the company's pharmaceutical R&D progress during the call, one year after he laid out his plans to reignite GSK's R&D engine, relying on human genetics, advanced technology and machine learning.

"I believe we've made significant progress over the past 12 months, resulting in a much stronger pipeline," Barron said. "We've also hired some outstanding people and established some exciting new partnerships."

The company has worked particularly toward building its oncology pipeline, both by accelerating internal programs and through acquisitions and partnerships. The company acquired Tesaro Inc. for $5.1bn, gaining the marketed PARP inhibitor Zejula (niraparib) and dostarlimab, a PD-1 inhibitor. *(Also see "GSK Embraces PARP Promise With Tesaro Buy" - Scrip, 3 Dec, 2018.)* In February, GSK paid €300m up front for rights to Merck KGaA's bifunctional immunotherapy M7824 (bintrafusp alfa), which the company has advanced into a Phase III trial in biliary tract cancer.

GSK also accelerated development of its B-cell maturation antigen (BCMA) antibody-drug conjugate, now named belantamab mafodotin, in multiple myeloma.

THREE ONCOLOGY FILINGS PLANNED

Those efforts will now deliver important catalysts in the second half of 2019 that could result in new drug approvals in 2020.

GSK confirmed that it is on track to report top-line pivotal data on BCMA in the DREAMM-2 trial in multiple myeloma patients in the third quarter, data that will support a US Food and Drug Administration filing for fourth-line treatment. The company said it will file for FDA approval before the end of the year.

"The program continues to advance at an impressive pace and is a good example of our cultural progress in terms of improving our focus and investing behind our most promising assets," Barron said. The BCMA category is setting up to be a competitive one in multiple myeloma, so being fast to market is essential. GSK has launched a full development program for BCMA, including for second-line treatment, first-line treatment and in combinations.

GSK is also on track to launch Zejula in first-line ovarian cancer in women regardless of genetic mutation. The company announced positive top-line data from the Phase III PRIMA trial in the broad patient population, showing an improvement in progression-free survival for women regardless of their BRCA status. *(Also see "GSK's Zejula Poised To Take On Lynparza In First-Line Ovarian Cancer " - Scrip, 15 Jul, 2019.)*

The pharma is studying Zejula in combination with the PD-1 antibody also acquired with Tesaro. That candidate is another one of the filings GSK has targeted for late 2019, based on the results of the GARNET study of dostarlimab monotherapy in patients with advanced solid tumors, including endometrial cancer, where it showed clinical activity in women with microsatellite-stability (MSI) high tumors. *(Also see "Tesaro's On The Right Path With Anti-PD-1 Dostarlimab In Endometrial Cancer " - Scrip, 22 Mar, 2019.)*

"We are very excited about these data and the potential to help these women, as endometrial cancer is the most common gynecologic cancer in the United States and GARNET is the largest study of an anti-PD-L1 monotherapy in patients with this form of advanced disease," Barron said.

The other three regulatory filings that are planned in 2019 fall outside of the oncology space: the triple inhaled respiratory drug Trelegy (fluticasone/umeclidinium/vilanterol) for asthma, the attachment inhibitor fostemsavir for HIV and the hypoxia-inducible factor prolyl hydroxylase inhibitor daprodustat for anemia associated with chronic kidney disease exclusively in Japan.

Barron said the company's pipeline progress over the last 12 months has resulted in a pipeline of 44 medicines and 13 vaccines in clinical development. The renewed pipeline includes 17 oncology assets in clinical testing.

SHINGRIX HELPS OFFSET ADVAIR AND BREO DECLINES

GSK delivered solid financial results in the quarter, considering the loss of its blockbuster Advair (fluticasone/salmeterol) to generic competition in the US in February. Group sales increased 5% to £7.8bn ($9.7bn) in the quarter. Pharmaceutical sales declined 1% to £4.3bn ($5.35bn), as generic Advair impacted sales of branded Advair and the follow-on respiratory drug Breo Ellipta (fluticasone/vilanterol).

US sales of Advair declined 60% to £105m ($130.7m) and worldwide sales of the brand fell 31% to £412m ($512.8m). Breo sales were also heavily impacted, declining 37% in the US in the quarter to £171m ($212.8m) and declining 9% worldwide to £453m ($563.8m).

