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GSK's Big Reveal: An R&D Overhaul Poised To Yield Long-Term Cultural Change

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GlaxoSmithKline PLC CEO Emma Walmsley may have spelled out the big pharma's R&D turnaround plan best while introducing the company's new Chief Scientific Officer and President-R&D Hal Barron to the stage during an investor event July 25.

"His job is to transform our pipeline and reignite GSK's reputation as an innovator," she said. "That is going to take some time, but I can assure you he is already having an impact."

Indeed, the big takeaway from the meeting – the first in which Barron addressed investors at length about his plans for pharma R&D – is that investors will need to be patient to see GSK deliver on its promise of innovation. GSK does not have a wealth of late-stage drugs in the pipeline and despite delivering advancements in core areas like respiratory disease and HIV recently, the company has fallen well behind rivals in important areas like oncology and immunology, where it's clear Barron plans to course correct.

Walmsley recruited Barron to GSK late last year to reinvent the company's pharmaceutical R&D, with an eye toward building in oncology. It was a big coup given his legacy in cancer as the former head of R&D at **Genentech Inc.** (*Also see "GSK Bags Barron As R&D Boss As Vallance Joins UK Government" - Scrip, 8 Nov, 2017.*) With a budding early immuno-oncology pipeline, Walmsley clearly has her eye on establishing GSK as an important player in the space.

The event in London was Barron's first opportunity to present his R&D strategy and coincided with the company's second quarter sales and earnings release.

"This is an ideal time to be thinking about reinventing R&D, because we are doing well. We are growing," Barron said.

PILLARS FOR INNOVATION

Investors have been eager to hear from the R&D legend, but with few near-term catalysts or big changes to the late-stage pipeline, they may be underwhelmed by the update.

Barron, meanwhile, is focused on delivering scientific and cultural changes that will yield breakthroughs over the long-term. He talked about a time horizon of 2021 to 2026, and he talked more high-level, rather than specifics, about incentives needed to drive innovation, the technologies that can help improve clinical trial success, and cultural changes. He said science, technology and culture are the three pillars needed to drive innovation, and all three must be in place to be successful.

GSK's focus will be on developing breakthrough medicines, rather than incrementally beneficial ones. As he explained it, "ones that are going to be very transformative, ones that don't stop after the first indication, ones that have a broad lifecycle and ones that when they help, they help in a fundamental way." He said the company would be more agonistic to therapy area and go where the science leads, underpinned by genetics.

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Pricing Debate
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from the editor

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The presentation of 18-month Phase II data for Biogen/Eisai's anti-amyloid-beta protofibril antibody BAN2401 generated the biggest buzz at the Alzheimer's Association International Conference last week (see p9).

But enthusiasm for the results was more a reflection of the context of repeated confusion and failure in the field of Alzheimer's R&D (and indeed the previous lackluster 12-month data in this very trial), than a ringing endorsement of this particular drug candidate. And Biogen reeled back from pre-presentation hints that the drug might be headed for a speedy FDA review on the basis of the Phase II results as skeptics raised their voices. Various factors cry out for caution and further analysis – including the numerical imbalance of carriers of the APOE4 genetic risk factor for Alzheimer's (far higher in the placebo group than in the highest treatment dose that showed most effect); the companies' adaptive trial design including a new Eisai-designed composite scale for measuring clinical outcomes in Alzheimer's; lack of clarity over the link between changing levels of amyloid plaque in the brain and clinical outcomes; and, more fundamentally, the fact that the trial has yet to be published and peer reviewed.

Meanwhile, second-quarter results season has been marked by changes at the top, with Gilead announcing the impending departure of CEO John Milligan and chair John Martin (p8), new R&D head Hal Barron dominating GSK's Q2 call (p1), Amgen announcing the retirement of R&D chief Sean Harper and commercial head Anthony Hooper and Bristol-Myers Squibb revealing that commercial head Murdo Gordon is to replace Hooper at Amgen (*see Scrip online for these latter two articles.*)

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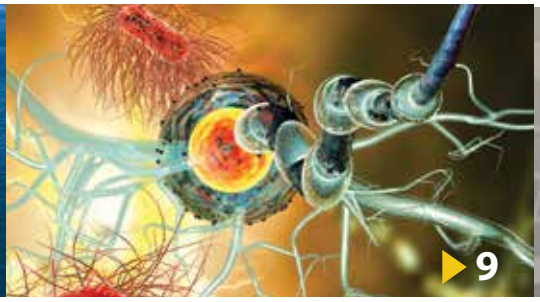
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exclusive online content

Hemlibra Effect Is Muted At Shire - For Now
https://bit.ly/2v2l13q
Hemlibra has taken a bite out of Shire's FEIBA sales, but compensatory boosts in other areas of the business helped CEO Ørnskov keep the business ticking over while awaiting the finalization of Takeda's takeover.

Buoyant Biotech Funding Environment Directly Impacts CRO Q2s
https://bit.ly/2vn9Lhq
The contract services industry is reaping the rewards of a resilient biotech funding environment, re-accelerating growth in the sector.

First-Line Chemo Combo Data Help Merck's Keytruda Power Past Opdivo
https://bit.ly/2ApgX2f
Keytruda sales are soaring on first-line lung cancer use, but with many new filings and approvals, Merck tells its second-quarter earnings call it's just the beginning.

Bristol Touts Opdivo's Stability – And Diversity – In Strong Q2
https://bit.ly/2v6YfXr
The recently launched Opdivo/Yervoy combination already has a leading position in first-line kidney cancer in the US – with a 30% share of new patients – but has been rejected in Europe.

Sanofi Top UK Exec Plans For Hard Brexit, Blasts 'Poor Access' To New Drugs
https://bit.ly/2KikHCC
The managing director for Sanofi in the UK says clinical trials there will become less likely in future if access to innovative drugs doesn't improve, causing comparative standards of care to deteriorate.

Harper, Hooper Exit As Amgen Revenues Rise
https://bit.ly/2O0qAGM
Amgen revealed better-than-expected second quarter earnings July 26 and said its R&D and commercial heads Sean Harper and Anthony Hooper are retiring. Harper, who's getting involved with start-ups, is being replaced from within by David Reese; Bristol's Murdo Gordon will take over for Hooper.

inside:

AstraZeneca's Oncology Business Delivers, Edging Toward CV/Metabolic As Top Contributor

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AstraZeneca PLC may soon be most recognized as an oncology company. The UK pharma's oncology portfolio is its dominant growth driver and will soon edge out the other two business units – cardiovascular/metabolic and respiratory – in terms of revenue contribution.

Powered by a notable 44% revenue growth in the second quarter, oncology sales outpaced respiratory sales and narrowed the gap significantly with CV/metabolic. Oncology generated $1.43bn in the quarter, representing 29% of AstraZeneca's revenues – a significant jump from 2017, when oncology accounted for 20% of revenues. Sales of respiratory products grew 12% to $1.23bn in the quarter, representing 24% of sales. Under pressure from generic competition to *Crestor* (rosuvastatin), CV/metabolic sales declined 9% to $1.62bn, or 32% of the company's sales.

SORIOT'S LONG GAME

Building AstraZeneca into a big oncology player has been CEO Pascal Soriot's ambition, though the company still has its work cut out for it when it comes to turning new cancer drugs like the PARP inhibitor *Lynparza* (olaparib), the PD-L1 blocker *Imfinzi* (durvalumab) and the BTK inhibitor *Calquence* (acalabrutinib) into blockbusters.

Nonetheless, Soriot took a moment to applaud AstraZeneca's turnaround initiative during the company's second quarter sales and earnings call July 26.

"The strategy we have been pursuing the last four or five years is starting to bear fruit," he said. "There is still a lot of hard work ahead of us, but the new products are starting to have an impact on our plan."

The company's consolidated revenues grew 2% to $5.16bn in the second quarter, and Soriot said he expected to see the momentum build in the second half of the year and that AstraZeneca is on track to reach its goal of returning to product sales growth in 2018. Core EPS declined 21%, however, but both sales and earnings were ahead of analyst consensus estimates.

"There is not just one product driving our growth," he said. "It is really an engine that is powered by multiple products."

Investors appear to be warming to AstraZeneca's story. The company's stock hit a 52-week high of $38.73 on the positive earnings news.

Deutsche Bank analyst Richard Parkes said the quarter was encouraging. "Overall solid results and good performance of the key drivers should reassure over the return to growth. AstraZeneca is our top EU pharma pick," he said.

BMO Capital Markets analyst Alex Arfaei said, "The strong ramp-up of launch products and effective management of mature products should allow AstraZeneca to meet its reaffirmed 2018 guidance."

CANCER SALES ADD UP

AstraZeneca Exec VP and Global Head-Oncology Business Unit Dave Frederickson talked to *Scrip* in June about the company's oncology growth drivers and expansion plans. (*Also see "AstraZeneca Looks To Deliver On Its Promises In Oncology" - Scrip, 26 Jun, 2018.*)

AstraZeneca's top-selling cancer drug is the third-generation EGFR inhibitor *Tagrisso* (osimertinib), which generated $422m in the second quarter, reflecting growth of 82%, driven by use in second-line non-small lung cancer in patients with T790M-mutations and a new indication that came in April in first-line EGFR-mutated lung cancer.

Lynparza generated $150m, though AstraZeneca shares profits on sales of Lynparza with **Merck & Co. Inc.** under a 2017 collaboration. Most of sales came from use in ovarian cancer, Fredrickson said, though Lynparza was recently approved in the US for treatment of patients with BRCA-mutated breast cancer. Lynparza has so far maintained commercial leadership in the PARP space.

The other drug investors are watching closely is the PD-L1 inhibitor Imfinizi, which remains well behind the PD-1 blockbusters like Merck's *Keytruda* (pembrolizumab) and **Bristol-Myers Squibb Co.**'s *Opdivo* (nivolumab). As the fifth to market PD-1/L1 inhibitor, Imfinzi generated $122m in the quarter, but it has a bit of a niche to focus on. Imfinzi is the only PD-1/L1 inhibitor approved for Stage III NSCLC in patients whose disease has not progressed on concurrent chemotherapy, though three other checkpoint inhibitors are approved for Stage IV NSCLC that has spread and which is more frequently diagnosed.

Outside of oncology, AstraZeneca is hoping the IL-5 inhibitor *Fasenra* (benralizumab) for eosinophilic asthma will be a big new respiratory growth driver. The drug generated $65m in the first quarter, after launching in late 2017. Severe asthma is a small subset of the broader asthma market, however, and **GlaxoSmithKline PLC**'s *Nucala* (reslizumab) has a head start. (*Also see "Severe Asthma Market Snapshot: A Competitive Therapy Area That Will Test Payers' Influence" - Scrip, 23 May, 2018.*) Nucala generated £141m in the second quarter.

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First-Line Chemo Combo Data Help Merck's Keytruda Power Past Opdivo

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Merck & Co. Inc. says that its *Keytruda* is now capturing two-thirds of new first and second-line lung cancer patients in the US – a 20% increase in share since April – helping the PD-1 inhibitor power past **Bristol-Myers Squibb Co.**'s competing *Opdivo* in the second quarter.

Merck reported second quarter sales on July 27, including $1.67bn in Keytruda (pembrolizumab) sales, whereas Bristol's competing PD-1 inhibitor Opdivo (nivolumab) had sales of $1.63bn in the same period.

In the US, about 60% to 65% of Keytruda sales derive from lung cancer, 15% from melanoma, 5% in bladder, 5% in microsatellite instability-high cancer, and the rest from all other indications, Adam Schechter, president of global human health at Merck, said during a same-day earnings call. Schechter didn't provide specific numbers ex-US, but said most of the revenue in Europe and Japan is coming from lung cancer, with melanoma as the clear second-largest contributor.

