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J&J Plans 10 Potential Blockbuster Filings By 2023

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Johnson & Johnson expects to achieve above-market compound annual growth in its pharmaceuticals business between 2019 and 2023, including from current and future growth drivers. The company highlighted its pharma portfolio in a six-hour analyst meeting at its headquarters in New Brunswick, NJ, on 15 May, the first such overview in two years.

Similar to the last meeting in May 2017, management provided investors with an update on blockbuster medicines already in the portfolio and targeted regulatory filing dates for new medicines. The company said it expects to have 14 currently marketed medicines with blockbuster-level sales and bring new $1bn-plus products to market.

"We will deliver on our robust pipeline of transformational medicines with at least 10 NME filings or launches anticipated through 2023, each with more than $1bn potential," Worldwide Chairman-Pharmaceuticals Jennifer Taubert said.

Among the current blockbusters are anchor brands like Stelara (ustekinumab) and Simponi (golimumab) in immunology, Imbruvica (ibrutinib) and Darzalex (daratumumab) in oncology, the Invega (paliperidone) franchise in neurology and Xarelto (rivaroxaban) in cardiovascular disease. But new brands like Tremfya (guselkumab) for psoriasis and Spravato (esketamine) for depression are viewed as future blockbuster brands.

"We will drive growth through additional market share gains, increased penetration and entry into new populations," Taubert said of the 14 current currently marketed drugs with growth potential. J&J is planning some 40 line extensions for those products through 2023, 10 of which could offer $500m or more in added revenue potential.

MIXED SUCCESS

Whether or not J&J will meet its goal to bring forward 10 new filings remains to be seen. The company had mixed success with the 10 drugs it promised investors it would deliver back in 2017, with three having been approved by FDA, but four having been discontinued or returned to partners. *(Also see "J&J Plots Five-Year Pharma Growth Plan Around Mega-Brands And Launches" - Scrip, 17 May, 2017.)*

Among the positive advancements were the approvals of Tremfya in 2017, Erleada (apalutamide) for prostate cancer in 2018, Spravato in March and Balversa (erdafitinib) for urothelial cancer in April. Tremfya was already pending at FDA at the time of the 2017 analyst meeting and was not included in the list of 10 filings.

Several drugs J&J had promised to file by 2021 have met their demise, like the interleukin-6 inhibitor sirukumab for rheumatoid arthritis, which was never brought to market as the commercial prospects diminished. *(Also see "J&J Immunology Growth Now Hinges On Stelara, Tremfya After RA Setback" - Scrip, 17 Oct, 2017.)* Another disappointment cost J&J substantially, when the company discontinued development of lumicitabine

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BROUGHT TO YOU BY THE EDITORS OF **PHARMASIA NEWS**, **START-UP** AND **SCRIP INTELLIGENCE**

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from the editor

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Out with the old and in with the new. This might be the motto for the biopharma industry, which invests more of its revenues in R&D than any other industry (16.3% for the top 29 pharma investors, according to EY). It's also something of a theme in this week's issue of *Scrip*.

Our cover story on Johnson & Johnson's vision of 10 new blockbusters to be filed over five years includes a reminder of how quickly hot new hopes can be consigned to the rubbish heap: of 10 promising filings J&J had spotlighted just two years ago, 40% are now discontinued or back in the hands of its partners.

We also bring you more detail on J&J's interest in the technologies du jour: cell, gene and RNA-based therapies (p4). Most big pharma companies are putting out some tentacles to get in on this act. Pfizer's another example: you can read an interview with the head of its gene therapy business Robert Smith on p8. Since cell and gene therapy enthusiasm has led to a number of notable acquisitions (eg Gilead Sciences/Kite Pharma; Celgene/Juno Therapeutics; Roche/Spark Therapeutics; Novartis/AveXis), it feels like there's a ticking M&A time bomb around firms in the space that remain independent. Bluebird bio is a case in point: read about its analyst day on p12.

Meanwhile, Takeda, still working through the Shire acquisition, is more focused on "out with the old" than most: it says 25% of revenue is "non-core" and it's looking to divest around $5bn worth of products after disposing of dry eye product Xiidra. Read more on p5.

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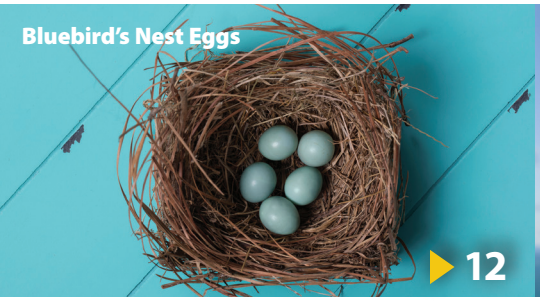

exclusive online content

Joy For SMA Patients As NICE And Biogen Break Spinraza Deadlock

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The news that NHS England has finally agreed to fund Biogen Inc.'s Spinraza looks like a victory for common sense, with the company, the country's healthcare cost watchdog and patient groups all lauding the negotiations that will finally result in the spinal muscular atrophy (SMA) treatment being made available to children with the rare and fatal muscle-wasting condition.

The National Institute for Health and Care Excellence (NICE) has recommended funding on the NHS for Spinraza (nusinersen) for the treatment of infants, children and adults with 5q SMA. The decision follows a managed access agreement (MAA) inked between NHS England and Biogen which will see the former fund treatment with the drug, an antisense oligonucleotide designed to treat the root cause of the life-threatening disorder for a time-limited period, allowing further data to be collected on its effectiveness.

Spinraza will be made available to the youngest and most severely affected (SMA type 1) patients immediately by Biogen, with NHS England offering funding on NICE's publication of final guidance next month. Those with less severe symptoms (SMA types 2 and 3) will get access shortly.

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

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for respiratory syncytial virus (RSV). *(Also see "Alios Buy Best Forgotten For Johnson & Johnson As RSV Failure Costs It Dear" - Scrip, 22 Mar, 2019.)*

The company also discontinued development of talacotuzumab for acute myeloid leukemia (AML) and it backed out of a deal with Geron Corp. to develop the telomerase inhibitor imetelstat for myelofibrosis. *(Also see "Geron Has Cash, But Does It Have The Imetelstat Data To Push On Without Janssen?" - Scrip, 27 Sep, 2018.)*

Several drugs mentioned in 2017 remain on the updated list: GlaxoSmithKline PLC's PARP inhibitor Zejula (niraparib) for prostate cancer, which Janssen has rights to in that indication, as well as pimodivir for influenza A, and an orexin-2 receptor antagonist seltorexant for major depressive disorder; the latter is partnered with Minerva Neurosciences Inc..

The updated list includes new additions, such as an anti-CD70 monoclonal antibody cusatuzumab for AML; a BCMA-targeting chimeric antigen receptor T-cell (CAR-T) therapy for multiple myeloma, JNJ-4528; lazertinib, an EGFR-tyrosine-kinase inhibitor for non-small cell lung cancer; and a gene therapy for retinal disease.

Other potential filings include JNJ-4500, an anti-NKG2D for Crohn's disease, as well as a vaccine for respiratory syncytial virus (RSV), a BCMA/CD2 regimen for multiple myeloma and a bispecific EGFR/cMET receptor inhibitor for solid tumors.

Near-term catalysts include building out existing brands, among which:

- J&J filed a supplemental biologics license application (sBLA) for Stelara in ulcerative colitis in December and is studying the drug in Phase III in lupus.
- A Phase III data readout and subsequent regulatory filing for Tremfya in psoriatic arthritis are expected later this year.
- The company expects to file Spravato for depression with suicidal ideation in the fourth quarter.
- J&J expects FDA approval of Darzalex in first-line multiple myeloma after filing in March and is developing a subcutaneous infusion that will deliver the medicine in five minutes.