Lower sales of Advair and Breo were offset by the strength of vaccines, namely the launch of the shingles vaccine Shingrix, which continued at an impressive pace.

"Shingrix continues to be a major driver of our growth," CEO Emma Walmsley said. Shingrix revenues were £386m ($480.5m) in the quarter. GSK is continuing to build out manufacturing capacity for the vaccine and said it is increasingly confident that it will achieve the upper end of its supply guidance.

GSK raised its 2019 financial guidance as a result of the solid results, now forecasting adjusted earnings per share to decline in the range of 3%-5% versus an earlier forecast of a decline of 5%-9%.

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Roche Raises Outlook Despite US Biosimilars, Sees Spark Buy By Year-End

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A strong performance by recently-launched drugs in this year's second quarter allowed Roche on 25 July to beat market forecasts and to raise its 2019 full-year outlook for the second time this year, boosted by management's rising confidence that it can ride out a wave of biosimilars entering the US market in the second half and continue growing earnings into 2020.

Roche said second-quarter group sales grew 9% at constant exchange rates, with the pharma division revenue up 11%, driven mainly by Ocrevus (ocrelizumab), Perjeta (pertuzumab) and Tecentriq (atezolizumab), as well as hemophilia therapy Hemlibra (emicizumab).

Management said a promising pipeline should keep the earnings stream at high momentum, offsetting the impact of biosimilars to its more mature drugs.

Roche has regularly guided to US launches of biosimilars to each of its big three cancer drugs, those being Avastin, Herceptin and Rituxan, by the end of 2019.

AMGEN 'AT RISK' MOVE

The decision by Amgen to launch its biosimilars to Avastin and Herceptin in the US market "at risk" with a 15% discount to the list prices has sown some uncertainty among investors. *(Also see "How Risky Is Amgen's At-Risk Launch Of Herceptin, Avastin Biosimilars?" - Pink Sheet, 21 Jul, 2019.)*But Roche used its second-quarter update to play down its impact.

CEO Severin Schwan said on a media call, "We expect to continue this strong growth beyond this year, despite the further market entries of biosimilars. There's a lot that is still coming from within our pipeline which further underpins our confidence."

The company now expects mid- to high-single digit sales growth for the whole of 2019 measured at constant exchange rates. Roche thus expects to further increase its dividend in Swiss francs.

"This improved outlook is entirely driven by the strong uptake of our new medicines," Schwan said.

The CEO said Roche will challenge Amgen's move in the US courts. He also said Amgen's move was not likely to trigger launches of other copy-cat versions of its medicines by biopharma groups with whom agreements are already in place.

"We are certainly going to defend our intellectual property," he said. "Amgen decided to launch 'at risk', so now the courts must decide on what happens now. But the other companies with whom we have settled, we have reached settlements and therefore they would not launch earlier based on Amgen's decision to launch on risk," Schwan told an analyst call later that same day.

Roche management said it did not have an overview of what amount of biosimilar stock had already been released into the market. "We haven't seen any major disruptions at this point," said Bill Anderson, who heads Roche's pharma division.

The company expects to first see a visible biosimilar impact on its earnings later this year.

Biosimilars to Roche products have already entered the market outside the US.

"We've always said that we would expect biosimilars to enter the US in the second half of 2019, and I would expect the effect to be bigger towards the end of the year, in the fourth quarter, rather than in the third quarter, as the biosimilars are being launched, but continuous earnings growth driven by our new medicines will also extend beyond the current year," Schwan said.

Analysts at Jefferies would seem to agree. The brokerage estimates that the raised outlook by Roche for 2019 "is suggesting 1%-5% potential earnings per share upgrades."

Jefferies regards Roche as its top European blue chip pick, and said in a reaction note on 25 July that when measured at net present value (NPV), which is the difference between the present value of cash inflows and the present value of cash outflows, "Roche's stock is discounting marketed drugs, ascribing no value to likely the most exciting pipeline in Pharma, with multiple innovative high-risk, substantial-reward readouts."