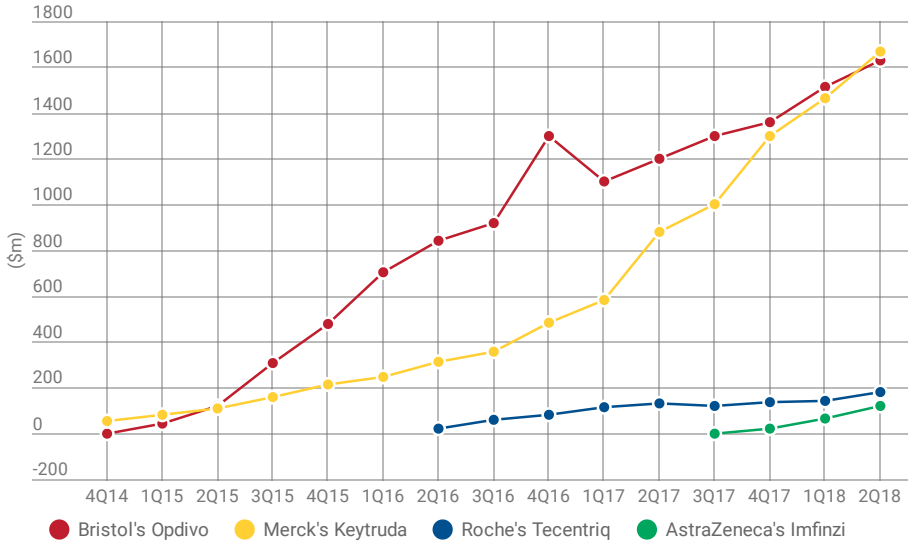
Keytruda was the first PD-1 inhibitor to step on the global stage, winning its first US FDA approval in relapsed metastatic melanoma in September 2014. Bristol's Opdivo was approved in December of that year for the same indication. Keytruda had a slight lead in sales at first, but by the third quarter the drugs were on the market Opdivo had caught up, and went on to win the first non-small cell lung cancer (NSCLC) approval and has by far dominated the PD-1/L1 landscape since (*see graph*).

Keytruda, however, has been catching up. (*Also see " Merck's Keytruda Keeps Nipping At Opdivo's Heels" - Scrip, 1 May, 2018.*) Data from the KEYNOTE-189 study showing that Keytruda with chemo has a survival benefit over chemo alone in first-line non-squamous NSCLC regardless of PD-L1 expression were presented at the American Association for Cancer Research (AACR) annual meeting in April with great fanfare. (*Also see "Merck's Keytruda Enjoys Clean Sweep In Lung Cancer, At Bristol's Expense" - Scrip, 17 Apr, 2018.*) Merck went on to present positive overall survival data for the Keytruda-chemo combination in squamous first-line NSCLC at the American Society of Clinical Oncology (ASCO) meeting in June. (*Also see "Roche, Bristol On The Defensive After Merck's Lung Cancer Wins At ASCO" - Scrip, 6 Jun, 2018.*) A filing for that use is under review with the FDA, with an Oct. 30 action date. (*Also see "Merck's Stellar Keytruda Squamous Lung Cancer Data Refute Naysayers" - Scrip, 23 May, 2018.*)

Lung cancer specialists at ASCO reaffirmed the importance of the gold standard of overall survival, and aside from Merck, none of the other PD-1/L1 sponsors have demonstrated a benefit for OS in first-line lung cancer to date.

Merck's Schechter told the earnings call that the Keytruda/chemo combo has been well received and that excluding patients with EGFR and ALK mutations, Keytruda is getting roughly two-thirds of new lung cancer patients. This includes Keytruda as a monotherapy and in combination with chemotherapy in first- and second-line indications, Merck clarified after the call. The two-thirds share of new patients represents about a 20-point increase in share versus what the company saw prior to the AACR meeting, Schechter said, adding that he expects continued substantial adoption in this indication throughout the rest of the year.

Sales Of PD-1/L1 Inhibitors



Keytruda is approved as a monotherapy for first-line lung cancer with PD-L1 expression over 50% and in combination with chemo for all comers in first-line NSCLC. No other PD-1/L1 inhibitors are yet approved for first-line metastatic NSCLC. Keytruda is also approved as a monotherapy in second-line metastatic NSCLC.

During its earnings call on July 26, Bristol said that it expects IO penetration in first-line lung cancer in the US will accelerate in 2018, reaching 70% to 75% by the end of the year, and that there will still be 25% to 30% on chemotherapy and eligible for a PD-L1 inhibitor in second-line NSCLC.

In addition to overtaking Opdivo, Keytruda is overshadowing other approved PD-1/L1 inhibitors that came to the market later. **Roche** reported CHF320m ($321m) in sales for the PD-L1 inhibitor *Tecentriq* (atezolizumab) for the first half of this year. **AstraZeneca PLC** reported $122m for *Imfinzi* (durvalumab), also a PD-L1 inhibitor, in the second quarter. **Pfizer Inc.** and partner **Merck KGAA** have not reported second quarter earnings yet for their PD-L1 inhibitor *Bavencio* (avelumab), first approved for the rare skin cancer Merkel cell carcinoma in March 2017 and soon after also cleared for bladder cancer, so it is not clear whether it has gotten off the ground yet. (*Also see "Pfizer's Avelumab Makes Its Debut, In Rare Form Of Skin Cancer" - Scrip, 23 Mar, 2017.*)

Merck was asked during its call about its strategy in pursuing approval for Keytruda in Stage III lung cancer, in light of AstraZeneca's success as the first PD-1/L1 inhibitor cleared in that segment. (*Also see "AstraZeneca's Imfinzi Scores First Early Lung Cancer Approval" - , 16 Feb, 2018.*) Merck Research Laboratories President Roger Perlmutter noted that Merck has some data for Keytruda in non-metastatic lung cancer and the company expects that there "will be additional data that will come forward in the months and years ahead that will permit a specific indication," but he declined to comment on regulatory strategy.

KEYTRUDA FOUNDATION FOR MULTI INDICATIONS

Like Bristol in its second-quarter earnings report, Merck stressed Keytruda's breadth, which it noted is now FDA approved in 12 indications across eight tumor types and similarly approved in multiple indications across tumor types in countries around the world. Merck announced approval on July 26 for Keytruda in second-line metastatic melanoma in China. Bristol's Opdivo was approved for second-line NSCLC with no EGFR or ALK mutations in China in June. *(Also see "Opdivo Approval Opens China I-O Doors But Pricing Key" - Scrip, 18 Jun, 2018.)*

Supplemental biologic license applications (sBLAs) are now under FDA review for Keytruda in advanced hepatocellular carcinoma and adjuvant melanoma, with user fee dates of Nov. 9 and Feb. 16, respectively.

Positive Phase II data were reported for small cell lung cancer in the KEYNOTE-158 study at this year's ASCO meeting.

The company also reported positive results on July 25 from an interim analysis for Keytruda as a monotherapy in patients with PD-L1 expression in the pivotal Phase III KEYNOTE-048 study of first-line or metastatic squamous cell carcinoma of the head and neck (SCCHN or HNSCC). The study compared Keytruda monotherapy or Keytruda with platinum-based chemotherapy and the 5-FU regimen against **Eli Lilly & Co.**'s *Erbitux* (cetuximab) with the same backbone chemo regimen. Keytruda monotherapy was associated with longer overall survival compared with the cetuximab and the chemo backbone. However, it has not yet demonstrated a significant improvement for progression-free survival, the co-primary endpoint, but the study continues. Merck said the results will be submitted to regulatory authorities worldwide and presented at n upcoming medical meeting.

MERCK'S Q2 KEY PRODUCT REVENUES

Drug	Actual sales vs. Consensus Expectation
Keytruda (pembrolizumab)	$1.67bn (Cons: $1.64bn)
Zepatier (elbasvir/grazoprevir)	$113m (Cons: $117m)
Januvia/Janumet (sitagliptin)	$1.53bn (ConsL $1.5bn%)
Zetia (ezetimibe)	$381m (Cons: $247m)
Vytorin (simvastatin)	$155m (Cons: $158m)
Remicade (infliximab)	$157m (Cons: $153m)
Gardasil (human papillomavirus 9-valent vaccine, recombinant)	$603m (Cons: $603)
Isentress (raltegravir)	$305m (Cons: $261m)
Nasonex (mometasone furorate)	$81m (Cons: $71m)
Singulair (Montelukast sodium)	$185m (Cons: $178m)
Cozaar/Hyzaar (losartan potassium)	$125m (Cons: $116m)
Zostavax (Zoster vaccine)	$44m (Cons: $71m)
Cubicin (daptomycin)	$94m (Cons: $1.06bn)
Animal Health	$1.09bn (Cons: $1.06bn)

Source: I. Hilliker, Jefferies

Keytruda received accelerated approval for treatment of recurrent or metastatic HNSCC with disease progression on or after platinum-containing chemotherapy in August 2016. However, in July 2017, Merck announced that the drug failed to show a survival benefit over investigator's choice of chemotherapy in the KEYNOTE-040 study of recurrent or metastatic disease. (*Also see "Merck's Keytruda Gets Benefit Of Doubt, Despite Failing in Head & Neck" - Scrip, 24 Jul, 2017.*)

Perlmutter said that numerous approvals and filings are "really just the beginning of what will be a very robust period of evaluation for Keytruda in both combination therapy and monotherapy settings."

More than 100 abstracts related to Keytruda were presented at the ASCO meeting, the exec noted. "Many of these represented progress reports that we expect will yield data supportive of registration in the not too distant future, including for the treatment of small-cell lung cancer and renal cell carcinoma," he said.

And in the future, the company expects data supporting use in breast and prostate cancers, he said. Pathological complete response results for Keytruda as a neoadjuvant therapy in I-SPY trials of early breast cancer were very impressive, he pointed out. (*Also see "Merck's Keytruda Offers Hope And Risk In Early Breast Cancer" - Scrip, 6 Jun, 2017.*) Keytruda is being studied for neoadjuvant and adjuvant use in the Phase III KEYNOTE-522 study of triple-negative breast cancer. Perlmutter said that going forward, he is very enthusiastic about where that could lead.

Schechter added that the company is excited to get into this market and already is calling on those physicians through its partnership with AstraZeneca on the PARP inhibitor *Lynparza* (olaparib), which

recently was approved for BRCA-mutated metastatic breast cancer. (*Also see "Lynparza Gets First Mover Advantage In BRCA-Positive Breast Cancer" - Scrip, 15 Jan, 2018.*)

"So we are ready to launch with Keytruda as soon as the data would be available and the indication available," Schechter said.

A GOOD QUARTER FOR MERCK

Keytruda's success came with the backdrop of a good quarter. Overall the company reported worldwide sales of $10.5bn in the second quarter, up 1% year-over-year and beating consensus of $10.3bn. Merck narrowed its full-year revenue range to between $42bn and $42.8bn.

"Expectations were high coming into the quarter, but we think these results should still be well received and allow for continued confidence in the story and upside in the stock as we move into 2H18, when we should see additional upside as the Keytruda rollout into first-line lung cancer continues," Credit Suisse analyst Vamil Divan said in a July 27 note.

Sales of Keytruda and most of the company's other key drugs were above consensus, helping offset the few misses for *Zostavax* (Zoster vaccine), which had sales of $44m versus consensus of $71m, and the cholesterol drug *Zetia* (ezetimibe) with $226m versus consensus of $247m, Jefferies analyst Ian Hilliker said in a July 27 note (*see table*).

Still, concerns remain about whether Merck is too dependent on Keytruda. During the call, Credit Suisse's Divan asked what is holding the company back from more aggressive deal-making and business development.