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Where Is J&J Investing For The Future? Cell Therapy, Gene Therapy And RNA

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Johnson & Johnson's Janssen unit is investing in cell therapy, gene therapy and RNA therapeutics as modalities that could deliver highly innovative new drugs, Janssen global head of R&D Mathai Mammen explained while outlining the company's research priorities during a pharmaceutical overview at the company's headquarters in New Brunswick, NJ, on 15 May.

The company also vowed to deliver 10 new drug filings by 2023 across its six therapeutic focus areas: oncology, immunology, neuroscience, cardiovascular/metabolic, infectious disease and vaccines and pulmonary hypertension. *(Also see "J&J Plans 10 Potential Blockbuster Filings By 2023 " - Scrip, 15 May, 2019.)*

Investors are also thinking about the next wave of drugs J&J will bring forward based on emerging technologies. That is where Mammen said J&J is scouring the horizon and making investments for the future now, both internally and through external partnerships.

"The world continues to uncover validated biological pathways and connect these to unwanted human phenotypes. Many of these will prove actionable through small molecule and monoclonal antibodies," he said. "But a great many others are going to requires new approaches, and sometimes addressing a complex human phenotype demands a complex therapeutic."

Mammen is relatively new to Janssen, having joined to lead global R&D in June 2017 from Merck & Co. Inc., where he was a senior VP at Merck Research Laboratories, responsible for research in cardiovascular, metabolic and renal diseases, oncology/immuno-oncology and immunology. The six-hour pharmaceutical overview was his first one at J&J, since the company last held one in May 2017.

Cell therapy, gene therapy and other gene-editing approaches are quickly becoming an important part of big pharma's development armamentarium as the first drugs developed on all three modalities have reached the market. Nonetheless, the development challenges in each of the areas remains daunting, and the manufacturing and commercial challenges are notable as well. J&J hasn't been as ahead of some peers in areas like immuno-oncology and gene therapy.

"WE BELIEVE IN CELL THERAPY"

In cell therapy, J&J is already developing a B-cell maturation antigen (BCMA)-targeting CAR-T therapy for the treatment of multiple myeloma, where it has a strong foothold with the CD-38 antibody Darzalex (daratumumab). The company is working in partnership with Legend Biotech Corp. to develop the autologous therapy JNJ-68284528, having paid $350m up front under the 2017 collaboration.

The companies announced the initiation of a Phase Ib/II study in the US in relapsed/refractory multiple myeloma in 2018 and said data should be available by the end of 2019 or early 2020. *(Also see "J&J Muscles Into CAR-T Field: Initiates Myeloma Studies" - Scrip, 31 May, 2018.)* A Phase II study is expected to begin in China in 2019.

Several drug makers are also exploring BCMA targets, however, further ahead in development, most notably Celgene Corp. and bluebird bio Inc., which are developing a CAR-T therapy, and GlaxoSmithKline PLC, which is developing an antibody-drug conjugate. Both of those drugs are on track for filing later in 2019.

Mammen said the first wave of autologous CAR-T therapies, based on individually engineered T-cells, have limitations and J&J is therefore looking to develop off-the-shelf solutions, while also exploring cell therapy for the treatment of solid tumors, where it has had less success than in blood cancers.

"The immediate challenges of creating autologous CAR-T cells lie in making the

cell and in all the logistics, and we're investing in every respect here," Mammen said. While he admitted the challenges are immense, he noted, "all in all, we believe in cell therapy. We are committed to being among the leaders in this area in short order."

IN GENE THERAPY, STARTING WITH EYE DISEASES

J&J is also building out in gene therapy, where it hasn't been among the earliest players. Spark Therapeutics Inc. – poised to be acquired by Roche – was the first to bring a gene therapy to the US market with the launch of Luxturna for inherited blindness, and Novartis AG is expected to bring the second shortly, Zolgensma, pending at the FDA for spinal muscular atrophy. Pfizer has invested substantially in gene therapy and has built out a pipeline of drugs in clinical development.

J&J expanded its capabilities in gene therapy through a partnership with MeiraGTx Holdings PLC in January, gaining rights to clinical-stage candidates for inherited retinal disease in exchange for $100m up front. *(Also see "MeiraGTx Signs J&J To Develop Gene Therapies For Rare Retinal Diseases" - Scrip, 31 Jan, 2019.)* But Mammen said the company has also been working internally and has plans to expand beyond ophthalmology.

"We're beginning in the eye for a variety of reasons. First, we have line of sight to vision-restoring medicines for retinal diseases. Second, we have with Meira very importantly sound and reliable manufacturing at the scale needed for the eye." J&J plans to expand to other therapeutic areas, but will do so in a disciplined way, understanding the need to build large-scale manufacturing in parallel.

Lastly, Mammen highlighted siRNA as an area targeted for investment and pointed to J&J's partnership with Arrowhead Pharmaceuticals Inc., under which the companies are developing a gene-silencing candidate for hepatitis B infection. *(Also see "J&J Bets Big On Arrowhead's Early Promise In Hepatitis B" - Scrip, 4 Oct, 2018.)*

"To thrive in tomorrow's marketplace, a successful large pharmaceutical company must understand how to be an integral part of the biotech ecosystem and not just compete against it." - Mathai Mammen

"We plan on exploring additional applications across therapeutic areas with siRNA, and we see a future to nucleic acid therapeutics that can also involve messenger RNA, replicating RNA and gene editing," he said. "We appreciate that delivery is a very significant problem, perhaps the problem to solve, and we're working very hard here with our partners to make progress."

The company will invest internally and externally, Mammen said, claiming that the biotech ecosystem is "thriving."

"To thrive in tomorrow's marketplace, a successful large pharmaceutical company must understand how to be an integral part of this ecosystem and not just compete against it," he said. The company has built a reputation for partnering, he added, pointing to a willingness to be flexible when it comes to licensing technology, collaborating with partners, incubating new companies, or buying an asset or company outright.

"We are a participant, a partner and an accelerator inside this vibrant ecosystem," he said.

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More Divestments In Store As Takeda Digests Shire, Faces Expiries

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While Takeda Pharmaceutical Co. Ltd. is "very pleased" with the recent deal to sell Xiidra to Novartis AG, "there will be more to come" as the Japanese firm continues to rationalize assets after the Shire PLC acquisition, CEO Christophe Weber says.

The deal for ex-Shire dry eye drug Xiidra (lifitegrast) is worth up to $5.3bn in total to Takeda, which has already said it will seek up to $10bn in total divestment value after its $62bn purchase of Shire.

This prompted questions at a fourth quarter results briefing in Tokyo over how the remainder of the target figure will be made up.

Weber confirmed Takeda remains committed to the overall figure, saying "we have a clear list of products that we have in mind," although the company is not publicly disclosing these while discussions progress. He noted that 25% of current group revenue is considered non-core, providing "plenty of scope" in terms of other lines that might be hived off.

Listed under this "other" column in the presentation - but not formally confirmed as divestment candidates - are gout drug Colcrys (colchicine), antihypertensive Azilva (azilsartan) and diabetes product Nesina (alogliptin). There has also been some market talk around mature product lines in developing markets, as Takeda pivots globally towards its newer innovative products.

Addressing other speculation, Weber did confirm that legacy Shire product Natpara (parathyroid hormone) for hypoparathyroidism is still considered core, and that there is "no intent to divest" this given its good fit with the combined company's rare disease focus.

The 14 May release of Takeda's results for the fiscal year ended 31 March included the first annual forecast for the combined business after the completion of the Shire deal in early January. Costs associated with the acquisition are expected to push the combined company to an operating loss of JPY193bn ($1.75bn) this fiscal year.