Schwan summed up by saying, "At the end of the day, in this industry, it all depends on the pipeline; as long as you are able to rejuvenate your portfolio, as long as you are able to come up with really, really differentiated medicines, then you will be able to defend a premium, you will be able to defend your margins."

ROCHE EXPECTS SPARK ACQUISITION BY YEAR-END

Roche played down the continuing delay to its plan to acquire Spark Therapeutics Inc., a US gene therapy group, after US regulators last month demanded more information about the $4.8bn deal. *(Also see "Roche $4.8bn Buy Sparks Hemophilia Gene Therapy Race " - Scrip, 25 Feb, 2019.)*

The Swiss pharmaceuticals group and Philadelphia-based Spark said on 10 June they had received another request for more information from the US Federal Trade Commission. As a result, Roche has extended until the end of July the deadline for Spark shareholders to tender their shares.

UK regulators are also examining whether they have jurisdiction over the acquisition and, if so, what the purchase would mean for competition. The Competition and Markets Authority has issued an interim enforcement order that would come into effect once the transaction is completed, requiring Roche to hold the Spark business separately.

"I cannot comment on the ongoing investigation by the FTC in the US or the one in the UK, but we are confident we can answer all their questions and believe that we will close the transaction as planned by the end of this year," Schwan said.

"Even though we would have hoped for a closing in the second quarter, I don't see any downside for the transaction. We are very committed to close this transaction," he added.

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Merck Positions MK-8591 As Backbone For HIV Treatment And Prophylaxis

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Merck & Co. Inc. views its first-in-class nucleoside reverse transcriptase translocation inhibitor (NRTTI) MK-8591 (islatravir) as a potential backbone agent for combination therapy in the treatment setting and also a means for entry into the pre-exposure prophylaxis (PrEP) market.

While the HIV market is led by Gilead Sciences Inc. and ViiV Healthcare, Merck has a long heritage in HIV and antiretrovirals. The company sells the blockbuster integrase inhibitor Isentress (raltegravir).

At the International AIDS Society (IAS) conference, held from 21 July to 24 July in Mexico City, the pharma presented 24-week and 48-week data from a Phase IIb dose-ranging study of '8591 demonstrating its potential for clearance of HIV RNA in a combination regimen with its doravirine (approved as solo agent Pifeltro and in the single-tablet combo pill Delstrigo in 2018) and Johnson & Johnson's lamivudine (Epivir, aka 3TC). *(Also see "Merck To Build Case For Doravirine-Based HIV Products On Efficacy, Safety Differences" - Scrip, 31 Aug, 2018.)*

In addition, Merck unveiled 12-week Phase I data showing safety and pharmacokinetics of an implantable formulation of '8591 for PrEP. Merck also has done modeling based on these data that it says indicates the implant could be work for 52 weeks or longer. *[Editor's note: This article has been revised to correct the drug class of islatravir, the size of a patient cohort and the length of the Phase I study.]*

In the Phase IIb DRIVE2Simplify study, Merck tested 0.25mg, 0.75mg and 2.25mg doses of '8591 as part of a combination regimen against a control regimen of Delstrigo, which includes the non-nucleoside reverse transcriptase inhibitor (NNRTI) doravirine, the nucleoside analog lamivudine and tenofovir disoproxil fumarate (TDF), a generic of Gilead's first-generation nucleoside reverse transcriptase inhibitor (NRTI). Patients received one of the doses of '8591 with doravirine and lamivudine for 24 weeks, and then if they achieved sufficient viral RNA reduction, the study drug was given with just doravirine for the next 24 weeks.

Given the 24-week and 48-week data, Merck now intends to move forward with a two-drug regimen of '8591 and doravirine, executive director Mike Robertson told *Scrip*. The main purposes of the Phase IIb study were dose-ranging and also to get a sense of safety and efficacy in HIV-infected patients, he said.

"What we saw in the trial was what we were hoping for … suppression of HIV RNA of less than 50 copies/mL, which is a standard measure of efficacy," Robertson said in an interview prior to IAS. "In each of those three dose levels, the percentage of patients suppressed at less than 50 copies/mL at 24 weeks and those that maintained it at 48 weeks was good and was comparable to the control arm."