CEO Kenneth Frazier said Merck is "actively looking for the best opportunities across all kinds of structures, including acquisitions and partnerships, collaborations and licensing." Over the past few years, some deals didn't pan out, either because the target was not a willing seller or because competition for that asset made the price untenable based on Merck's assumptions, the exec said.

There also generally has been a dearth of M&A across the industry recently as significant investment has flowed into small biotechs, reducing their need to sell right now in order to fund development programs.

"But I want to assure you that augmenting our pipeline through business development, nevertheless, remains an important priority, and so we'll continue to scour the landscape carefully," Frazier said.

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CONTINUED FROM COVER

"Sometimes we may have taken molecules and pushed them towards a disease because of where they were therapeutically discovered," he explained. "Had we had a disease-agnostic approach, even further complimented by human genetics, that might not have been the first indication."

Barron did come to the meeting with one tangible piece of news for investors, a collaboration with the genetics leader **23andMe Inc.** focused on using genetic data to develop new medicines. GSK made a $300m equity investment in exchange for a four-year collaboration to work with 23andme exclusively for drug target discovery programs.

RESTRUCTURING TO SUPPORT MORE R&D INVESTMENT

GSK also unveiled a strategy for investing more in R&D. The company unveiled a new restructuring program focused on improving supply chain and reducing administrative costs. The program is expected to yield annual savings of around £400m by 2021, savings that will be redirected to R&D investment and commercial support for new launches. The program is expected to cost £1.7bn until 2021.

Walmsley declined to say by how much GSK would increase R&D investment directly, however. The company spent £4.48bn on R&D, or 14.8% of revenue, in 2017, 19% higher than the investment in 2016.

The company has 40 new molecular entities in the clinical pipeline, with late-stage opportunities including two treatments for HIV, dolutegravir/lamivudine and carboteravir/ripilvirine, and the company's most advanced oncology treatment, a potential first-in-class, anti-BCMA antibody-drug conjugate in pivotal trials for multiple myeloma.

Certainly, Barron made it clear he doesn't believe more is better. He quoted former Apple CEO Steve Jobs as saying, "Innovation is saying no to thousands of things." Barron added, "This is the kind of culture that I would love to have at GSK R&D." Programs should be swiftly killed after Phase II if they don't show an effect, he said, but also noted Phase II studies need to be appropriately powered to yield a strong signal.

Barron did highlight a few promising programs in addition to BCMA, which has shown notable efficacy in heavily pre-treated multiple myeloma patients and has been prioritized for development. He also talked about potential in cell therapy through GSK's collaboration with **Adaptimmune Therapeutics PLC** and noted, "We think we can do this better than maybe anyone."

He pointed to GSK '794, a TCR T-cell therapy targeting the NY-ESO peptide that is in development for sarcoma but could have broader utility in other solid tumors. GSK has five targets it is exploring under the program with Adaptimmune. The company's early oncology portfolio also includes an ICOS agonist, a OXO40 inhibitor, a potential first-in-class PRMT5 inhibitor and a BET inhibitor.

As Barron put it, "Any of the cancer things can go from not-so-wow to wow pretty quickly."

The R&D overview overshadowed an encouraging second quarter financial performance, in which consolidated revenue increased 4% to £7.3bn, pharma sales increased 1% to £4.2bn and vaccines increased 16% to £1.3bn. Vaccine sales benefited from the launch of the shingles vaccine *Shingrix,* which GSK is now expected to deliver sales of £600m-£650m in 2018, its first full year on the market.

The strong launch of Shingrix and a delay in the launch of a substitutable generic version of GSK's big asthma drug *Advair* led the company to raise its financial expectations to the year. The company expects adjusted EPS to grow 7%-10% in 2018 as long as a substitutable generic continues to be delayed. If one launches by Oct. 1, that growth would be more like 4%-7%. **Mylan NV** received a complete response letter from the FDA for its generic version of Advair in June. (*Also see "Branded Advair Breathes Another Day; Mylan Says A CRL Is On The Way For A Generic" - Scrip, 13 Jun, 2018.*)

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Milligan's Retirement Means New CEO For New Gilead

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While **Gilead Sciences Inc.** posted solid financials during the second quarter, the surprise announcement that President and CEO John Milligan is stepping down at the end of 2018 shifted focus from the company's past performance to its path forward.

Chairman John Martin also announced during Gilead's July 25 second quarter earnings investor call that he will step down from his role at Gilead when Milligan's successor takes over. Milligan succeeded Martin in the CEO role in early 2016; both have been with Gilead since 1990.

In that time, the company has grown into a dominant force in antivirals, both for HIV and hepatitis C, and demonstrated excellence in building portfolios and pursuing lifecycle management in competitive fields.

As the HCV market and HIV portfolio have matured, there has been significant pressure for Gilead to diversify. and It's biggest step in a new direction came with the $11.9bn acquisition last August of **Kite Pharma Inc.**, just before the approval of its chimeric antigen receptor T-cell (CAR-T) therapy *Yescarta* (axicabtagene ciloleucel). (*Also see "What's Gilead Getting From Kite For Nearly $12bn?" - Scrip, 29 Aug, 2017.*)

But now, delivering on that strategic shift will be the new CEO's challenge.

Gilead has had a meteoric rise on the backs of the hepatitis C direct-acting antivirals, with total sales for that business estimated to surpass $111bn. Milligan took over from Martin in late January 2016, around the time that Merck's competing HCV combination *Zepatier* (elbasvir/grazoprevir) came to market at a deep discount compared to Gilead's dominant HCV franchise headed by *Harvoni* (sofosbuvir/ledipasvir) and *Sovaldi* (sofosbuvir).

The decline in Gilead's HCV fortunes continued through 2016, leading to a February 2017 decision in which Gilead split sales guidance for HCV from the rest of its portfolio and offered clear projections of a sustained downturn for the HCV franchise. Milligan oversaw a rumor-heavy period where Gilead was the center of consistent M&A speculation as analysts and investors


John Milligan

believed the company needed a new therapeutic direction to restore growth. (*Also see "Gilead Cites 'More Sophisticated' Process As Pressure For A Major Deal Increases" - Scrip, 20 Mar, 2017.*)

Gilead has followed up on the Kite acquisition with similar immuno-oncology deals around cell therapy platforms, including transactions involving **Cell Design Labs Inc.**, **Sangamo Therapeutics Inc.** and **Gadeta BV**.

- *Also see "Gilead Acquisition Of Cell Design: The Next Logical Step" - Scrip, 8 Dec, 2017.*
- *Also see "Gilead Partners With Sangamo For Gene Editing As It Builds Up Kite's Cell Therapy Platform" - Scrip, 22 Feb, 2018.*
- *Also see "Deal Watch: Gilead Continues To Add To IO Armamentarium In Collaboration With Gadeta" - Scrip, 20 Jul, 2018.*

"Now that the company is on solid footing for the future, the board and I have agreed it is a good time to turn the reigns over to a new leader," Milligan told the July 25 earnings call. He added that he thinks Gilead will move forward from a position of "tremendous strength" with a growing HIV franchise and an "industry-leading cell therapy program," plus its late-stage pipeline assets in inflammation and non-alcoholic steatohepatitis (NASH). He noted there also are resources to continue investing in the pipeline.

Milligan will stay in his current role while the board conducts a CEO search.

As for the qualities the industry should expect in his successor, Milligan listed areas of expertise that he said are not his strengths: "I think the next leader should be somebody who brings expertise – scientific, commercial or other – into new opportunities for us to grow, for example, people who have launched products into new markets such as we're doing [in] NASH or people who really know how to compete in the oncology area where I have less experience," he said. "I think we are looking for a new leader who will bring new ideas, a previous history and experiences we don't have, and one who will take the baton from me and move it forward."

In a same-day note, Jefferies analyst Michael Yee questioned whether a "New Gilead" is coming. He said the move seemed driven by the board of directors "to invigorate the company and to bring on fresh leadership to turn Gilead from pharma-like to more biotech-like."

The transition likely brings short-term uncertainty for investors, especially until the new CEO is named, Yee added. "We think the good news is a 'new' future will hopefully lead to more pipeline, more bold steps, more aggressive [business development] and a chance for [profit and earnings] expansion and stock appreciation," he wrote.

Gilead gave a promising pipeline update for one of the bolder moves it has made, with the NASH candidate selonsertib. The company expects Phase III data in the first half of 2019 and possible regulatory filings in mid-2019, which means Gilead could claim first place in the race to bring a NASH drug to market.

Quarterly sales were largely as expected, with Yescarta continuing its growth trajectory, solid growth for the HIV franchise and a plateau in the hepatitis C business, which has been in decline. (*Also see "As Gilead Seeks New CEO, Second Quarter Shows Stability" - Scrip, 25 Jul, 2018.*)

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Biogen, Eisai Report BAN2401 Seemingly Positive In Alzheimer's; Others Skeptical

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Biogen Inc. and **Eisai Co. Ltd.** reported that the highest dose of BAN2401 significantly cleared amyloid from the brain and improved cognition in patients with mild Alzheimer's disease, but questions remain about the exclusion of certain individuals from the high dose arm and whether that confounded the results from the large Phase II trial.

Reflecting some investor uncertainties over the data, Biogen's stock declined by more than 11% in after-hours trading after Eisai Chief Medical Officer Lynn Kramer reported the much-anticipated detailed results at 18 months from the 856-patient Study 201, presented on July 25 as a late-breaking oral presentation at the Alzheimer's Association International Conference (AAIC) in Chicago.

In Tokyo, Eisai's share price also was strongly down in mid-afternoon trading, falling by a similar percentage as investors digested the new data.

Results for the amyloid-beta protofibril-targeting antibody were largely in line with expectations following the top-line data released recently, which generated huge interest in the Alzheimer's community and around the validity of the amyloid hypotheses, which is that accumulations of the protein contribute to the development of the disease.

One exception was the new disclosure that patients who carried the APOE4 gene – associated with early onset of Alzheimer's disease and rapid decline – were excluded from the high-dose BAN2401 group at the request of ex-US regulators.

DEBATE OVER APOE4 ROLE

APOE4 carriers tend to experience amyloid-related imaging abnormalities (ARIA) at higher rates than non-carriers, which was the case in the BAN2401 study. However, there was some debate during Biogen's same-day call with analysts and investors about whether APOE4 carriers have a worse response to treatment.

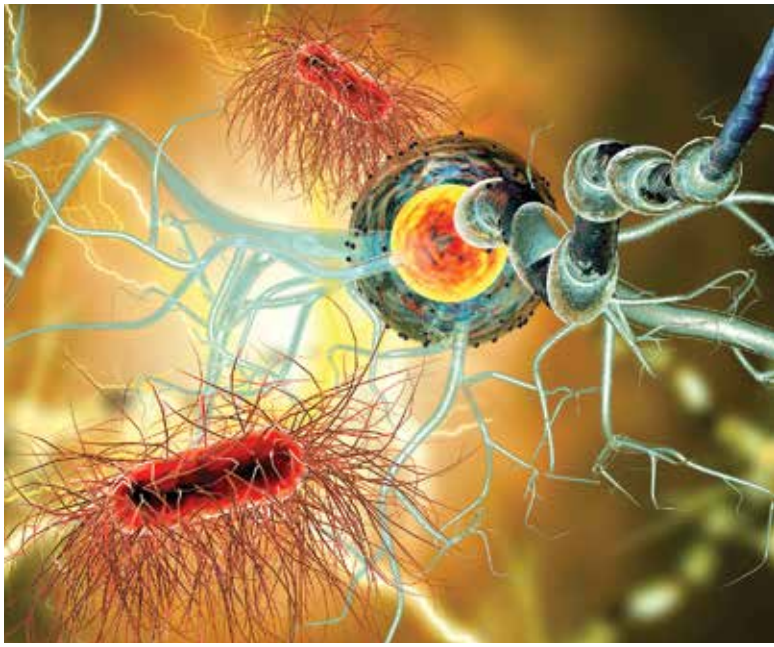
If so, the higher dose of BAN2401 would perform better than placebo and the lower doses, because that arm of the trial had fewer APOE4 carriers.