$2BN AT GENERIC RISK

Chief financial officer Costas Saroukos told the briefing that, along with multiple myeloma drug Velcade (bortezomib), expiries of exclusivity for other drugs mean that "we're looking at approximately $2bn of [combined] impact in fiscal year 2019."

While this is "extraordinarily large" the impact will lessen after this fiscal year, he noted.

The company is assuming the entry in July of an additional US generic (and the first in subcutaneous form) for Velcade, but remains unsure over the actual likelihood of this. The CFO also pointed to the loss of exclusivity for other products in the US, such as Firazyr (icatibant) for hereditary angioedema and Uloric (febuxostat) for gout (both in July), and for Enbrel (etanercept) in Japan.

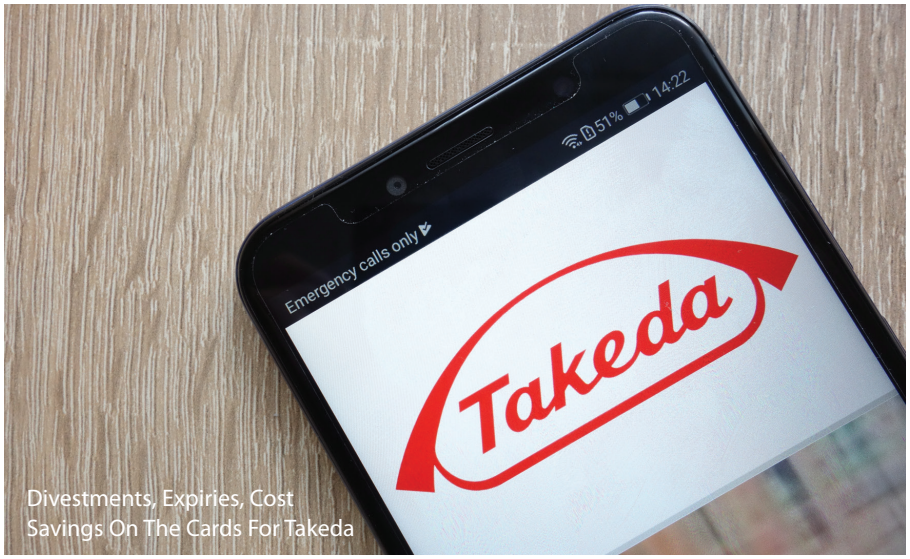
But the company expects its "well balanced" portfolio of 14 newer global growth products, and underlying 5-6% business growth, to absorb most of this impact, with blockbuster inflammatory bowel disease biologic Entyvio (vedolizumab) leading the way.

In his presentation, Weber said the company has raised the peak sales estimate for its already top-selling product, which is now estimated to generate $4-5bn annually at maximum. This will be helped by increasing use in biologic-naïve patients (where it now has a 25% share), new markets such as China (where a submission may be made in fiscal 2020) and the roll-out of a more convenient subcutaneous formulation.

In the oncology sector, Ninlaro (ixazomib) for multiple myeloma is expected to lead growth, and is now seen rising to peak annual sales of $1.5-2bn. Trial data readout for maintenance use in transplant-ineligible patients is slated in the second half of this fiscal year (ie, sometime after September), R&D president Andrew Plump told the meeting.

Elsewhere in the commercial portfolio, the enlarged Takeda expects a mid-term decline for its rare hematology franchise, due to pressure on Feiba (anti-inhibitor coagulant complex) and Advate (recombinant antihemophilic factor).

But strong growth is predicted for Takhzyro (lanadelumab) for hereditary angioedema, which has already been launched in the US and is being positioned as a first-line prevention treatment.



Divestments, Expiries, Cost Savings On The Cards For Takeda

COST SAVING SOURCES

As already reported, Takeda has just raised its three-year annual recurring cost synergy and savings target to $2bn from $1.4bn, with total cumulative implementation costs of $3bn.

A broad swathe of rationalization measures to achieve this will continue across general, administrative and manufacturing functions, as well as from overlapping office costs and central functions, while further procurement savings from major suppliers are also being sought. The synergy targets are embedded in management incentive schemes and are tracked closely.

"We are also targeting sales and marketing efficiencies," Saroukos added. A US sales force reduction became effective from April, and Takeda confirmed last year that it was closing down its Deerfield, IL site in the US. *(Also see "Deerfield To Go As Takeda Plans Realignment Of Post-Shire US Ops " - Scrip, 12 Sep, 2018.)*

In Europe, there has been a rationalization of London operations and the formation of a new European hub in Zurich, Switzerland.

PIPELINE GAINS/LOSSES

In an R&D update, Plump highlighted key late-stage pipeline catalysts over the next few months, including readout from a pivotal Phase II trial with the NAE inhibitor pevonedistat (TAK-924) in myelodysplastic syndrome, and a Phase III start for the EGFR/HER2 inhibitor TAK-788 in first-line non-small cell lung cancer. A US approval decision on Entyvio SC for ulcerative colitis is expected in the fiscal second half, when a US submission of the formulation for Crohn's disease is also planned.

The main strategic investment focus at the moment is on the "middle bucket" of the clinical pipeline and next wave of innovation, Plump said.

A review of the updated pipeline reveals a few losses from the ex-Shire clinical portfolio over the past few months, including the C1 esterase inhibitor Cinryze (SHP616/TAK-616) for acute antibody mediated rejection and subcutaneous administration in hereditary angioedema, with work in both settings discontinued at Phase III.

Other recently dropped projects include the D-amino acid oxidase inhibitor TAK-831 for Friedreich's ataxia and the CDC7 inhibitor TAK-931 for metastatic colorectal cancer (both at Phase IIa).

On the positive side, 44 new collaborations with bioventures and academia were signed last fiscal year.

WEBER UPBEAT

Despite the challenges and substantial projected loss for the year, Weber remained resolutely upbeat at the briefing on the benefits of the Shire deal.

"We are on track to execute the integration…are making great progress on the R&D side with 18 assets in Phase II and III. I think we are really on track to be a growing R&D-driven values-based pharmaceutical company."

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Takeda Sees Strong Fundamentals Despite Post-Shire Loss Outlook

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In its first full fiscal year outlook since completing the $62bn acquisition of Shire PLC in early January, Takeda Pharmaceutical Co. Ltd. expects the newly merged business to achieve "flat to slightly declining" underlying revenue growth, affected in part by increased US generic competition to one of its top products.

A mid-twenties percentage increase in underlying core earnings margin is foreseen, while underlying core EPS should be in the JPY350-370 range, the Japanese firm said on 14 May in releasing figures for its last fiscal year ended 31 March.

For the current 12-month financial period ending on the same date in 2020, Takeda anticipates reported revenue will jump 57% to JPY3,300.0bn ($30.07bn) on the first full annualized inclusion of Shire, with core earnings surging 92% to JPY883.0bn on the same basis, helped by higher than expected cost synergies.

But the transaction's integration costs of JPY154.0bn in the year will weigh heavily on reported profits, which on an operating basis are now expected to involve a loss of JPY193.0bn, and a JPY383.0bn net loss, of which JPY241.0bn is attributable to Shire impact.

Takeda said the new forecast also assumes the US launch this July of one additional, non-therapeutically equivalent competitor (in both intravenous and subcutaneous formulations) to its multiple myeloma drug Velcade (bortezomib), which brought in JPY105.7bn (-7%) in the US last fiscal year.

The lack of additional generics last fiscal year resulted in less than expected sales erosion for the original product. If no further generic is actually launched however, overall pro forma underlying revenue growth would change to "flat to slightly increasing," the company said.

ENTYVIO, LEGACY TAKEDA STRONG

Without the loss from Velcade, chief financial officer Costas Saroukos said the top line would improve by 6-7 percentage points, helped by continued strong global growth for key products including the biologic for inflammatory bowel disease, Entyvio (vedolizumab).