EFFICACY, SAFETY SEEN AT 24, 48 WEEKS

At 24 weeks, 90% of patients who received the 0.25mg dose (26/29), 100% of patients receiving the 0.75mg dose (30/30) and 87% (27/31) achieved and maintained that viral RNA threshold, compared to 87% (27/31) in the control arm. There were no deaths, serious adverse events or discontinuations due to treatment-related AEs in any of the arms.

At 48 weeks, 90%, 90% and 77% of patients had HIV-1 RNA counts of 50 copies/mL or lower across the three dosing groups of '8591, compared to 84% for the control arm. Roughly 90% of patients in each of the three study drug arms were switched to the two-drug '8591/doravirine regimen, Merck said. In terms of protocol-defined virologic failure (PDVF), five of 90 patients in the study drug arms (5.6%) failed with four rebound cases and one non-response. One of 31 patients in the control arm (3.2%) had PDVF.

Robertson said Merck is happy with the efficacy, safety and tolerability profile indicated by the Phase IIb data. The company used a three-drug regimen in the study because it was the first trial for '8591 in chronic HIV patients, rather than healthy volunteers. "At the time we started this trial, doravirine was not approved either, so it was two investigational products – and I think the FDA was more comfortable having a three-drug regimen, which was the standard regimen that had been available for many years," he explained.

Now, Merck wants to test '8591 with doravirine in treatment-naïve HIV-infected patients. It's too early to say if the pharma will move toward approval of '8591 as a solo agent – as it did with doravirine – or just as part of a combination pill.

"For treatment, you always need more than one drug. That has been the paradigm for many years and I think patients really prefer single-tablet regimens," Robertson said, "so I think the most attractive option for patients would be an STR that had the full regimen in one pill."

Because of the drug's potency and half-life, Merck also plans to investigate dosing beyond once-daily, such as weekly, for both a convenience edge and a patient-compliance advantage that physicians might appreciate. However, Wolfe Pharma analyst Tim Anderson pointed out in a 16 July note that to make a weekly regimen viable, Merck would need to pair '8591 with another weekly HIV therapy. None of its marketed HIV drugs or candidates that

have advanced as far as Phase II would meet those characteristics, he noted.

"Weekly dosing would start to differentiate '8591, but – and this is an important point – only if Merck has another weekly agent to combine with," Anderson wrote. "Ideally this would be a weekly INSTI [integrase inhibitor] – I think they may have one in early development but they are being coy about it. Merck has various Phase I assets [for HIV] but they often won't say what they are. If Merck eventually gets a once-weekly combination regimen of 8591+INSTI, then suddenly this becomes a more meaningful product."

Such a regimen could enable Merck to begin competing with Gilead and its two-drug combos that use TDF or second-generation tenofovir alafenamide (TAF) as a backbone, the analyst asserted. But Merck is unlikely to produce such a product any earlier than 2022-2023, he said.

Meanwhile, the Phase IIb data Merck is presenting as IAS offer questionable market potential, Anderson continued, because the '8591/doravirine combo does not include an integrase inhibitor, a mechanism of action widely preferred by physicians in treating HIV, and the comparator was Delstrigo, which both lacks an integrase inhibitor and includes TDF rather than Gilead's second-generation TAF, which offer bone and renal health safety advantages over TDF.

USING CONTRACEPTIVE MODEL FOR LONG-TERM PROPHYLAXIS

Gilead is also Merck's target if it tries to move into the PrEP space – right now Truvada (emtricitabine/TDF) is the only agent approved by the US Food and Drug Administration for PrEP, although Gilead is seeking approval of Descovy (emtricitabine/TAF) in prophylaxis patients as well.

Merck is presenting 12-week data for a drug-eluting implant formulation of '8591 in prophylaxis at IAS. The pharma's success with implantable, long-term contraception is its guidepost here – and Robertson said the applicator used in the study for administering the '8591 implant is similar to the one incorporated in Nexplanon (etonogestrel implant 68mg).

Robertson emphasized, though, that it is very early days for its long-acting PrEP version of '8591. "The study that we're showing at IAS is our first in-human trial with that implant," he said. "It was a very small study, the results are good and what we were hoping to see, but there's a lot of work still to be done with that."