Biogen Vice President of Clinical Development Samantha Budd Haeberlein argued during the company's call that APOE4 status has an impact on the age of Alzheimer's disease onset, but not on the efficacy of treatment.

Haeberlein noted that amyloid was cleared from patients' brains in a dose-dependent manner, according to PET scans, which would lead her to believe that APOE4 status did not play a role in BAN2401's effect on cognitive decline.

Biogen Executive Vice President and Chief Medical Officer Alfred Sandrock added that the APOE4 carrier versus non-carrier subgroup analysis probably will be the first subgroup analysis that Biogen and Eisai will conduct, and those data would be shared as soon as possible.

The second subgroup analysis, he said later in the call, probably will look at prodromal (pre-symptomatic) patients versus those with mild cognitive impairment.



Analysts seemed to agree that the APOE4 carrier versus non-carrier analysis is most important and that no conclusions can be drawn about the BAN2401 data until that is done.

Analysts seemed to agree that the APOE4 carrier versus non-carrier analysis is most important and that no conclusions can be drawn about the BAN2401 data until that is done.

Evercore ISI analyst Umer Raffat looked at other studies to see if APOE4 status impacted drug efficacy and had mixed findings, but he said the BAN2401 effect on cognition may be large enough that even with APOE4 patients in the mix the results could still be significant.

AMYLOID CLEARING'S LINK TO COGNITIVE BENEFITS DEPENDS ON ANALYSIS

Biogen and Eisai reported earlier in July in the top-line results that BAN2401 at its highest dose provided statistically significant reductions in amyloid plaques and slowed the rate of cognitive decline in the large Phase II trial, which enrolled patients with mild cognitive impairment (MCI) due to Alzheimer's disease or mild Alzheimer's with confirmed amyloid pathology in the brain.

BAN2401, which targets amyloid beta protofibrils by selectively

binding to and neutralizing soluble, toxic amyloid beta aggregates, was originated by Swedish bioventure BioArctic and acquired globally by Eisai in late 2007, then brought under the 2014 multi-asset Alzheimer's drug development partnership with Biogen.

Eisai's strategic alliance with Biogen in Alzheimer's dates back to 2014. As well as BAN2401 and the beta amyloid-targeting antibody aducanumab, this includes the Eisai BACE (beta-site amyloid precursor protein) inhibitor elenbecestat and a Biogen anti-tau antibody.

The firms will co-promote any marketed drugs under the alliance in major markets, and for BAN2401 (and elenbecestat), they are equally splitting overall costs including R&D expenses, with Eisai to book sales for both drugs and profits to be shared equally.

Biogen suggested on July 24, the day before the AAIC presentation, that the company and its partner may be able to pursue accelerated approval in the US based on the Phase II results, but noted such a decision depends on future discussions with the FDA. (*Also see "Enthusiasm Builds For Biogen's BAN2401 In Alzheimer's, But SMA Gene Therapy Hits A Snag" - Scrip, 24 Jul, 2018.*)

> The data presented on July 25 don't make the possibility of approval ahead of Phase III data any clearer given the APOE4-related concerns.

The data presented on July 25 don't make the possibility of approval ahead of Phase III data any clearer given the APOE4-related concerns. Some analysts have already said that a further large randomized Phase III study with a pre-specified endpoint appears necessary, but this has yet to be confirmed by Eisai or Biogen.

Patients were treated with 2.5 mg/kg of BAN 2401 every two weeks, 5 mg/kg once-monthly, 5 mg/kg bi-weekly, 10 mg/kg monthly, 10 mg/kg bi-weekly or placebo. A Bayesian adaptive randomization trial design meant that patients could be randomized into treatment arms with a higher likelihood of efficacy after interim assessments of the data.

That meant that there were 247 patients in the placebo arm, 52 in the 2.5 mg/kg bi-weekly arm, 51 in the 5 mg/kg monthly arm, 92 treated with 5 mg/kg bi-weekly, 253 in the 10 mg/kg monthly arm and 161 in the 10 mg/kg bi-weekly arm.

The primary endpoint was a Bayesian assessment at 12 months of the likelihood of success in terms of the Alzheimer's Disease Composite Score (ADCOMS), which was not statistically significant at any dose. An 80% chance of providing a 25% slowing in ADCOMS was needed, but the highest dose of BAN2401 achieved only a 64% likelihood of meeting the 25% threshold.

However, at the 18 month stage, Biogen and Eisai reported at AAIC that the reduction of accumulated amyloid plaques in the brain was statistically significant at all doses. These were measured using standardized PET (positron emission tomography), and scans of patients treated with the highest dose of BAN2401 (10 mg/kg bi-weekly) and assessed by the Centiloid scale showed an observed mean reduction from 74.5 at baseline to 5.5 at 18 months (no p-value was reported).

A Mixed Effects Model with Repeated Measures (MMRM) assessment showed a mean reduction in amyloid load of 70 units ($p<0.0001$). PET scans also showed that 81% of patients treated with the highest BAN2401 dose converted from amyloid positive to amyloid negative at 18 months, which reached significance with a p value of <0.0001.

In addition, an analysis against predefined clinical endpoints at 18 months confirmed a slowing in cognitive decline from baseline based on ADCOMS, which was dose-dependent. At the highest dose this was 30% versus placebo ($p=0.034$), but a statistically significant slowing of decline was seen on ADCOMS as early as six months ($p<0.05$), and at 12 months ($p<0.05$).

Bayesian analysis of ADCOMS at 12 months gave an estimated probability that the highest dose slowed clinical decline more than placebo of 98%.

COGNITION EFFECTS MIXED

Biogen noted in its call that that, given BAN2401's mode of action, there is a "complex relationship between plasma exposures and what's going on in the brain – Cmax is important to achieve."

But in terms of effect on cognition, Biogen and Eisai reported dose-dependent effects via two out of three secondary endpoints. The highest BAN2401 dose showed a 30% slowing in clinical decline as assessed by ADCOMS compared with placebo at 18 months ($p=0.034$), and statistically significant slowing also was observed at six months ($p<0.05$) and 12 months ($p<0.05$).

Also, the highest BAN2401 dose slowed clinical decline by 47% compared to placebo at 18 months, according to the Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-Cog; $p=0.017$).

However, the slowing in cognitive decline from baseline as assessed by Clinical Dementia Rating Sum of Boxes (CDR-SB) was not statistically significant, though the companies said there was a dose-dependent slowing in cognitive decline from baseline, in excess of the pre-specified difference of 25% over the course of the study, and reaching 26% at 18 months for the highest dose versus placebo (the decline in the latter being in line with earlier research).

Dose-dependent increases in amyloid-beta levels were observed in cerebrospinal fluid ($p<0.0001$ at the highest dose at 18 months), and there was a statistically significant reduction in total tau levels against placebo in both of the 10mg/kg dose regimens ($p<0.05$).

ARIA, INFUSION REACTIONS MOST COMMON ADVERSE EVENTS

Biogen and Eisai said their drug "demonstrated an acceptable tolerability profile through 18 months of study drug administration." The treatment-related adverse event rate was 26.5% for the placebo arm, 53.4% for the 10 mg/kg monthly treatment arm and 47.2% for the 10 mg/kg bi-weekly treatment arm.

Serious adverse event rates were 17.6% for the placebo arm, 12.3% for the 10 mg/kg monthly arm and 15.5% for the 10 mg/kg bi-weekly arm.

ARIA and infusion-related reactions were the most common treatment-related adverse events, and there was a 9.9% rate of ARIA with edema (ARIA-E) at the highest BAN2401 dose, but ARIA-E did not occur in more than 10% of patients in any of the treatment arms.

However, the rate of ARIA-E in APOE4 carriers was 14.6% at the highest dose; all patients with MRI-confirmed ARIA-E were discontin-

ued from the study. Concerns around safety related to ARIA meant that regulators wanted to limit number of patients in the high-dose group who were carriers.

APOE4 STATUS MAY OR MAY NOT BE AN EFFICACY PREDICTOR

"Confounding the data, the proportion of subjects in the 10mg/kg [bi-weekly] arm that were APOE4+ was substantially lower than the placebo arm and other dose groups, which may have impacted the baseline rates of cognitive decline between the various arms and contributed to the appearance of benefit compared to placebo," Leerink analyst Geoffrey Porges wrote in a July 25 note.

The percentage of patients who carried the APOE4 gene was just 30% in the highest dose arm and 70% to 91% in all other arms in the Phase II study.

"The reason behind this difference in patient enrollment was due to a request from health authorities outside of the US that APOE4+ subjects be removed from the highest dose arm and randomized solely to the other lower doses of BAN2401 or placebo," Porges said.

Haeberlein said during Biogen's call that data to date for the alliance's Phase III study with aducanumab had not shown a connection between APOE4 status and treatment efficacy.

Evercore ISI's Raffat noted that aducanumab results show that APOE4 carriers may do slightly worse on amyloid-reducing therapy than non-carriers, but the difference in cognitive decline may not be enough to make an anti-amyloid drug ineffective.

The analyst also looked at data from a 1,901-patient Phase III study for Merck's BACE inhibitor verubecestat, which appeared to show that non-carriers had worse efficacy than APOE4 carriers.

The forthcoming analysis of APOE4 carriers versus non-carriers may or may not settle the debate related to BAN2401, however, without a large Phase III dataset.

"Is APOE4 confounding results? We'll find that out soon," Biogen's Sandrock said.

AMYLOID DOUBTS REMAIN REGARDLESS OF APOE4 SUBANALYSIS

Datamonitor Healthcare analyst Zara Fulton told *Scrip* that the BAN2401 data were unconvincing in terms of the amyloid hypothesis without Phase III results showing that reducing amyloid plaques in the brain will result in a slowing of Alzheimer's disease progression.

The amyloid hypothesis has yet to be proven in a Phase III trial, despite many efforts, but Biogen and Eisai remain confident in this approach via BAN2401, the Phase III BACE inhibitor elenbecestat for which Phase II results were presented at AAIC, the anti-amyloid agent aducanumab with Phase III results expected in 2020 and other programs.

"I find these Phase II [BAN2401] data unconvincing as patients on lower doses did numerically worse than those on placebo, and only the highest dose, tested in 161 patients, met the primary endpoint. Unfortunately, promising Phase II data often do not play out in Phase III trials," Fulton said.

"I understand why Biogen/Eisai would want to race for FDA approval based on these results as replicating the statistically significant benefit for the highest tested dose in a large Phase III trial is far from a sure bet," she continued.

"The companies are likely banking on the FDA being swayed by the extremely high unmet need in AD, acute public awareness and lack of disease-modifying therapies."

Biogen's CMO Sandrock stood by BAN2401 as proof of the amyloid hypothesis, however, noting that it's important to attack "more aggregated forms [of amyloid plaques] with the right antibody and the right approach."

He noted that the very next step would be to have discussions with regulators, because there is a "range of possibilities here" on how to proceed. "Colleagues at Eisai are talking about additional trials," he added.

Leerink's Porges wrote that BAN2401 largely lived up to expectations, but more data are needed to confirm efficacy observed to date.

"The results presented today have exceeded the Street's expectations on ADCOMS, but do not provide confirmatory evidence that BAN2401 had a meaningful benefit on standard cognitive measures due to the differences in baseline patient characteristics across the arms," the analyst wrote.