In the fiscal year, the therapy for ulcerative colitis and Crohn's disease saw global sales surge by 34% to JPY269.2bn, helped by expanded US share in biologic-naïve patients. Velcade successor Ninlaro (ixazomib), a once-weekly proteasome inhibitor, was also strong, rising 34% to JPY62.2bn worldwide.

At the ex-Shire business, the application of Takeda distribution policies led to a one-off impact of "significantly decreased" days on hand of commercial product at wholesalers across the range. But more widely, the enlarged Takeda's results for the fiscal year ended March 31 were in line with the revised guidance that was issued earlier this month.

Consolidated revenue rose 19% to JPY2,097.2bn, of which JPY309.2bn came from Shire over the three months since completion, although operating and net profit fell, by 15% and 42% respectively to JPY205.0bn and JPY109.1bn.

Excluding the impact of Shire, legacy Takeda revenue was up 1% to JPY1,788.0, while operating profit rose 70% to JPY411.8bn and net profit by 67% to JPY312.9bn.

> The Shire transaction's integration costs of JPY154.0bn in the year will weigh heavily on reported profits

This strength extended to the forecast, with operating profit for instance expected to rise 39% to JPY654.0bn without Shire. Takeda noted that it does not expect the recent divestment of ex-Shire dry eye drug Xiidra (lifitegrast), to Novartis AG for up to $5.3bn, to have any material impact on the reported forecast, although this may be updated later. *(Also see "Takeda Offloads Xiidra As Expected, For $3.4bn Upfront To Novartis " - Scrip, 9 May, 2019.)*

Saroukos said Takeda expects its underlying core earnings margin to reach the mid-20s this fiscal year, rising to the mid-30s over the mid-term.

COST SYNERGY TARGET RAISED

Despite the loss outlook, CEO Christophe Weber described the results as "excellent" saying the integration was progressing as planned, and added that "we have also identified opportunities to realize greater cost synergies."

Saroukos noted that a review of such synergies and savings post-Shire completion had resulted in this target figure now being raised to around $2bn in annual recurring savings by the end of fiscal 2021, up from $1.4bn previously.

The CFO characterized margin improvement and cash generation as "superb" with consolidated free cash flow in the past fiscal year rising 5% to JPY378.1bn, around JPY200bn of which came from asset divestments.

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BI Bags Third Place For Humira Biosimilar in US With AbbVie Pact

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Boehringer Ingelheim GmbH will be able to launch its biosimilar rival to AbbVie Inc.'s Humira (adalimumab) in the US from 1 July 2023 after settling patent litigation with the originator, putting it ahead of many of its competitors.

The agreement marks the end of all Humira-related patent litigation in the US, after a host of other biosimilars sponsors previously settled with AbbVie, garnering market entry dates ranging from 31 January 2023 to 15 December 2023.

BI said the deal offered "a clear path to secure patient access" to its version, called Cyltezo, for which it received US Food and Drug Administration approval in August 2017. Moreover, the company noted, the entry date places Cyltezo "among the first to compete with Humira in the US".

Settlements agreed by AbbVie offer biosimilar entry dates of:

- 31 January 2023 for Amgen Inc.;
- 30 June 2023 for Samsung Bioepis Co. Ltd.;
- 1 July 2023 for BI
- 31 July 2023 for Mylan NV;
- 30 September 2023 for both Fresenius Kabi AG and Sandoz International GMBH;
- 20 November 2023 for both Momenta Pharmaceuticals Inc. and Pfizer Inc.; and
- 15 December 2023 for Coherus BioSciences Inc.

BI will pay royalties to AbbVie for licensing its Humira patents once Cyltezo is launched, with further terms of the settlement – which relates only to the US – remaining confidential.

"We are proud of the role we play in raising public awareness of biosimilars and being able to stimulate competition to bring more affordable treatment options to US patients," commented BI's US general counsel for legal and government affairs and public policy, Sheila Denton.

"This resolution provides clarity regarding the availability of Cyltezo and allows us to focus on serving patients who need to manage their chronic disease."

The settlement comes shortly after Allan Hillgrove, head of BI's human pharma business, told *Scrip* that the firm had abandoned biosimilars, other than Cyltezo in the US, where it intends to pursue an interchangeability designation.

AbbVie said the deal with BI was "an important settlement as it resolves all Humira-related patent litigation in the US and provides access for another biosimilar manufacturer seeking to enter the US."

"As an innovation-driven biopharmaceutical company," AbbVie said, "we will continue to develop novel cures for the toughest health challenges and rely on a robust patent system to protect that investment in innovation."

The originator has previously been criticized for the 'patent thicket' surrounding Humira, with BI itself having claimed that AbbVie engaged in a "pattern of pursuing numerous overlapping and non-inventive patents" to frustrate biosimilar competition.

News of the deal came as a bit of a surprise given that BI had repeatedly stated that it was committed to making Cyltezo available to US patients as soon as possible and was confident of a launch before 2023. However the German family-owned firm appears to have decided that a settlement with AbbVie makes more sense given the risks involved in litigation, as well as significant costs.

Recently, a US class action lawsuit was filed claiming that settlements around Humira constituted an "unlawful market division between the US and European markets." *(Also see "AbbVie's 'Unjustified' Humira Settlements Divide Market, Claims Class Action" - Generics Bulletin, 26 Mar, 2019.)*

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Pfizer's Smith On Building A Gene Therapy Business

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With Pfizer Inc. pivoting from seeking big M&A deals to grow to investing in internal R&D and smaller, earlier-stage transactions under new CEO Albert Bourla, its gene therapy unit is looking increasingly interesting as a crucible for innovation and potential growth.

The strategy has most recently seen it pay €45m for an option to buy France's Vivet Therapeutics, with its lead program in Wilson's disease and other earlier programs in liver-directed or -affected inborn errors of metabolism. *(Also see "Pfizer Buys Option For Vivet In Latest Gene Therapy Tie-Up" - Scrip, 20 Mar, 2019.)* And just last month, Bourla suggested that the company's investment in gene therapy manufacturing would see it become a "partner of choice" for other gene therapy developers. *(Also see "Pfizer's Business Development Transition: From "Revenues Now" To Pipeline Development" - Scrip, 30 Apr, 2019.)*

Robert Smith has been senior vice president of Pfizer's global gene therapy business since May 2016, having previously led business development activities for the company's R&D organization. He spoke to *Scrip* about the unit's strategy and the outlook for gene therapies as they move through approval and mature to the commercial space.

BUILD, BUY, PARTNER

Pfizer set up its gene therapy business unit in late 2014 and has adopted a "build, buy and partner" strategy to develop a portfolio of R&D candidates in four selected therapeutic areas of rare monogenic diseases in hematology, neuromuscular, CNS and inborn errors of metabolism.

Since then it has expanded its activities through a series of deals. Its pipeline now consists of seven preclinical and three clinical programs.The clinical programs are:

- Phase III pivotal study in hemophilia B (in partnership with Spark Therapeutics)
- Phase I/II study in hemophilia A (in partnership with Sangamo Therapeutics)
- Phase I/II study in Duchenne muscular dystrophy

"I would expect that we'd continue to be very active [in deal making]" as part of Pfizer's "aspiration to be a leading player", Smith told *Scrip*. At present the unit employs around 300 people, with many of those in manufacturing.