"The prototype is not what the final implant formulation will look like," he continued. "We're excited by it – if you could have an implant that would last for a year or even longer, that might be a really good option for a lot of people."

Anderson said Merck could make an impact in the PrEP market with a long-acting product because patient compliance has been low in PrEP, but said it would take Merck a long time to reach market, perhaps out to 2025. By that time, generic Truvada may be available for PrEP patients.

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ViiV Says Latest Data Back Two-Drug Approach, Plans Year-End Fostemsavir Filing

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GlaxoSmithKline PLC's HIV medicines unit ViiV Healthcare, which represents about 20% of GSK's sales, believes its two-drug therapy Dovato (dolutegravir/lamivudine) will see better acceptance and a boost in its sales following positive data presented at this week's International AIDS Society meeting in Mexico City.

And good results also presented at the AIDS conference from ViiV's Phase III BRIGHTE study demonstrated strong efficacy of investigational candidate fostemsavir in heavily treatment-experienced HIV patients at 96 weeks, giving the company adequate confidence to file the novel agent with the US Food and Drug Administration before the end of the year, Kimberly Smith, head of global medical research & strategy at ViiV, told *Scrip* in an interview.

GEMINI 1 & 2

ViiV Healthcare used the Mexico City event to present data from its Phase III GEMINI 1 & 2 studies in treatment-naive patients through to week 96 which showed the two-drug regimen of dolutegravir plus lamivudine continued to offer non-inferior efficacy to a three-drug regimen of dolutegravir plus two nucleoside reverse transcriptase inhibitors, tenofovir disoproxil fumarate/emtricitabine and with no cases of treatment emergent resistance seen.

> "The goal for us at ViiV is to reassure providers about the efficacy, the potency, the durability and maintaining the high barrier to resistance of the two-drug regimen." - Kimberly Smith

The week 96 data from the GEMINI studies demonstrated that the clinical benefits of dolutegravir plus lamivudine seen at week 48 are sustainable. "That allows us to use these two drugs while still getting efficacy non-inferior to that of a dolutegravir-based three-drug regimen, Smith said.

"The goal for us at ViiV is to reassure providers about the efficacy, the potency, the durability and maintaining the high barrier to resistance of the two-drug regimen," she explained.

TANGO DETAIL

Furthermore, ViiV Healthcare announced positive week-48 results in its Phase III TANGO trial, the first study to evaluate treatment

switch from three-drug TAF (tenofovir alafenamide fumarate) containing regimen to two-drug regimen of dolutegravir/lamivudine for HIV-1 infection.

Smith noted that tenofovir alafenamide fumarate (TAF) was chosen because it had a better side effect profile than tenofovir disoproxil fumarate which was used in the GEMINI 1 & 2 studies.

"What was most remarkable was that there were no patients on the dolutegravir/lamivudine regimen who experienced confirmed virologic failure."

A few weeks ago, ViiV presented topline data from the Phase III TANGO switching study. *(Also see "A Switch To ViiV's Two-Drug Dovato Keeps HIV Suppressed" - Scrip, 10 Jul, 2019.)*

"What was presented in Mexico City was a deeper dive to the data released earlier this month, which needed to be made public due to its potentially material nature for ViiV and also for the GSK stock price," Smith explained.

BRIGHTE FOSTEMSAVIR

The new data for fostemsavir show its promise for another group of patients. Fostemsavir has a novel mechanism of action as an attachment inhibitor and it is being developed as a treatment for individuals who have high levels of treatment experience. "So, this treatment is aimed at patients who have had multiple treatment regimens in the past and who are running out of options for their HIV," Smith said.

"In the BRIGHTE trial we were able to show that at week 96, 60% of patients receiving fostemsavir plus OBT (optimized background therapy)were able to get their viral load down to undetectable, which is a higher percentage of patients than at week 48, which is very significant," Smith said.

"This new agent is showing very good effectiveness in this study, and we will consequently be filing fostemsavir for approval in the US before the end of this year."

Since fostemsavir has breakthrough status because of the very important role it could play as a life-saving agent for many individuals, this could lead to an accelerated approval, Smith said. "But that of course remains to be seen."

VIIV CONFERENCE TAKEAWAY MESSAGE

Smith said the data revealed in Mexico City by ViiV should serve to accelerate the uptake of Dovato.