"We do believe the data today is supportive of the amyloid hypothesis, but continue to believe that aducanumab remains Biogen's most valuable asset in this indication."

With contributions from Ian Haydock in Tokyo.

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UCB Looks To Its Next Wave Of Innovative Products

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The sales growth of **UCB Group**'s five core products is allowing the Brussels, Belgium-based company to invest and prepare for the launch of its next wave of new products, and to support the early clinical-stage development of potential therapies which include an anti-tau antibody, UCB0107, and a potential myasthenia gravis therapy, rozanolixizumab.

However, work on one clinical-stage candidate, the potential Sjogren's syndrome therapy, seletalisib, has been halted internally because of the need to prioritize other agents, the company said during its 2018 half-year results briefing on July 26. Seletalisib has produced positive results in early-stage clinical studies in Sjogren's syndrome and activated PI3K delta syndrome, and no new safety signals were observed, UCB noted.

We are "pleased with the maturation of the pipeline, with two products, romosozumab and midazolam nasal spray (for acute repetitive seizures) in the final phases of development, bimekizumab progressing well in Phase III in three different indications, and two products in Phase II (padsevonil and rozanolixizumab)," reported UCB CEO Jean-Christophe Tellier.

Bernstein analysts concurred. "The second half will be weaker but the pipeline is progressing nicely," they commented. In addition to its pipeline, UCB has been strengthening its business development and deal making activities.

REDUCING TAU SPREAD

UCB0107 has been designed to block the spreading of "tau seeds" from dying neurones, a UCB executive noted. These small aggregates of tau infect other neurones and induce the formation of tau oligomers and neurofibrillary tangles. UCB0107 has been specifically developed to prevent the spread of tau seeds from human material, and this second-generation anti-tau antibody was reported to be progressing well in Phase I studies; it has potential for the treatment of progressive supranuclear palsy and Alzheimer's disease, delaying or stopping their progression, the company said.

Another early-stage clinical compound is the anti-FcRn antibody, rozanolixizumab, which has produced positive results in a Phase IIb proof-of-concept study for the treatment of IgG auto-antibody-mediated disease. Subcutanous rozanolixizumab has potential in the treatment of myasthenia gravis (MG), immune thrombocytopenia (IP) and chronic inflammatory demyelinating polyneuropathy (CIDP), and results in MG and IP are expected during the second half of 2018. A registration study in the first of these conditions could start in the first quarter of 2019.

Novel products closest to the market include the potential osteoporosis therapy *Evenity*, which was resubmitted in the US by UCB and its partner Amgen for use in postmenopausal women at high risk of fracture.

A further compound, dapirolizumab pegol, is in Phase II studies for systemic lupus erythematosus, with Phase IIb results expected in the fourth quarter of 2018. Phase IIb results are expected in the first half of 2020 for padsevonil in the treatment of highly drug-resistant epilepsy.

NEW PRODUCT WAVE

Novel products closest to the market include the potential osteoporosis therapy, *Evenity* (romosozumab), which was resubmitted for US approval earlier this month by UCB and its partner **Amgen Inc.** for use in postmenopausal women at high risk of fracture.

Phase III studies of bimekizumab in moderate to severe psoriasis were started during the first half of 2018, with two of those involving active comparators, ustekinumab and adalimumab, with results expected by the end of 2019. A Phase IIIb study comparing bimekizumab with secukinumab was started in June.

And Phase III studies of bimekizumab for psoriatic arthritis and ankylosing spondyloarthrosis are expected to start in the fourth quarter of 2018.

In the first half of 2018, UCB recorded revenues of €2.27bn (+2%, or +6% at constant exchange rates (CER)), driven by *Cimzia* (certolizumab pegol), *Vimpat* (lacosamide), *Keppra* (levetiracetam), *Briviact* (brivaracetam) and *Neupro* (rotigotine), which had combined net sales of €1.8bn (+3%, or +12% at CER) in the 2018 first half. UCB's profits totaled €551m (+28%) in the half.

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Chugai Explores New Tech In Strategic Push For Innovation

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Chugai Pharmaceutical Co. Ltd. is taking steps to explore new potentially disruptive technologies and strengthen its R&D infrastructure in a strategic pursuit of innovation, as it seeks to think more broadly about the products and services it could potentially provide beyond pharmaceuticals.

The Japanese firm, majority owned by Swiss parent **Roche**, is building out its antibody discovery activities in Singapore, investigating potential applications of artificial intelligence, and expanding early-stage production process capabilities as part of the moves.

New CEO Tatsuro Kosaka told *Scrip* in an interview earlier this year that Chugai was planning in general to think much more about "around the pill" and "beyond the pill" in areas such as genomic medicine, given his prediction that "destructive technologies will greatly change our society."

SINGAPORE ANTIBODY EXPANSION

In the first of the new moves, all unveiled at the time of its second quarter results, the company will expand its Chugai Pharmabody Research subsidiary in Singapore, established in 2012 to focus on the discovery of novel targeted antibody drugs and related proprietary engineering technology.

Guaranteed funding for the facility has been extended for a further five years, with Chugai to invest a total of SGD282m ($207m) over the 2022-26 period.

Located in the major Biopolis biocluster, the life of the wholly owned subsidiary - chaired by renowned UK cancer researcher Sir David Lane - had already been extended for five years from 2016 and then again for the same period, with total investment now set to reach SGD476m in the 2012-21 timeframe.

Chugai Pharmabody will work with the company's Kamakura and Fuji Gotemba research sites in Japan to develop its expertise, and expects its workforce to reach around 125 by 2026.

The site has already contributed to the development of several novel pipeline antibodies, including SKY 59 (RG6107) and ERY974. The former, an anti-C5 recycling antibody licensed to Roche, is now in a Phase I/II multinational study for paroxysmal nocturnal hemoglobinuria.

ERY974, in Phase I for solid tumors, is a bispecific antibody targeting Glypican-3/CD3.

Although Chugai did not mention any such support, Singapore's Economic Development Board typically provides a range of attractive incentives to invest in and conduct life science research in the city state, such as administrative and facilities support and possible tax measures.

TECH-DRIVEN DRUG DISCOVERY

Separately, Chugai has invested JPY700m ($6.3m) in a third-party allocation of shares in Preferred Networks (PFN), as part of a new partnership agreement with the Tokyo-based technology company.

The companies will look jointly at new technologies such as Internet of Things (IoT, referring to a network of connected devices) and artificial intelligence (AI), and how they may be applied to the large amounts of data generated in the life science/pharma, including in both the clinical/non-clinical fields and information from devices.

PFN was founded in 2014 to focus on novel technology applications in areas including biotech/healthcare, transportation, and manufacturing, and has developed an open source, deep learning framework, Chainer, and related distributed ("edge-heavy") data processing methods.

The hope under the Chugai tie-up is to apply data analysis technologies in the R&D and value chain across discovery, development and manufacturing, to generate new insights and value, improve innovation and productivity, and better meet medical needs.

Chugai's Foundation Medicine Inc. unit, which is now being set up as an independent division, this March filed for the approval in Japan of a broad genomic profiling assay for solid tumors, as part of the company's push into Personalized Healthcare. An expedited review of the product was granted in May.

In the last of the newly announced moves to support innovation, Chugai is to construct a JPY4.5bn, 4,925sq m building at its Ukima Research Laboratories in Tokyo, to bolster process development for small and "middle" molecule high-potency active ingredients.

Aimed at the early development of processes for investigational drugs, from early stage through to commercial scale, the facility is due to start operations in January 2020.

SOLID Q2 GROWTH

The changes came as Chugai, 59.9% owned by Roche, reported a 13% rise in revenues in the fiscal first half ended June 30 to JPY285.1bn, with operating profit surging 41% to JPY66.6bn and net income rising to JPY49.0bn (+34%).

Oncology again led the way, and although sales in this segment fell slightly due to the general April reimbursement price cuts in Japan, Japanese sales of top product *Avastin* (bevacizumab) were up 3% to JPY45.4bn in the six months.

The overall figures were also boosted in part by first-quarter gains from the transfer of a portfolio of long-listed older products in Japan to Teva-affiliated generic firm **Taiyo Pharmaceutical Industry Co. Ltd.**.

Chugai has so far left its full-year forecast unchanged, and is expecting a core operating profit of JPY71.6bn (+66%) on revenues of JPY285.1bn (+53%) for the 12 months to December 31.

From the editors of PharmAsia News.

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AbbVie HCV Revenue Surprises Again, But Falloff Is Coming

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As **AbbVie Inc.** continues to report *Humira* growth and investors continue to worry about biosimilar competition, the Chicago-area pharma offered a surprise when it presented its second quarter earnings: a better-than-expected performance for the hepatitis C franchise, bringing it on par with rival **Gilead Sciences Inc.**.

Overviewing its second quarter financials July 27, AbbVie reported that its HCV franchise, led by *Mavyret* (glecaprevir/pibrentasvir), yielded global sales of $973m, up more than 100% from second-quarter 2017. During the first quarter, the franchise brought in $919m, 61% higher than consensus estimates of $572m, but the company talked down HCV's longer-term prospects. (*Also see "HCV Sales Drive AbbVie's Great Quarter, But Gains Won't Last" - Scrip, 26 Apr, 2018.*) Now, AbbVie is still predicting some decline in HCV – both in the US and in Japan – but is also admitting the immediate future for the franchise is hard to predict.

HCV totaled $422m in net sales in the US for the quarter, with ex-US sales reaching $551m – both numbers more than 100% increases year-over-year. Mavyret, the first oral, pan-genotypic eight-week regimen for HCV, generated a significant majority of the franchise's sales with $932m. (*Also see "AbbVie's Mavyret Is First 8-Week Pan-Genotypic Combination For HCV" - Scrip, 3 Aug, 2017.*) Chief Financial Officer William Chase told the investor call that given Mavyret's momentum, AbbVie is now increasing its projected full-year 2018 HCV sales to more than $3.5bn.

That puts AbbVie largely even with HCV leader Gilead, which projected full-year HCV sales of $3.5bn-$4bn at the start of the year.

"The pace of Mavyret's uptake continues to exceed expectations, driven by strong market share performance globally as well as higher treatment volumes from warehoused [direct-acting antiviral] failure patients in certain markets," Chase said.

CEO Rick Gonzalez touted that Mavyret has a "market-leading position in the US" and strong leadership positions in other major markets, including Japan, Germany, Spain and Italy, "based on its compelling clinical profile and our commercial execution."

ABBVIE RISES WHILE GILEAD CONTINUES TO FALL

Mavyret's ascendancy occurs in the context of significant HCV revenue slippage by Gilead, once the dominant leader in the space. During its second quarter earnings call on July 25, the Foster City, Calif., firm – which has pivoted focus recently to immuno-oncology and HIV – reported $1bn in sales for its three-product HCV franchise, basically level with the prior quarter's total of $1.05bn. (*Also see "As Gilead Seeks New CEO, Second Quarter Shows Stability" - Scrip, 25 Jul, 2018.*) That total still was down substantially from $2.9bn in the second quarter of 2017, and Gilead has been frank during recent quarterly calls that HCV is a declining franchise, both domestically and internationally. (*Also see "Gilead Admits It Needs M&A To Resume Growth, But Stays Quiet" - Scrip, 8 Feb, 2017.*)

Leerink Partners analyst Geoffrey Porges noted July 26 that Gilead's second-quarter performance, a 4% sequential decline in HCV revenue, was the lowest quarterly decline it had seen in HCV since the fourth quarter of 2016. "Gilead's management team anticipates a much more gradual and stable decline in HCV sales going forward," he added.