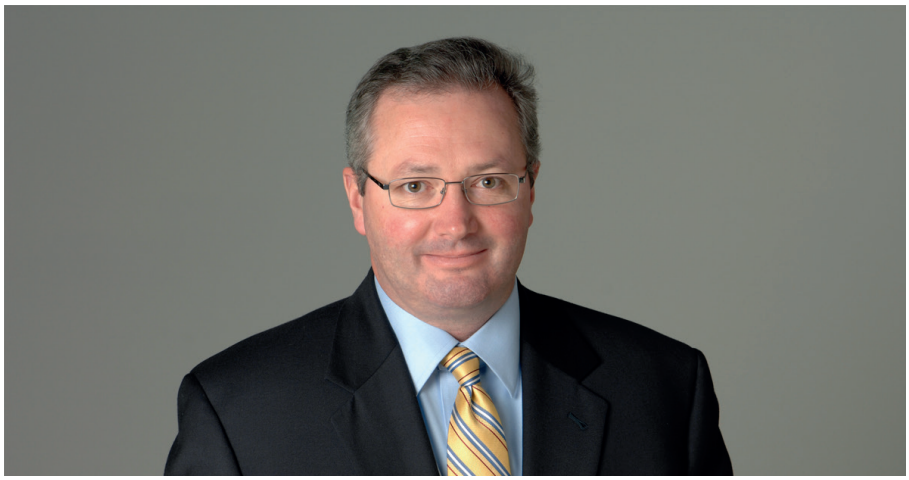
The company has three manufacturing sites in North Carolina: Kit Creek, which operates at research scale and research grade; Chapel Hill, with GMP and clinical scale, and Sanford, which is larger scale for late stage clinical and commercial. Sanford is its largest facility, employing around 100 people. Over the next two years it will expand and employ more than 300 people, Smith said. Pfizer also has an internal discovery group at its rare disease research unit in Cambridge, MA.

Smith views gene therapy as "probably the most exciting area of medicine to work in." But building a presence in an area from scratch is not easy. Relying heavily on diverse smaller companies brings its own set of business challenges, not least how to approach integration so that the strengths of nimble biotechs with deep expertise in a narrow field can be retained at the same time as applying the benefits of scale that a global pharma company can bring.

INTEGRATING EXTERNAL ACTIVITIES

"It's always a very delicate balance when you have partnerships and acquisitions in fields where a vast preponderance of the future value creation is through the human capital component of the transactions," Smith acknowledged. "We try very hard to make sure we leverage the best capabilities of both partners."

In practice this means that partners are entrusted with a "vast degree of responsibility" for completing their preclinical and early clinical work, before the pivotal program and manufacturing, regulatory and commercial activities are transferred to Pfizer. That's been the case with partners Spark Therapeutics Inc., Sangamo Therapeutics Inc. and now Vivet. "It's best to have our smaller but more expert partners do the preclinical work, file the IND, do the early studies, because it's not as resource intensive."



"These are the most constructive and productive interactions that industry and regulatory agencies have had in the whole history of the development of medicines." – Robert Smith

But as a global organization with operations in more than 100 countries, Pfizer is better placed to complete larger-scale, later-stage clinical development and commercialization activities. "Our aim is to advance medicines as quickly and completely as we can."

PREFERRED VECTOR

Pfizer has homed in on *in vivo* adeno-associated virus (AAV)-mediated gene addition or gene transfer for its delivery method.

While other companies, including bluebird bio Inc. with Zynteglo (LentiGlobin, autologous CD34+ cells encoding βA-T87Q-globin gene) and Novartis AG with Kymriah (tisagenlecleucel), are using lentivirus vectors in their gene therapies, Pfizer decided not to do so "largely because we felt that AAV was a more experienced type of gene addition delivery methodology," explained Smith. Furthermore, when AAV delivers a transgene to a transduced cell, the transgene is not integrated, whereas with lentivirus the transgene becomes part of the host cell's genetic material.

"When that cell potentially divides, depending on where the site of insertion of the transgene is, there's a risk that you could have some unintended side effects, and despite that other companies are using lentivirus, we just thought that was where [there were] some types of safety and regulatory risk that we would rather not take on, and that's why we built our platform on AAV."

Pfizer is also strategically avoiding *ex vivo* approaches in which an individual patient's cells are harvested, engineered whether through gene addition, deletion or editing, and re-infused into the patient, who must often undergo immune conditioning.

"That's a very complicated, individualized procedure as well as a kind of pharmaceutical product. With our *in vivo* AAV-mediated gene therapy, in contrast, each patient receives the same identical product at a dose that's appropriate for them and their particular disease. We have a much higher degree of uniformity in terms of manufacturing, quality control testing, etc. We just think that is more "pharmaceutical" in terms of a "product in a vial", which is very compatible with our existing infrastructure in terms of our manufacturing, regulatory, quality control, physical product distribution, administration to a patient, and so on," Smith explained.

The company is doing some work also in gene silencing, for example using RNAi approaches, principally in collaboration with partner Sangamo looking at using gene

editing tools "in the realm of *in vivo* AAV-delivered gene interference or gene editing approaches" for diseases where simple gene transfer or gene addition does not work. This could be diseases where the problem is not a missing or dysfunctional gene, but a "gain of function disease" in which the aim is to stop excess production of a protein, or the accumulation of a dysfunctional protein that causes disease.

REGULATORS' LEARNING CURVE

As a member of the executive committee of the Alliance for Regenerative Medicine (ARM)'s board of directors, Smith is involved in working across the different stakeholder groups in the field – from academia to biotech and pharma companies and from patient groups to regulatory bodies.

He noted how genetic medicine is breaking new frontiers not only for drug developers but also for regulatory authorities, but despite the latter's lack of experience in the area he is optimistic. He commended the European Medicines Agency and the US Food and Drug Administration for "how collaborative and interactive they have evolved to be in a very short period of time". EMA executive director Guido Rasi, recently departed FDA commissioner Scott Gottlieb and acting FDA commissioner Norman Sharpless "have all looked at the advanced therapeutics medicinal product space as something that's a challenge collectively" and recognized that "they know that [industry] won't be successful unless they have the expertise, and vice versa."

Smith added: "These are the most constructive and productive interactions that industry and regulatory agencies have had in the whole history of the development of medicines, so it's very exciting."

VALUE CONUNDRUM

It's not just the regulatory pathway that must be forged, though. One significant uncertainty still surrounding gene and cell therapy is the where the balance between price, value and affordability will settle.

With relatively few treatments so far commercialized, every late-stage treatment approaching market is the subject of much speculation and analysis regarding how much it will cost and how payment will be structured.

"I think we're at a tip of the spear moment, now that we have just a handful of these types of product that have received regulatory approval and are going through the early stages of commercialization. We're seeing that there are certainly some challenges. Some people would describe them as obstacles or barriers, but we more optimistically look at them as challenges that need to be tackled so that you can have broad access," Smith said.

That is not to underestimate the importance of tackling these challenges: "We don't want to do anything with such a high degree of innovative science and medicine that is going to be a detriment for patients just because we can't solve some of these other policy and commercial issues."

Noting that "the current access pricing and reimbursement environment doesn't really have the mechanical aspects of how best to value a one-time treatment and how best to make them affordable for patients," Smith said that Pfizer was working with organizations like ARM to encourage "the conversations and the required legislative and policy changes" that will facilitate new options like value-based contracting with performance guarantees, "where there's a shared risk for patients, payers and industry sponsors."

These conversations are happening with private and public payers alike.

TALKING TO ENGLAND'S NHS

For example, in January ARM CEO Janet Lambert, Smith and other directors of ARM met the chair of NHS England, Lord Prior, "in a very open forum for a few hours to just talk to him about what we're trying to achieve in this space, why we need changes in how an organization like NHS England implements policies and procedures [...] and just thinking through what needs to change."

Even in a single-payer system like the NHS, such changes are complex to bring about, so "we're highly engaged in leading these conversations: we want to be in the room, fully engaged, making sure that we're doing our very best to change the overall ecosystem for delivering and paying for these types of medicines," he explained.