"The world was impressed by the Dovato data at week 48 data, but opinion leaders wanted to see the durability and they wanted to see the switch data and at this meeting we're providing everything they've asked for – durability, high barrier to resistance, and incredibly strong switch data."

"In light of this I think providers who might have been a bit hesitant are going to be more reassured by this data. We are leading a paradigm shift to a two-drug regimen approach, and that doesn't happen overnight. It takes time for folks to embrace something that is new."

She added, "At the same time, providers are very drawn to the idea of being able to provide less drugs. If we can reduce the number of drugs – and the number of adverse events associated with treatment – then we are also upholding our oath to 'do no harm'," Smith concluded.

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Vadadustat Emerges As Japan HIF-PHI Leader With First Filing Globally

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Mitsubishi Tanabe Pharma Corp. (MTP) has made the first approval filing globally, in Japan, for vadadustat (MT-6548), its oral hypoxia-inducible factor prolyl hydroxylase inhibitor (HIF-PHI) licensed from US venture Akebia Therapeutics Inc.

First Filing For Novel Anemia Therapy Vadadustat

The pioneering regulatory submission, if approved, is expected to lead to the first launch of the molecule worldwide. It also means vadadustat has now emerged as the clear leader within the vanguard of novel anemia therapies moving through development in Japan, where multiple products in the class are in late-stage trials.

MTP, which holds development and commercialization rights in Japan and other selected Asian markets under a 2015 deal with Akebia, has applied for manufacturing and marketing approval for renal anemia due to chronic kidney disease (CKD).

A standard review could see an approval being granted within a year, and Akebia president and CEO John Butler hailed the submission as "an important milestone for Akebia and our collaboration partner."

Intravenously administered erythropoiesis-stimulating agents (ESAs) are currently the standard of care in Japan, and vadadustat - like others in its class - would provide a more convenient once-daily oral option. The HIF-PHIs are also seen as generally safer than ESAs and reduce the need for concomitant use of IV iron preparations.

Amid generic challenges to its aging cardiovascular portfolio, vadadustat is also expected to be important commercially for MTP. Datamonitor Healthcare sees it as a "significant growth driver" over the mid term, generated sales of around $296m in Japan by 2026.

POSITIVE TRIAL DATA

The companies said the new submission is supported by two pivotal Phase III studies in Japanese subjects with renal anemia due to CKD, and two additional Phase III single-arm studies in peritoneal dialysis and hemodialysis patients.

Positive top-line data from these trials were announced by Akebia and MTP in March 2019, in which vadadustat met its primary non-inferiority endpoints in terms of mean hemoglobin levels versus the ESA darbepoietin alfa in both non-dialysis-dependent and hemodialysis patients. In the non-dialysis-dependent CKD group, actual mean hemoglobin at week 24 was 11.66g/dL versus 11.93g/dL for darbepoetin.

Vadadustat is in Phase III development globally and a US NDA is planned by the end of this calendar year. Akebia linked up in late 2016 with Otsuka Pharmaceutical Co. Ltd., another Japanese company, in a potential $1bn+ co-development and commercialization deal for the US market.

Under the 2015 agreement with MTP, the new Japanese filing triggers a $10m milestone payment to Nasdaq-listed Akebia, which the companies said is expected to be booked in the third quarter. Cambridge, MA-based Akebia is also eligible to receive up to approximately $205m in additional milestone payments linked to regulatory and sales milestones, and MTP will pay tiered double-digit royalties of up to 20% on sales of vadadustat in Japan and its other Asian territories. *(Also see "Akebia Strikes $350m+ Asian Vadadustat Alliance" - Scrip, 15 Dec, 2015.)*

LARGE POTENTIAL MARKET

Japan is a large potential market for the HIF-PHIs, as there are around 13 million people with chronic advanced CKD in the country, and about 10% of those with Stage 3-5 CKD have renal anemia.

The class acts to mimic the physiologic effects of high altitude and low oxygen, stimulating production of hypoxia-inducible factor and thereby iron mobilization and erythropoietin production to increase the number of red blood cells and oxygen delivery.