During its July 27 second quarter earnings call, **Merck & Co. Inc.** revealed that its two-drug HCV combo *Zepatier* (elbasvir/grazoprevir) brought in $113m during April, May and June, slightly below consensus expectations of $117m, making the New Jersey pharma a distant third-place player in HCV.

Gonzalez said AbbVie still expects a bit of a step-down in HCV revenues during the quarter, due to market factors in Japan and the US. But, he added, the pharma had expected those factors to impact HCV sales during the second quarter and instead franchise sales grew. AbbVie projects third-quarter HCV revenue of $850m, which would be a 13% decline sequentially.

In Japan, Mavyret is being used to treat patients who failed previous therapy on an all-oral DAAI regimen, a number AbbVie expected to decline during the second quarter. "I can't tell you that there's perfect data in Japan on how many of those patients there are, but we had forecasted that that would go down somewhat in the second quarter and will continue to go down in third and fourth quarter," Gonzalez explained. "It didn't go down as much as we had assumed in the

second quarter. It did go down some, but it didn't go down as much as we assumed. We are assuming another step function down of those patients in third and fourth quarter."

In the US, AbbVie had anticipated decreasing patient starts – one of the primary factors in the sharp drop-off in revenue for Gilead's HCV products – but that hasn't yet occurred as greatly as projected. "It's a similar phenomenon as we were seeing patient volumes higher than we would have expected," the CEO said. "Again, we had projected that they would come down somewhat in second quarter. We didn't see that come down. We are projecting some reduction in patient volumes in the third and the fourth quarter. We'll have to see how that plays out, but that's the basic difference."

Even if AbbVie begins to see HCV sales fall off beginning this quarter, Morningstar analyst Damien Conover predicts steady and substantial annual revenue for the franchise in the near-term. "We expect AbbVie's hepatitis C platform to support over $3bn annually for several years based on reaching more patients despite the curative impact of the drug," the analyst concluded July 27.

HUMIRA GROWTH UNABATED, IMBRUVICA'S RISE CONTINUES

Overall, AbbVie's quarter offered more of the consistent drumbeat of Humira (adalimumab) growth, progress with the cancer franchise of *Imbruvica* (ibrutinib) and *Venclexta* (venetoclax), and the potential of two Phase III Humira successors, upadacitinib and risankizumab. The pharma also pointed to the recent approval of *Orlissa* (elagolix) for endometriosis as part of its strategy to manage the impact of direct biosimilar competition to Humira.

AbbVie posted second quarter global revenue of nearly $8.3bn, up 17.1% over the second quarter of 2017. Humira totaled nearly $5.2bn for the quarter, $3.5bn in the US (up 10%) and $1.7bn internationally (up 4.4%). Imbruvica posted $850m in global sales, a nearly 60% increase, with US sales of $693m, up 31% year-over-year.

Morningstar's Conover predicted that adalimumab biosimilars will launch this October in Europe and quickly put significant pressure on Humira's EU sales. "We expect European biosimilars to erode AbbVie's Humira sales at an annual rate close to the mid-20% rate seen with *Remicade* (**Johnson & Johnson**'s infliximab)] when it faced biosimilar competition in Europe," he said. "Additionally, we continue to model an at-risk launch of a US Humira biosimilar by late 2020, likely by **Pfizer Inc.**, which has shown a willingness to launch at-risk in the past with its Remicade biosimilar *Inflectra* launch in 2016."

On the topic of possible drug pricing policy changes in the US, Gonzalez offered a wide-ranging answer which culminated with him pointing out that while there aren't many specifics yet on Trump's blueprint for addressing health care costs, "when we looked at the framework, at least for AbbVie's business … there were probably more positives than there were negatives based on the kinds of products that we have."

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AbbVie Prices Oral Endometriosis Drug Orilissa In Value Range, Focusing On Access

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AbbVie Inc. says it set the price tag for its newly US FDA approved oral endometriosis pain drug *Orilissa* at about $850 per month, with a view toward enabling patient access when the product launches in retail pharmacies in early August.

About one in 10 women of reproductive age have the condition, which can cause debilitating pelvic pain. Furthermore, the number of women in North America aged 15 to 49 with endometriosis is set to grow from 8.2m in 2017 to 8.5m in 2025 (worldwide, from 188m to 196.6m worldwide), according to Datamonitor Healthcare projections.

On July 24 the FDA approved two doses of Orilissa (elagolix) for moderate-to-severe endometriosis pain – a 150 mg once daily dose for use up to 24 months and a 200 mg twice daily dose cleared for use up to six months. The oral gonadotropin releasing hormone (GnRH) antagonist is associated with a dose-dependent decrease in bone-mineral density, hence the higher dose is intended for a shorter period of use.

> The ICER pricing review group said that the launch price, which amounts to $10,138 per year, falls within the annual value-based price benchmark range its experts established for the treatment in a June report.

ABBVIE PRICES TO OPTIMIZE ACCESS

Commenting on the $844.87 per month price tag, before rebates or discounts, the company told Scrip that it has been thoughtful and responsible in its approach to pricing in order "to optimize patient access."

The Institute for Clinical and Economic Review (ICER) commented that the launch price, which amounts to $10,138 per year, falls within the annual value-based price benchmark range its experts established for the treatment in a June report: $8,800-$12,800.

ICER explained that its value-based price benchmark reflects the hypothetical price for a prescription drug that aligns with the clinical benefits patients receive from that treatment.

However, the independent health

technology assessment organization said when releasing the report that that while the drug was efficacious in trials of women with endometriosis, "treatment still could potentially challenge short-term budgets given the large number of women affected by endometriosis."

Despite the favorable preliminary cost-effectiveness findings, ICER concluded, "only about 26% of women with endometriosis-related pain could be treated before spending crossed ICER's potential budget impact threshold of $915 million per year."

Elagolix is also in Phase III development for treating heavy bleeding associated with uterine fibroids. Updated Phase III data are expected in the fourth quarter, followed by a filing in 2019.

NEED FOR NEW TREATMENT OPTIONS

Traditional treatment options have included nonsteroidal anti-inflammatory drugs (NSAIDS) and oral contraceptives. AbbVie's injectable GnRH antagonist *Lupron* (leuprolide), now available as a generic, and other subcutaneously delivered drugs in the same class have also been available for endometriosis, but are associated with amenorrhea and loss of bone mineral density. Lupron is also approved for prostate cancer.

San Diego, Calif-based **Neurocrine Biosciences Inc.** originally developed elagolix as an alternative to injectable GnRH antagonists and outlicensed exclusive worldwide rights to AbbVie in 2010 in a deal worth $75m upfront and another $500m in development, regulatory and commercial milestones, plus sales royalties. AbbVie is solely managing commercialization

At its peak, Lupron had sales of about $4.5bn for the treatment of male cancer, but only $100m in endometriosis, Neurocrine CEO and founder Kevin Gorman told *Scrip*. Lupron had big downsides for patients, who are typically young and of reproductive age, in that it would send them straight into menopause, with symptoms like hot flashes and night sweats, and the bone loss was "devastating," he said. "The drug was never embraced for endometriosis."

The oral elagolix was designed to lower estrogen enough to work on endometrial lesions and dramatically reduce pain, but to be much better tolerated, he explained.

AbbVie funded two identical pivotal studies of almost 1,700 women with moderate-to-severe pain associated with endometriosis that supported the filing of the drug. The trials showed Orilissa was associated with significantly higher response rates for reducing menstrual pain and non-menstrual pain after three and six month, relative to placebo.

The filing for elagolix had priority review and a decision was initially expected in April. However, the agency extended the review period by three months until August to review liver function data.

Liver safety has also been a big post-approval concern in a European Union safety review of **Gedeon Richter PLC**/**Allergan PLC**'s selective progesterone receptor modulator *Esmya* (ulipristal acetate), which was initially authorized for use in treating abnormal bleeding in women with uterine fibroids in that region in 2012. (*Also see "Liver Damage Worries Lead To Further EU Restrictions On Richter's Esmya " - Pink Sheet, 21 May, 2018.*) That drug is also under review for the same indication in the US; the decision date for the filing was extended from May to August.

FDA labeling for elagolix includes a warning about dose-dependent liver enzyme elevations along with dose- and duration-dependent decreases in bone mineral density that may not be completely reversible, reduced ability to recognize pregnancy, suicidal ideation and mood disorders, and reduced efficacy for estrogen-containing contraceptives.

"Most common adverse reactions (>5%) in clinical trials included hot flushes and night sweats, headache, nausea, insomnia, amenorrhea, anxiety, arthralgia, depression-related adverse reactions and mood changes," labeling advises.

Elagolix is also in Phase III development for treating heavy bleeding associated with uterine fibroids. (*Also see "AbbVie's Got A Competitive Edge With Elagolix For Women With Uterine Fibroids" - Scrip, 21 Feb, 2018.*) Updated Phase III data are expected in the fourth quarter, followed by a filing in 2019.

Other oral GnRH antagonists in the pipeline include relugolix, from the Allergan/**Roivant Sciences GMBH**-backed women's health startup **Myovant**, which is in Phase III for uterine fibroids, endometriosis and prostate cancer, and linzagolix, from **ObsEva SA**/**Kissei Pharmaceutical Co. Ltd.**, which is in Phase III for uterine fibroids and Phase IIb for endometriosis.

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Interview: Silence Therapeutics' Chair On Why Keeping Quiet Has Done The Biotech No Favors

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This is a key moment in time, says Annalisa Jenkins, executive chair of **Silence Therapeutics PLC**, for both the company and the interfering RNA (RNAi) space, likening it to the development of antibody technology several years ago.

The crux of the science lies at the ability of RNA interference to inhibit gene expression by neutralizing targeted mRNA molecules. The space is hotting up, with **Alnylam Pharmaceuticals Inc.**'s selective RNAi agent, patisiran, expected to be reach the market for the treatment of hATTR amyloidosis in the near future. (*Also see "Alnylam Set For Transformation As Patisiran Nears Market With Data Upgrade" - Scrip, 25 Apr, 2018.*) If approved this will herald the next phase of growth and evolution of the sector, and Jenkins believes that Silence can play a key role on the growth of the RNAi industry.

IN THE CLINIC

Silence's lead program is SLN124, which seeks to target and silence the repressor of hepcidin, a protein which lies at the center of iron metabolism in the body, in order to upregulate it. The company is now progressing towards filing a Clinical Trial Authorization (CTA) and expects to be dosing patients in 2019. It is currently working in beta thalassemia and myelodysplastic syndrome and exploring the potential for moving this molecule into hemochromatosis, a genetically-based disease of iron overload. It is also working on a next generation version of that molecule using novel technology coming out of its lab.

It is also proceeding preclinically in alcohol abuse. This area will come under review over the summer, Jenkins confirms. "We will be moving it forward and looking for a partner along the way, and so it has the potential to dose patients next year but I think that largely depends on the strategy that we come up with," she says. An area Jenkins is excited about is metabolism. A target is yet to be decided upon but there will be announcements in the second half of this year.

Having been at big pharma for a large part of her career, Jenkins is clearly still enthused about the nimble nature of the biotech and the ability to follow the science. "We have a platform that can reasonably quickly identify a target, create a series of candidates and move them through an engine of discovery to candidate selection within about 9 to 12 months, including early phase *in vivo* pharmacology," she explains. "And then with that data in hand, we can make choices as to whether we want to move that internally or we want to partner." The company has just recently identified three new targets and programs that are moving through that internal engine.

While there is an ability to flex in the preclinical discovery to candidate selection, the manufacturing aspect is more of a challenge. Jenkins says the company needs to "clarify" its manufacturing strategy. It will be investing in the area and deciding what it wants to build in-house and what it will look to do through third parties. But this is just one of the many strategies Jenkins has had to navigate at her relatively short time at the company.