In the US, Spark Therapeutics' Luxturna (voretigene neparvovec), for a rare inherited blindness, is priced at $850,000 for both eyes. Among other expected-to-be one-time gene therapies approaching approval decisions, there has already been discussion on specific pricing. In February BioMarin Pharmaceutical Inc.'s CEO Jean-Jacques Bienaimé hinted that its Phase III hemophilia A gene therapy could be priced at around $2-3m, while there have been public debates over the likely pric-

Patient Input For Maximum Impact

"We have a culture that we call "patients first", and every activity on our end-to-end spectrum of gene therapy is fundamentally focused on what's best for patients."

As Pfizer's SVP global gene therapy business explained, this means partnering with patient advocacy groups and foundations on a local, country level as well at a global level, to incorporate patient input into clinical study protocol design and ensure that endpoints that "really matter to patients" are included. "There's a component of clinical endpoints that you need to measure for regulatory purposes – because regulatory authorities want to make sure that the medicines we're developing are safe and effective – but there are certain endpoints that are more relevant to patients in terms of their hour-to-hour, day-to-day, week-to-week, month-to-month living with their disease. You can have an endpoint that's relevant for a regulatory authority but if it's not important for a patient we feel like we're not doing them full justice with the value of our medicines, so we incorporate patient input into the protocol design."

Pfizer also has patient representatives on the external monitoring committees for all of its clinical trials.

"And then throughout the continuum of research, clinical development, commercialization, we are very close with all of the patient groups, making sure that we are developing products that have very meaningful impact to them, because at the end of the day this is why we're doing all this research, development, manufacturing activity – it's to bring the maximum patient impact."

Pfizer's Gene Therapy Activity: A Timeline

Pfizer has been active in gene therapy for less than five years. Here's how it has built up its unit.

December 2014

Pfizer establishes gene therapy platform, appointing Michael Linden of Kings College London to lead research (on secondment for two years).

December 2014

Pfizer signs deal with Spark Therapeutics to collaborate on AAV gene therapy for hemophilia B. Spark is responsible for soon-to-start Phase I/II trials. Pfizer is responsible for Phase III trials and global commercialization and manufacturing.

January 2016

Pfizer invests in 4D Molecular Therapeutics, gains option on AAV vectors for cardiac disease targets.

January 2016

Pfizer acquires 22% of Bamboo Therapeutics for $43m.

June 2016

Pfizer and Spark present positive early data from Phase I/II trial of SPK-9001 in hemophilia B.

August 2016

Pfizer acquires Bamboo Therapeutics for $150m up front with milestones worth $495m. Includes Phase I/II recombinant AAV gene therapy manufacturing facility and preclinical/Phase I assets in DMD, Friedrich's ataxia, Canavan disease, giant axonal neuropathy.

May 2017

Pfizer enters collaboration with Sangamo Therapeutics for hemophilia A gene therapy, including SB-525. Pfizer pays $70m up front with milestones worth $475m.

August 2017

Pfizer selects Sanford NC site for clinical and commercial scale gene therapy manufacturing site.

January 2018

Pfizer signs deal with Sangamo for zinc finger protein transcription factor technology in gene therapy for ALS and frontotemporal lobar degeneration. $12m up front with milestones worth $150m.

July 2018

Pfizer assumes responsibility for Spark's hemophilia B candidate SPK-9001, now named fidanacogene elaparvovec. Begins Phase III study.

March 2019

Pfizer acquires a 15% interest in Vivet Therapeutics for €45m. Has option to acquire firm for up to €560m in total. France-based Vivet is working on liver-directed AAV gene therapy for Wilson's disease (VTX-801) and other conditions. Vivet is responsible for Phase I/II trial.

April 2019

Pfizer and Sangamo announce positive Phase I/II interim data on hemophilia A gene therapy SB-525.

ing and fair value of Novartis's Zolgensma (onasemnogene abeparvovec) for spinal muscular atrophy, with ranges varying from less than $1m to $5m. Commenting on how to view fair value for a hypothetical one-time gene therapy for hemophilia, Smith pointed out the annual cost of replacement factor treatment for such patients could be around $200,000-300,000 per year (although this could vary widely depending on dose, product, frequency of use, whether they use it prophylactically or on demand). But assuming an illustrative example of $200,000-300,000 cost per year, then over a decade that would come to $2-3m, rising commensurately for every year of the patient's life. "Just assuming that a company had a $2m price tag for its gene therapy that was paid for over five or 10 years but then beyond that they didn't receive any subsequent compensation for the therapy: healthcare systems in the second, third, fourth decade are going to save significant amounts of money."

But "where the conversation gets really difficult is around who's going to bear the risk in the case that the gene therapy only works for five years, not the expected 20 or 30 years," Smith acknowledged.

WILLING RISK SHARERS

"That's why we, and other sponsors, are very willing to engage in risk-bearing arrangements where, if the therapy doesn't last for, say, 10 years, then we as industry participants wouldn't get paid, or there would be some kind of rebating.

"Industry's very willing to step up to the plate and take on more risk, but it requires a lot of changes in the payer environment and also some changes in the healthcare delivery environment where mechanisms also need to be put in place to appropriately monitor and test patients to see whether the therapy works and that payers are satisfied with the outcomes of those tests and monitoring, and that industry is comfortable.

"There is a lot of complexity in how to implement this, and with these early products and subsequently with products that we're expecting to bring to market, we're very engaged in trying to help shape the environment to be more conducive to these types of novel business practices, and partnership with regulatory agencies and payers."

Pfizer and others in the field are very proactive in this sphere because after many years gene therapy technology is emerging as a viable treatment for patients, and industry believes it has a lot of potential for an ever-widening spectrum of diseases.

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Bluebird Lays Some New Eggs, But They'll Take Time To Hatch

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While bluebird bio Inc. is gearing up to launch its first commercial drug – the gene therapy Zynteglo for transfusion-dependent beta-thalassemia (TDT) – shortly in Europe, the company is building out its pipeline with a focus on immuno-oncology and rare diseases.

Bluebird held an analyst day in New York City on 9 May to highlight commercial plans for Zynteglo (previously LentiGlobin) and programs it is advancing into late preclinical and early clinical development. The company unveiled four immuno-oncology programs and one rare disease program that it is advancing in preclinical and early clinical development.

The pipeline is innovative but early, so the near-term value of the company is tied to the launch of Zynteglo in Europe and eventually the US, likely next year. Zynteglo was approved by Europe's Committee for Medicinal Products for Human Use in March and is awaiting formal action by the European Commission. *(Also see "Bluebird's BCMA CAR-T Sings At ASCO, But How Will It Fly In Early Multiple Myeloma?" - Scrip, 2 Jun, 2018.)*

As the commercial portfolio and the pipeline grow, CEO Nick Leschly said the company is exploring ways to share the development risks and rewards.

"We definitely have a privileged set of programs and technologies and capabilities, and there is a point where we can't do it all," Leschly said in an interview after the presentation. "Now we are approaching that point where we are dangerously close to that."

"There are probably things that we can't do on our own or that we are going to have to allow other people to do," he added.

While bluebird developed Zynteglo on its own and is moving forward with commercialization independently, the company partnered the chimeric antigen receptor T-cell (CAR-T) therapy bb2121, targeting B-cell maturation antigen (BCMA), with Celgene Corp. in 2013, now to be partnered with Bristol-Myers Squibb Co. The drug is on track for filing later in 2019.

Bluebird has a goal to file for two additional drug approvals through 2022, and to file one to two investigational new drug applications with FDA in 2020 and each year beyond.

"THE CHIPS WILL FALL WHERE THEY MAY"

Bluebird is growing but one question is if it can remain independent, given that gene therapy and immuno-oncology are hot areas of business development. Roche announced in February plans to buy the gene therapy developer Spark Therapeutics Inc. for $4.8bn, or $114.50 per share.

Leschly admitted he frequently gets asked about bluebird being a takeout target, but said he tries to stay focused on moving the business forward.