Japan Tobacco Inc. and commercial subsidiary Torii Pharmaceutical Co. Ltd. announced recently that they are planning a Japanese filing for their contender enarodustat, following positive top-line Phase III results. However, the exact timing of this is still not clear. GlaxoSmithKline PLC/Kyowa Hakko Kirin Co. Ltd.'s (KHK) daprodustat is also in Phase III in Japan, with an approval application expected sometime this year.

Meanwhile, KHK's ESA Nesp (darbepoetin alfa) saw the approval around a year ago in Japan of its first biosimilar, although this was an authorized version developed by the company itself.

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GW Pharma's Cannabidiol For Seizures One Step Closer To European Approval

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GW Pharmaceuticals PLC's orphan drug Epidyolex (cannabidiol) has been granted a positive opinion by the European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP).

The product, an oral solution, is recommended to be used alongside clobazam to treat seizures associated with the rare conditions Lennox-Gastaut syndrome and Dravet syndrome in patients aged two years and older. It is set to become the first plant-derived cannabinoid medicine to be approved under the EU centralized procedure.

A positive opinion from the CHMP usually leads to approval by the European Commission about two months later.

In its annual general meeting in June 2019, GW Pharma noted that it had a commercial team in place in five major European markets. This included a field-based team of 17 medical science liaisons (MSLs), country and medical leads already recruited. The company was preparing for early reimbursement in France and early commercial launch in Germany and the UK, with later launches in Italy and Spain depending on pricing and reimbursement.

The UK's health technology assessment body NICE is already appraising the clinical and cost effectiveness of the treatment in the Dravet syndrome setting, with expected publication of its appraisal in November 2019. GW has already established early access programs in five major countries. It has plans in place to progress with pricing and reimbursement in a second wave of 10 EU markets.

Epidyolex is an oral solution of highly purified plant-derived cannabidiol that shows little affinity to cannabinoid receptor 1, which is associated with psychoactivity.

GW Pharma submitted a marketing authorisation application to the EMA in December 2017, after completing submission 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, 19–25 JULY 2019

Event Stage	Lead Company/Partner	Drug Name	Indication	Comments	Change To LOA (%)	LOA (%)
Phase III Published Results	FibroGen/AstraZeneca	roxadustat	Anemia Due to Chronic Renal Failure, Dialysis-Independent	FGCL-4592-808 (China); NEJM, 24 July, 2019	0	74
Phase III Published Results	FibroGen/AstraZeneca	roxadustat	Anemia Due to Chronic Renal Failure, Dialysis-Dependent	FGCL-4592-806 (China); NEJM, 24 July, 2019	0	73
Phase III Published Results	AstraZeneca/Merck & Co	Lynparza (olaparib)	Pancreatic Cancer, Metastatic	POLO; NEJM, 25 July, 2019	0	45
Phase III Updated Results	ViiV Healthcare	fostemsavir	HIV/AIDS, Heavily Pretreated	BRIGHTE; Virologic Responses To First-In-Class	0	65
Phase III Top-Line Results	Intec Pharma Ltd.	carbidopa/levodopa Accordion pill	Parkinson's Disease	ACCORDANCE; Missed Primary Endpoint	-10	46
Phase III Top-Line Results	Acadia Pharmaceuticals, Inc.	Nuplazid (pimavanserin)	Schizophrenia, Adjunct	ENHANCE-1; Missed Primary Endpoint	-39	12
Phase III Top-Line Results	Chiasma, Inc.	Mycapssa (octreotide), Oral Capsules	Acromegaly, Maintenance	CHIAMA OPTIMAL; Met Endpoints	12	67
Phase III Top-Line Results	Myovant Sciences Ltd.	relugolix	Uterine Fibroids	LIBERTY 2; Positive Results	1	79
Phase IIb/III Top-Line Results	Essex Bio-Technology/Mitotech	Visomitin (SkQ1)	Dry Eye, Moderate To Severe	VISTA -1; Mixed Results, Next Program Planned	-4	49
Phase III Trial Initiation	FibroGen Inc.	pamrevlumab	Idiopathic Pulmonary Fibrosis	ZEPHYRUS; 52-Week Study	50	74
Phase III Trial Initiation	The Medicines Co/Alnylam	inclisiran	Hypercholesterolemia	ORION-8; Long-Term Extension Study	0	57
Phase III Trial Initiation	Oyster Point Pharma Inc.	OC-01 nasal spray	Dry Eye Disease	ONSET-2; In Two Doses	27	57

Source: Biomedtracker | Informa, 2019

CONTINUED FROM PAGE 21

a rolling new drug application (NDA) in the US in October 2017.