GETTING TO KNOW YOU

Having spent the past 10 months as non-executive chair getting to the know the inner workings of the genetic medicine company, its programs, investors and management team, her priority is clear; to unlock the value of the company's platform as the wider sector strides on. Priority number one has been to transition to become a drug development company with an end-to-end R&D model, she explains, and priority number two is to ensure the company is well capitalized.

She believes the AIM-listed company is fundamentally undervalued. "I think it's fair to say that today, in the UK, the AIM listing does not work well for companies of our size and shape, and stage. And therefore, that doesn't create the opportunity at this point for the right amount of liquidity for bringing the right investors into the company," she says. The company is now looking at the combination of access to capital through new investors in Europe and the US, and business development deals.

"We're sitting at the moment with a valuation on AIM of about $160m. Dicerna and Arrowhead are sitting north of $500m in the US and of course, we all know that Alnylam is multiple billions. I do not believe that those relative valuations actually reflect the fundamental value that sits within those companies," she says. "I don't think that the inherent, fundamental value within our portfolios across Arrowhead and Silence is that much different and yet, they're north of $500m valuation and we're sitting at $150m." The lack of liquidity in AIM is obviously a frustration for Jenkins, as is, ironically, the prior silence of the company before she joined the board.

One of the reasons why ex-Zealand CEO David Horn Solomon has been chosen as the company's new chief executive is his previous strong relationship with investors, the banks, and with the capital markets. "He's also credible because of his very robust academic background, so, he's able to translate that science and medicine through to the capital markets, and I think that's going to be extremely important for the next phase of growth of the company."

Jenkins likens Silence to a "hidden gem. It was almost as if nobody had heard about us, and when they did hear about us, it was really to talk about the Alnylam litigation," she explains.

LITIGATION AND LEGACY

The patent fight was started by former CEO Ali Mortazavi. In 2017, it launched legal action stating that Alnylam and The Medicines Company. The various claims to be heard at the trial in December 2018 will include a decision on the infringement of one of Silence's European patents by patisiran.

"Success for us would be an injunction and damages for past infringement and the recognition of the foundational chemical modifications that were invented by our Berlin scientists many years ago," Jenkins explains. "When I joined the company most of

the media, and the analysts, thought of our company as the company that was suing Alnylam," she says, but she hopes to turn those perceptions around with the industry and its observers looking on Silence as a drug development company with a platform and a long legacy. "Part of our strategy, like any company, will seek to uphold our patent position and pursue those that wish to use our inventions. But it's not core to our story, it's just part of our story." The court case will be heard in the UK in December, and a decision is expected in January 2019.

Jenkins came to the company in October 2017, a veteran of R&D, having worked at **Bristol-Myers Squibb Co.** and **Merck Serono SA** after leaving the British Navy. Latterly she had left big pharma to try her hand at the corporate side of biotech. She launched from her global R&D head role to become CEO of **Dimension Therapeutics Inc.**, and chairs the boards of **Cell Medica Ltd.**, Vium, and Cocoon Biotech. She is also CEO of PlaqueTech, a company that looks for novel biomarkers and inflammatory pathways in cardiovascular disease.

As a former R&D leader, Jenkins is passionate about protecting science. "I believe it all starts as a science, the quality of science, having the focus on unmet medical needs and how to benefit patients. And then building the team and raising the money that allows you to execute on that," she says. "I also believe that the bedrock of our industry, an innovative biopharma sector, depends on the ability to translate those discoveries and inventions into patents that basically create the market. And I believe that my position is entirely consistent with [that of] the president and chairman of BIO, the premier industry association led by John Maraganore." Maraganore is, of course, president and CEO of Alnylam.

OPERATING IN A MAN'S WORLD

While Jenkins is emphatic about the protecting her scientists works, she also does not shy away from conflict or difficult decisions. She decided to move back to the UK from the US because of the "enormous opportunity" in the health, life science, and biotech sectors in the UK as the second pillar of the UK industrial strategy post-Brexit. "It's absolutely clear that this is a major opportunity and that the [UK] government has articulated this and I would like to help make sure that that can be successfully executed," she explains.

"I learnt how to operate as a woman in a man's world and I learnt how to operate in an environment of conflict."
– Annalisa Jenkins

The UK's biotech sector is in a much worse state than in the US, in terms of female leadership, she believes. "There are actually no more than one or two board chairs in the biotech sector that are women. There are very few female CEOs and in fact there are very few C-suite women. And I will tell you that it's not a lack of pipeline, it's just that women in the UK have found it tremendously challenging to make their way through to chief exec and board positions," she opines.

"And so, I came back [to the UK] with the goal to do two things. One was to secure a couple of chair roles of significant companies in the UK and show that a woman can survive and fly, and create value, in that role. And I also came back to help a number of the British companies be connected with talented women who could also take their role whether that be as a CEO or as a C-suite to help drive those forward."

Jenkins' lessons in leadership were imprinted on her from an early age while serving in the Royal Navy. "I learnt the importance of valuing everybody equally; I learnt the importance of teams, I learnt the importance of grace under fire. And I learnt the importance of basically having a plan, being decisive, getting on and getting stuff done. And I learnt that through military leadership."

Jenkins was the first female physician to serve on the frontline at war in 1991 with the Mine Sweeper Squadron in the Northern part of the Gulf. The most important part of her experience, she recalls, was being the only woman serving at sea with a squadron of 700 men while under fire. "I often say that was the best preparation for what I subsequently have had to experience in the pharmaceutical industry, because I learnt how to operate as a woman in a man's world and I learnt how to operate in an environment of conflict."

OPPORTUNITIES

Jenkins characterizes the RNAi space as "graduating". While still in a relatively early phase, there is a huge amount of opportunity to come as new targets are identified. While the field still has relatively few players, there is an increasing number of non-gene therapy companies that want to access the "RNAi toolbox". And there are not that many companies that can allow larger firms access to that.

"I think that what you're going to see is a number of the mid- to large-cap companies looking for opportunities for partnerships and collaborations, and access to RNAi platforms, and I believe that Silence is going to be able to play a role in that," she says. "There's going to be generation three, and there's going to be generation four. And we fully intend to be front and centre of the next phase of evolution and innovation in the space."

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Innovation Critical As Japan Pharma Faces Continued Pricing Pressures

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Ten major Japanese pharma firms will add $11.4bn in revenues from new drugs reaching the market in the 2017-27 period, but the low expected compound annual growth rate of 1% for the peer set reflects an expected concomitant $4.8bn in patent expiries for major products and other core product sales losses.

The net positive gain of $6.6bn will give combined total predicted revenues of $69.5bn for the group - **Astellas Pharma Inc.**, **Daiichi Sankyo Co. Ltd.**, **Eisai Co. Ltd.**, **Kyowa Hakko Kirin Co. Ltd.**, **Mitsubishi Tanabe Pharma Corp.**, **Ono Pharmaceutical Co. Ltd.**, **Otsuka Pharmaceutical Co. Ltd.**, **Shionogi & Co. Ltd.**, **Sumitomo Dainippon Pharma Co. Ltd.**, and **Takeda Pharmaceutical Co. Ltd.** - predicts the Japan Pharma Outlook 2027 report from Informa's PharmaVitae.

The Japanese industry is already facing challenges from ever-tightening drug reimbursement cost controls under the national health insurance scheme, and these are expected to continue as the population becomes increasingly top heavy.

At the other end of the age spectrum, a declining birth rate, and therefore working population and tax revenues, will create continued pressure on health system funding.

PRICING PRESSURES

"The policy environment for Japan is a complicated mix of positive and negative government factors, depending on portfolio and business strategy," the report states.

The pharma industry has long faced regular price cuts every two years, but the shadow of annual cuts is looming from 2020 after a two-year review period, while government policies continue to support the use of generics.

The official goal is to increase to 80% the volume share of such products in the substitutable market by 2020, and with this figure already nearing 75% the target looks set to be reached even earlier. In addition, under changes introduced this April, the repricing of products with sales that expand beyond JPY35bn ($315m) will be considered four times a year, opening the way to more frequent additional cuts.

HIGHER INNOVATION HURDLES

Meanwhile, higher hurdles for drugs to be considered innovative and to qualify for a revised system of price premiums for novel products, and the adoption this year of more regular assessments of cost-benefit analyses, will further dampen market growth.

Under the new system of "innovation ratings" for companies - which is based on factors including number of clinical trials conducted, drugs in development, and completion of government-requested projects to commercialize high-need products - PharmaVitae predicts that only fewer than half of all Japanese companies will be eligible for the highest tier status in the new system, qualifying them for pricing premiums.

STRATEGIES FOR GROWTH

Against this backdrop, cost-saving measures by the peer set, including continued job cuts and divestments of non-core or older branded products with generic competition, are expected.

Some consolidation is foreseen: "PharmaVitae believes Japan Pharma will at least partially revisit the consolidation approach seen in the 2000s as mid-sized companies seek greater economies of scale to become more competitive".

Mid-sized companies with established positions in the US may "seriously consider mergers in the near term to strengthen their US market penetration through existing commercialization rights," forecast the report, which looks at the complex mix of policy, regulatory, commercial, external and R&D factors facing the industry in Japan.

However, following the expected completion of the Takeda/Shire merger, no further global-scale M&A activity is anticipated in the near term.

KEY THERAPY AREAS

Alongside, PharmaVitae expects there to be an increased focus on key therapeutic growth areas such as oncology and CNS, the US and emerging markets, while regenerative medicine - helped by a supportive regulatory environment - provides attractive opportunities in Japan.

The oncology market for the peer set is forecast to grow by $5.4bn (3.9% CAGR) to reach $17.0bn in 2027, and CNS to increase by $3.6bn (3.0% CAGR) to $14.1bn over the same period.

MAIN WINNERS

Helped by a presence in these areas, the main growth companies out to 2027 are expected to include Eisai with an additional $1.54bn added to the top line, helped by new Alzheimer's disease drugs, and Takeda with an additional $1.27bn (excluding the planned Shire acquisition).

Daiichi Sankyo is seen losing $802m, mainly due to patent expiries.

Eisai's Alzheimer's therapy aducanumab (partnered with Biogen) is seen becoming the highest-selling pipeline product with $1.9bn in sales by 2027, but Astellas's pipeline is seen as the most valuable pipeline overall, with eight launches adding $2.6bn to top line revenue by the same year.

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WATCH

A webinar on the outlook for Japan Pharma and the contents of the report can be found here. https://bit.ly/2v6IS1P

Pfizer's CEO Is Bullish On Rebate Changes That Could Power New Launches

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After both a phone call and a White House meeting with President Donald Trump, **Pfizer Inc.** CEO Ian Read was pushed during the firm's second quarter earnings call for his thoughts on what could be on the horizon when it comes to drug pricing and rebate reform – and the CEO was notably optimistic about US policy changes that could impact the pharmaceutical industry.

Read said he expects drug rebates will be eliminated under public health insurance plans in a policy shift that will spill over to the private sector. At the same time, he said there will continue to be room for net drug prices to increase, commensurate with health care inflation.

"The removal of rebates will be very beneficial to patients and our industry, especially [for] those companies who are launching new products over the next five years or so," Read said during the company's second quarter sales and earnings call July 31.

THE MARKETING POWER OF REBATES

His comments raise a point pharmaceutical manufacturers don't usually bring up when it comes to the debate around rebates, generally around how much money the pharmaceutical industry spends on the offsets and where and how the savings are applied. But rebates have also been a vital marketing tool industry has wielded to its advantage. As Read pointed out, big rebates for mature medicines can be used effectively to block market access for newer medicines.