"I don't spend a lot of time thinking about it and neither does my board and hopefully neither do any of the employees," he said. "It's obviously there, and it's something, but it's not something I can control." A small biotech's focus and nimbleness are part of what he believes delivers a high level of innovation.

"It's not that I'm against small company/big company. It's just let's figure out what each of us is really good at and then go do it," he said. "The chips will fall where they may."

The company's stock price is up 28% from the beginning of the year, opening at $125.32 on 14 May, with a current market capitalization of $7bn.

Half of the investor presentation was devoted to addressing the upcoming commercial launch of Zynteglo in Europe and the company's goal of rolling out a unique five-year installment payment model for what is expected to be a seven-figure therapy. At the J.P. Morgan Healthcare conference in January, Leschly laid out the payment scheme and set a price cap of $2.1m on the cost of Zynteglo. *(Also see "J.P. Morgan Notebook Day 2: Biogen, GSK, Bluebird, Roche, Amgen, Biohaven, Lilly And FDA's Gottlieb" - Scrip, 9 Jan, 2019.)*

But the company did not provide any update on pricing for Zynteglo and said market access and pricing would need to be worked out on a country by country basis, with an initial focus on Germany, Italy, the UK and France.

NEW ONCOLOGY AND RARE DISEASE PROGRAMS

The other half of the meeting was dedicated to the pipeline and unveiling interesting new opportunities, all of which are at early stages of development, beyond ongoing programs in multiple myeloma, sickle cell disease and cerebral adrenoleukodystrophy.

In oncology, bluebird is focused on advancing next-generation CAR and TCR technologies. Among the programs outlined by bluebird is a program moving into clinical testing, where Merkel cell polyomavirus TCR-engineered autologous T cells will be combined with Pfizer Inc.'s PD-L1 inhibitor *Bavencio* (avelumab) and studied in a Phase I/II single-arm study in Merkel cell carcinoma patients with the Fred Hutchinson Cancer Research Center.

Another program is a preclinical T-cell immunotherapy approach that would address some of the challenges specific to treating acute myeloid leukemia (AML), where the five-year survival is still around 25%. To address issues like heterogeneity, bluebird is leveraging a technology that allows T-cells to target multiple antigens on the surface of cancer cells as well as its own proprietary Dimerizing Agent Regulated Immunoreceptor Complex (DARIC) platform that could allow engineered T-cell activity to be turned on or off in vivo. The company announced a partnership with Seattle Children's Research Institute to study the technology in exploratory development.

Chief Scientific Officer Philip Gregory called the partnership an "inside-out collaboration." As he explained, "most of the time when you think about academic collaborations, it's the company buying a technology or licensing technology out of academia into the company. We're actually sort of doing it the other way around."

"We've got an internal technology we're really excited about and we're partnering here for translational expertise and speed and flexibility," he said.

A MAGE-A4 TCR developed in collaboration with Medigene AG is expected to enter the clinic for solid tumors in 2020. Lastly, a preclinical program is focused on next-generation technologies for diffuse large B-cell lymphoma (DLBCL) combining dual-targeting directed to two novel antigens, a unique CAR construction to enhance T cell activation, and gene editing for potential potency and durability enhancements.

In its rare disease pipeline, bluebird highlighted a new program for mucopolysaccharidosis (MPSI), also known as Hurler syndrome. It's only been tested in animal models, but the company believes it has developed a technology that could deliver genetically-modified hematopoietic stem cells across the blood-brain barrier, overcoming limitations of potential enzyme replacement therapies. The company said lessons learned from its ongoing work with LentiGlobin for sickle cell disease and beta thalassemia have helped to inform the company's work in the area.

As CEO Leschly explained to *Scrip* after the presentation, "It's not about any one of the programs. It's about how the learnings from that program adds a Lego piece to our overall capability because now it gets really powerful."

"There's no one else that has that kind of depth in our field," he said. "There's lots of one-offs, lots of competition, lots of single programs." But bluebird will need to deliver commercial revenues from the launch of Zynteglo, get bb2121 to market and deliver more clinical results if it is going to keep investors enthusiastic about the long-term opportunities.

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What Late-Breakers To Look Out For At ASCO 2019

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ASCO drew back the curtain on 15 May on what to expect at its annual meeting later this month, providing a sneak peek as to what will be presented during its late-breaking sessions. Drawing on a ASCO preview report from Pharma Intelligence's Biomedtracker and Datamonitor Healthcare, here is a look at the most notable studies for the industry that will be in the spotlight at the Chicago meeting from 31 May to 4 June.

ASTRAZENECA'S POLO LYNPARZA FOR PANCREATIC CANCER

Just how effective AstraZeneca PLC/Merck & Co. Inc.'s market-leading leading PARP inhibitor Lynparza (olaparib) is in potentially its third indication – pancreatic cancer – will be seen when the first numerical data from the Phase III POLO trial are presented (LBA4).

The companies announced in February that the POLO trial met its primary endpoint of improving progression-free survival (PFS) in BRCA-mutated pancreatic cancer patients whose disease had not progressed on first-line chemotherapy. At that time, AstraZeneca's global medicines lead for Lynparza, Greg Rossi, said a 2020 approval was on track, based on the high unmet need in this indication.

The Biomedtracker/Datamonitor analysts commented: "Assuming no major red flags are raised in the numerical data, Lynparza is likely to become not only the first PARP inhibitor approved for pancreatic cancer, but also the first targeted therapy approved for pancreatic cancer since Tarceva was approved in 2005."

Lynparza received US orphan drug designation for pancreatic cancer in 2018, and AstraZeneca plans to file for approval in the second half of 2019.

Lynparza is ahead of its rival PARP inhibitors Pfizer Inc.'s Talzenna (talazoparib) and Clovis Oncology Inc.'s Rubraca (rucaparib), both in terms of sales and development stage in pancreatic cancer. Talzenna and Rubraca are both in Phase II for pancreatic cancer, while GlaxoSmithKline PLC/Tesaro Inc.'s Zejula (niraparib) does not appear to be in clinical development for this indication. GSK moved into the space with the bid for Tesaro last December, and intends to expand the drug into multiple tumor types. *(Also see "GSK Embraces PARP Promise With Tesaro Buy" - Scrip, 3 Dec, 2018.)*

In 2018, AstraZeneca reported Lynparza sales of $647m, representing year-over-year growth of 118% (116% at CER), driven by expanded use in the treatment of ovarian cancer and the its first breast cancer approvals. The recent approval of Lynparza as a first-

line treatment of patients with BRCAm ovarian cancer in the US, which was received earlier than anticipated, is expected to support further expanded use. *(Also see "First-Line Ovarian Cancer Approval Solidifies Lead For AstraZeneca's Lynparza " - Scrip, 19 Dec, 2018.)* This was based on the highly positive SOLO-1 study, which showed that maintenance therapy with the PARP inhibitor extended PFS by three years in this setting. *(Also see "Stellar Survival Data For AZ's Lynparza Hailed At ESMO" - Scrip, 22 Oct, 2018.)*

CAN KISQALI GO ONE BETTER IN BREAST CANCER?

In a CDK4/6 inhibitor showdown, observers will be keen to see if Novartis AG can up the ante in first-line metastatic HR+/HER2- breast cancer by reporting the first significant benefit in overall survival (OS) with a drug from this class in its latest update from the Phase III MONALEESA-7 trial of Kisqali (ribociclib) (LBA1008).

Kisqali and Eli Lilly's Verzenio (abemaciclib) have been chasing Pfizer's class-leading Ibrance (palbociclib) in this lucrative indication, and an OS benefit would give Kisqali a competitive boost.