US COMMERCIALIZATION PROGRESS

In the US, the medicine was accepted for priority review and received approval under the brand name Epidiolex from the Food and Drug Administration in June 2018, leading the company to receive a Rare Pediatric Disease Priority Review Voucher (PRV). GW Pharma sold the PRV to Biohaven Pharmaceutical Holding Co. Ltd. for $105m, saying it would use the proceeds to advance additional cannabinoid candidates and to support the commercial launch of Epidiolex/Epidyolex in the US and Europe.

GW's US subsidiary Greenwich Biosciences launched the product in the US in November after the US Drug Enforcement Administration (DEA) evaluated its potential for abuse and reclassified it from Schedule I, covering substances with no accepted medical use, a lack of accepted safety for use under medical supervision and a high potential for abuse, to Schedule V, which comprises controlled substances with a proven medical use and low potential for abuse.

US Epidiolex sales totaled $33.5m in the first quarter of 2019. SVBLeerink estimates that GW Pharma's revenues will rise from $15.6m in 2018 to $205m in 2019 thanks to Epidiolex.

US Epidiolex sales totaled $33.5m in the first quarter of 2019. SVBLeerink estimates that GW Pharma's revenues will rise from $15.6m in 2018 to $205m in 2019 thanks to the launch of the epilepsy product. In a 28 June research note it forecast that Epidiolex would reach sales of $1.8bn in 2026. Both SVBLeerink and Morgan Stanley believe that a substantial proportion of revenues will come from off-label use of Epidiolex in refractory pediatric epilepsies beyond the indications on its label.

Epidiolex/Epidyolex is also in a Phase III trial in patients with treatment-resistant tuberous sclerosis complex (TSC), a rare genetic condition that causes tumors to grow in different organs of the body and is associated with frequent focal and generalized seizures. Top-line results announced in May 2019 showed the drug met its primary endpoint of reduction in seizure frequency versus placebo; GW plans to file for supplemental approval in the US in the fourth quarter of 2019. TSC affects about 1-2 million people worldwide, with more than 90% of patients affected by epilepsy, and more than 60% of those failing to achieve seizure control with standard treatments.

GW has a platform of cannabinoid products in clinical trials for a number of indications and is also developing new formulations of Epidiolex including in a capsule formulation and as part of combination products.

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APPOINTMENTS

Executive	To Company	New Role	From Company	Previous Role	Effective Date
Don Vidic	Agenus Inc	Vice President and Head, Commercial	Ideal Rx Consulting	Managing Member	18-Jul-19
Kristin Taylor	Escient Pharmaceuticals	Vice President and Head, Clinical Development	Zafgen Inc	Vice President and Head, Clinical Development	17-Jul-19
Elizabeth A. Tarka	Idera Pharmaceuticals Inc	Chief Medical Officer	Complexa Inc	Vice President, Clinical Development	23-Jul-19
Robert Hayes	Immusoft Corp	Chief Scientific Officer	Amgen Inc	Head, Biologics	17-Jul-19
Friedrich Graf Finckenstein	Iovance Biotherapeutics Inc	Chief Medical Officer	Roche Pharma Research	Global Head, Oncology Translational Medicine	18-Jul-19
Manoj Pananchukunnath	Julphar Gulf Pharmaceutical Industries	Chief Scientific Officer	Mylan	Head, Global Injectable Scientific Affairs	21-Jul-19
Rahul Kakkar	Pandion Therapeutics	Chief Executive Officer and Director	Corvidia Therapeutics	Founder, Chief Medical Officer and Chief Strategy Officer	17-Jul-19
Satyavrat Shukla (Sath)	Ziopharm Oncology Inc	Chief Financial Officer	Vertex Pharmaceuticals	Vice President, Global Head, Corporate Finance	24-Jul-19

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