In that sense, removing the rebate structure could level the playing ground for new medicines launching into a competitive category. That could present advantages for some and disadvantages for others, which probably explains why some pharma leaders have come out strongly in favor of sweeping rebate reform while others have sounded less persuaded.

Read pointed to Pfizer's rheumatoid arthritis drug *Xeljanz* (tofacitinib) as an example of a drug that would have benefited from launching into a system without rebates. Xeljanz initially had slow uptake but has steadily grown into a blockbuster. Part of the problem for Xeljanz, though not the only issue, was that the entrenched rival anti-TNFs delivered bigger rebates to payers, not because of the size of the rebate necessarily but because of the high volumes associated with older medicines. Sometimes drug manufacturers also tie rebates for one drug to other drugs, a tactic known as bundling, which can also be effective for securing market access.

The situation is not dissimilar to the one Pfizer has run up against with the launch of the biosimilar *Inflectra* (infliximab-dyyb), which has struggled to gain a foothold in the market, largely because of **Johnson & Johnson**'s competitive rebating strategy with *Remicade* (infliximab). In the case of Inflectra, the situation has gotten more attention – and Pfizer has filed a lawsuit against J&J for it – because it affects the emerging market for biosimilars in the US, but the strategies are ones frequently used in the brand drug space.

"I think the removal of the rebate trap will be advantageous to Xeljanz and be advantageous to our biosimilars program," he said.

Read said Pfizer realizes about 58% of the list price of the drugs it sells. "The rest goes to subsidize profitability of PBMs, insurance companies and frankly premiums of those that are healthy," Read said. "This is not a sustainable position."

Investors and industry watchers have been eager to hear Read's thoughts on pharma policy after the chief executive had a face-to-face meeting with President Trump. The relationship started off cool, with Pfizer being the topic of an angry Tweet from Trump, after the company raised prices on dozens of drugs in July. (*Also see "Trump Tries To Shame A Defiant Pfizer On Drug Pricing" - Scrip, 9 Jul, 2018.*) But Trump then praised Pfizer, after the company vowed to walk back the price increases following a phone conversation. Pfizer agreed to return drug prices to their pre-July 1 level and also promised not to increase the prices of any drugs before the end of the year or until the president's drug pricing blueprint goes into effect.

Read later met with Trump at the White House. "My conversations with the president were centered around the blueprint and the actions he wants to take in those blueprints," he said.

Several other big pharma companies have followed Pfizer's lead, vowing not to increase drug prices for the remainder of the year – even though some had already taken more than one round of prices hikes so far this year. Trump's drug pricing blueprint includes a lot of ideas that could impact the drug industry, but most of those require substantial policy changes, and thus time, to put in place.

There's a lot of uncertainty over what changes, if any, will come first, but changes to the rebate structure appear likely. The HHS Office of Inspector General is preparing a proposed rule to eliminate negotiated drug rebates by removing the safe harbor from the anti-kickback statute that allows them. Read said he believes rebate changes could happen rather quickly. "I see a huge sense of urgency on the part of the administration to act on the rebate part," he said. "I expect the administration to act on that with as much urgency as they can."

Changes will initially occur under government healthcare programs but Read said those would spill over to the private sector.

"Initially, their reforms will be focused on the public sector, where they have the authority to take the rebates out of the safe harbor, but I believe that will extend to the commercial business very, very quickly, as I can't really see a bifurcated system where half the system is on net price and the other is on a rebate," he said. "The transparency won't allow that."

As for what new policies could mean for drug prices, Read said the company will focus on net price increases, rather than list price increases, and those should fluctuate around the same rate as health care inflation.

"I don't see any obstacle to us growing to middle- to high-single digits," he said.

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

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

Selected clinical trial developments for the week 20 July–26 July 2018

LEAD COMPANY/PARTNER	COMPOUND	INDICATION	COMMENTS
PHASE III INTERIM/TOP-LINE RESULTS			
Almirall/Athenex	KX2-391 (KX-01)	actinic keratosis	AK003, AK004; achieved primary endpoint.
Sunovion	dasotraline	binge eating disorder	SEP360-321; met primary endpoint.
Takeda	*Alunbrig* (brigatinib)	non-small cell lung cancer, ALK-positive	ALTA-1L; met PFS endpoint versus crizotinib.
AstraZeneca/ Merck & Co.	selumetinib	thyroid cancer	ASTRA; missed primary endpoint.
Johnon & Johnson/ Gilead	*Symtuza* (darunavir/ emtricitabine/ tenofovir alafenamide/ cobicistat)	HIV/AIDS	DIAMOND; effective and well tolerated.
Merck & Co	*Keytruda* (pembrolizumab)	head and neck cancer, first-line	KEYNOTE-48; met overall survival primary endpoint.
Celgene	*Revlimid* (lenalidomide) with rituximab	indolent non-Hodgkin's lymphoma, marginal zone lymphoma	AUGMENT; PFS improved.
CSL Ltd	*Hizentra* (IgG)	chronic inflammatory demyelinating polyneuropathy	PATH Ext.; sustained efficacy and tolerability.
Eton Pharma	EM-100	allergic conjunctivitis	Ora-CAC; positive results for preservative-free formulation.
UPDATED PHASE III RESULTS			
Alnylam pharma	patisiran	transthyretin-related hereditary amyloidosis	APOLLO; improved overall health status.
EyePoint Pharmaceuticals (formerly pSivida Corp.)	*Yutiq* (fluocinolone acetonide) three-year intravitreal implant	uveitis	Positive 12-month efficacy and safety data.
Clearside Biomedical Inc.	CLS-1001, supra-choroidal injection	uveitis	PEACHTREE; met primary endpoint.
ViiV Healthcare	dolutegravir plus lamivudine	HIV/AIDS	GEMINI 1, 2; efficacy similar to three-drug regimen.
Merck & Co	doravirine	HIV/AIDS	DRIVE-FORWARD; met primary endpoints.
Regeneron pharma	*Eylea* (aflibercept)	diabetic retinopathy	PANORAMA.
PHASE III INITIATED			
Leo Pharma	tralokinumab	atopic dermatitis	ECZTRA6; in adolescents.
Aldeyra Therapeutics	reproxalap	icthyosis	Associated with Sjogren-Larsson syndrome.
Otonomy	*Otividex* (dexamethasone) otic formulation.	Meniere's disease	To support US registration.
Roche	RG6264	breast cancer	Fixed dose combo of subcutaneous pertuzumab and trastuzumab.
Paion	remimazolam	general anesthesia	In the EU.

Source: Biomedtracker

Lysosomal Storage Disorders: Azafaros Takes Aim At Small Molecules

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Biotech and pharma companies have had some success in the past developing enzyme replacement therapies for lysosomal storage disorders such as Fabry disease and Gaucher disease, and a new European biotech company, **Azafaros**, spun out of Leiden University in the Netherlands, is aiming to build on that achievement by developing a new generation of agents for rare metabolic disorders.

The potential new class of therapeutic agents are small-molecule orally active, aza-sugar compounds which interfere with the metabolism of glycolipids and are expected to tackle some of the underlying causes of LSDs, conditions often linked with enzyme deficiencies and the accumulation of glycolipids in cells and tissues.

Azafaros has obtained an exclusive license to a library of novel compounds and patents discovered by Prof. Hans Aerts and colleagues at Amsterdam UMC and Leiden University, and is collaborating with the researchers on development. A seed financing round, led by the founding investor, Bio-Generation Ventures (BGV), has just closed for Leiden, Netherlands-based Azafaros. "We strongly believe that these new compounds have the potential to offer better clinical outcomes for patients in the future," said BGV managing partner Edward van Wezel, a member of Azafaros's board.

BGV is based in Naarden, the Netherlands, and is active in finding and supporting scientific projects and research teams and taking innovative breakthroughs to the next level, including the setting up of new companies. For example, it was a founding investor in **Acerta Pharma BV**, a biotech that was divested to **AstraZeneca PLC** in 2015 in a multi-billion-dollar deal thought to be one of the largest exits to date for a privately held European biotech company.

Azafaros has appointed Olivier Morand, an executive experienced in rare metabolic disorders and orphan drugs, as CEO; Morand was most recently at **Idorsia Pharmaceuticals Ltd.**, and before that at **Actelion Pharmaceuticals Ltd.** and **Roche**.

Azafaros is not alone in focusing on the treatment of LSDs, a broad class of severe and sometimes life-threatening conditions. Other companies developing small molecule therapeutics for such conditions include **Amicus Therapeutics Inc.**, whose *Galafold* (migalastat) has a US PDUFA date in August for the treatment of Fabry disease.

Also, **BridgeBio Pharma** has licensed **Alexion Pharmaceuticals Inc.**'s ALXN1101 for the treatment of molybdenum cofactor deficiency type A, and is evaluating it in a Phase II study expected to complete in 2020.

And Cambridge, MA-based **AVROBIO Inc.** is evaluating in preclinical and clinical studies several gene therapies for the treatment of lysosomal storage disorders, including for Fabry disease, Gaucher disease, cystinosis and Pompe disease.

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John Milligan is to stand down as CEO of **Gilead Sciences Inc.** at the end of the year. Former CEO and current chair ***John Martin*** will also stand down upon the appointment of a new CEO. Milligan said he was looking forward to a "well-deserved break" and would then move on to "new and different opportunities".

Senior departures have also been announced at **Amgen Inc.**, where executive vice president of research and development ***Sean Harper*** and executive vice president of global commercial operations ***Anthony Hooper*** are retiring. Harper will be succeeded by ***David Reese***, hitherto senior vice president of translational sciences and oncology, with immediate effect, although he will remain at the company for a period to facilitate the transition. Hooper will retire in September, to be replaced by ***Murdo Gordon***, currently chief commercial officer of **Bristol-Myers Squibb Co.**, effective Sept. 3.

Purdue Pharma LP has appointed corporate turnaround specialist ***Steve Miller*** as chairman, reporting to president and CEO Craig Landau. Miller's previous challenges have included the turnaround of Chrysler; he will be looking to rehabilitate the firm in the wake of the OxyContin scandal. In addition, ***Marc Kesselman*** has been appointed senior vice president and general counsel, replacing Maria Barton. Kesselman's most recent roles have been in the food and beverage industry; he will be responsible for the company's overall legal strategy, ethics and compliance, government affairs and corporate governance.

Sirnaomics Inc. co-founder ***David Evans*** has been appointed chief scientific officer of the company, to lead its preclinical programs for novel RNAi therapeutics. His prior biotech experience includes stints at **Millennium Pharmaceuticals Ltd.**, Serono Pharmaceuticals, Tgen (Translational Genomics Research Institute), **Dharmacon Inc.** and Frederick National Laboratory for Cancer Research.

Pandion Therapeutics Inc., a biotech firm focused on developing antibody therapeutics for autoimmune and inflammatory diseases and transplant rejection, has appointed ***Nancy Stagliano*** as an independent director. Most recently Stagliano was CEO of **True North Therapeutics Inc.**, until its acquisition by **Bioverativ Inc.** She has also been CEO of **iPierian Inc.** and **CytomX Therapeutics Inc.**.

Cardiovascular disease-focused **Cardurion Pharmaceuticals LLC** has appointed ***Rebecca Frey*** chief operating officer. Frey joins from **Prevail Therapeutics Inc.** where she was vice president of operations. Before that she spent 11 years at **Alexion Pharmaceuticals Inc.**

Robert Ashworth has been appointed vice president of regulatory at **OncoSec Medical Inc.**l, which is developing intratumoral cancer immunotherapies. Ashworth was previously vice president, regulatory affairs, quality and compliance at **Advaxis Inc.**, and before that held the role of vice president, global regulatory affairs at **NPS Pharmaceuticals Inc.** and **Otsuka Pharmaceutical Development, Inc**.

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