Ibrance, which had a two-year head start in the market, narrowly missed its OS endpoint in postmenopausal metastatic HR+/HER2- patients that progressed on prior endocrine therapy in the Phase III PALOMA 3 trial. "However, in that trial Ibrance did significantly improve OS in a subgroup of patients that remained sensitive to prior endocrine therapy despite progression," noted the Biomedtracker analysts.

MONALEESA-7 is testing the drug in premenopausal patients, who generally have a poorer prognosis. The drug was first approved in 2017 for first-line use in postmenopausal patients, and its indication was expanded late last year in the US and EU to include pre and perimenopausal women based on the MONALEESA-3 and -7 studies. Kisqali's first-quarter sales grew by 115% to $91m driven vy this expanded label, the company said. Such sales, however, are by still a far cry from Ibrance's revenues of $1.13bn over the same timeframe.

BOOST EXPECTED FOR XTANDI'S MOVE TO EARLIER PROSTATE CANCER

In prostate cancer, Biomedtracker/Datamonitor are expecting to see positive OS data from the ANZUP ENZAMET trial, a global, academically sponsored study testing Pfizer/Astellas Pharma Inc.'s androgen receptor inhibitor Xtandi (enzalutamide) and standard androgen-deprivation therapy (ADT) against ADT alone in metastatic hormone-naïve prostate cancer patients (LBA2).

"Positive OS results from this trial are likely given the LBA [late-breaker abstract] status, but also because of the recent trend of next-generation hormone therapies demonstrating strong efficacy in earlier prostate cancer patient segments," the analysts said. Xtandi has already demonstrated a 61% reduction in radiographic progression or death over ADT in a similar patient group in the Phase III ARCHES trial; PFS and OS results are not mature. *(Also see "Pfizer, Astellas Accelerate Xtandi's Timeline In Early Prostate Cancer" - Scrip, 23 Aug, 2018.)*

"Strong survival results from ARCHES, with a boost from ENZAMET, will be important as competing next-generation hormone therapies such as Johnson & Johnson's Zytiga and Erleada are also sliding up the treatment algorithm."

Zytiga (abiraterone acetate) was approved for use in metastatic high-risk castration-sensitive prostate cancer, a somewhat similar patient population to that of the ENZAMET trial, in February 2018, and Erleada (apalutamide) is under review by the FDA for metastatic castration-sensitive prostate cancer based on the Phase III TITAN trial, which met both PFS and OS primary endpoints. *(Also see "Erleada Keeps Pace With Xtandi After Positive TITAN Study" - Scrip, 31 Jan, 2019.)*

Also in the mix in this area is Bayer's investigational androgen receptor antagonist darolutamide, which is awaiting EU and US approval in non-metastatic castration-resistant prostate cancer.

CAN KEYTRUDA MAKE ANY HEADWAY IN FRONT-LINE GASTRIC CANCER?

Merck & Co's all-conquering PD-1 inhibitor Keytruda (pembrolizumab) has already been approved for PD-L1-positive gastric cancer patients in the third-line or later, but ASCO will see the presentation of the drug's initial Phase III data in the first-line setting (LBA4007).

Merck & Co has already announced that the Phase III KEYNOTE-062 trial produced mixed results. While Keytruda monotherapy was found to be non-inferior to chemotherapy in terms of overall survival in PD-L1-positive patients, the combination of Keytruda plus chemotherapy was not found to be any better than chemotherapy.

"It is likely that the numerical data presented [at ASCO] will help shed some light on potential reasons for this outcome. Furthermore, the data may help better define the drug's chances of success in its other Phase III trials in the first-line setting, KEYNOTE-859 and KEYNOTE-811," the analysts said.

Keytruda had already disappointed in the Phase III KEYNOTE-061 in second-line advanced gastric cancer in late 2017, missing both OS and PFS endpoints, but that failure had little commercial impact as it did not lead to any change in the product's labelling despite it coming after an accelerated US approval in third-line PD-L1-positive advanced/metastatic gastric cancer (for use after fluoropyrimidine- and platinum-containing chemotherapy and, if appropriate, HER2/neu-targeted therapy). *(Also see "Commercial Fallout From Merck's Failed Keytruda Gastric Cancer Trial May Be Limited" - , 15 Dec, 2017.)*

Rivals Pfizer/Merck KGaA's Bavencio (avelumab) also failed to significantly improve OS in a Phase III third-line gastric cancer JAVELIN Gastric 300 study in late 2017. *(Also see "Pfizer/Merck KGAA's Bavencio Gastric Cancer Failure Not As Bad As It Seems" - Scrip, 28 Nov, 2017.)*

ENFORTUMAB VEDOTIN: A NEW OPTION FOR BLADDER CANCER

Details are keenly awaited for Seattle Genetics Inc. and Astellas Pharma's EV-201 study of their antibody-drug conjugate (ADC), enfortumab vedotin, in locally advanced or metastatic urothelial cancer (LBA4505).

Top-line results for EV-201 released in March 2019 showed an impressive 44% overall response rate in urothelial cancer patients that had previously received treatment with both platinum-based chemotherapy and a PD-1/PD-L1 inhibitor. The duration of responses was not given but reported to be consistent with

that in a previous Phase I study (EV-101; estimated median PFS and OS were 5.4 months and 12.5 months), and the most common treatment-related adverse events included fatigue, alopecia, decreased appetite, rash and peripheral neuropathy. *(Also see "Enfortumab Vedotin Impresses In Urothelial Cancer After Chemo, Immunotherapies" - Scrip, 28 Mar, 2019.)*

PD-1/PD-L1 inhibitors have become an important part of bladder cancer treatment, but with limited treatment options for patients that relapse or are refractory to these agents, there is an increasing need for effective drugs in the post-PD-1/PD-L1 setting, the analysts said. "We expect more detailed results to be shown at the ASCO presentation and will be looking for consistency with the earlier readout."

Astellas and Seattle Genetics plan to submit data from the Phase II EV-201 trial to support US registration, while results from the Phase III EV-301 trial will be used for global filings.

Enfortumab vedotin appears to be the only ADC targeting nectin-4, a transmembrane antigen expressed in several tumors including urothelial cancer. Astellas has previously estimated the peak potential size of the market for the anticancer at JPY50-100bn ($500m-$1bn).

The product comprises a nectin-4 targeting antibody attached to a microtubule disrupting agent, monomethyl auristatin.

WHERE IT WENT WRONG FOR LILLY'S LARTRUVO IN SARCOMA

Finally, interested parties will be able to pick over the bones of Eli Lilly's failed Phase III ANNOUNCE study of Lartruvo (olaratumab), which led to the withdrawal of the sarcoma therapy from the market. The study provides a cautionary tale for regulators on the of the risks of issuing quick conditional approvals on the back of early-stage promise that withers in Phase III (LBA3).

Lilly will present the first numerical results from ANNOUNCE, which tested it in combination with doxorubicin against placebo and doxorubicin in patients with advanced or metastatic soft tissue sarcoma but did not meet the primary endpoints of OS either in the full study population or in the leiomyosarcoma (LMS) subgroup. *(Also see "Lartruvo Phase III Fail Rocks Lilly Oncology Plans" - Scrip, 21 Jan, 2019.)*

The failure, announced in January, and Lartruvo's subsequent revocation of marketing authorization in all geographies have left Lilly facing associated charges expected to be 0.13 cents per share in 2019. Until then, the product had been a decent contributor to Lilly's balance sheet, posting sales of $203m in 2017 and $305m in 2018, and consensus forecasts were $500-$600m by 2022-2023.

"These results will provide much needed clarity following the January 2019 news that the study failed to impart a survival benefit despite the positive results in the Phase I/II JGDG trial that were used for accelerated approval in a similar patient population," the analysts said.

Lartruvo, a platelet-derived growth factor receptor alpha (PDGFR-α) blocking antibody, was approved in late 2016 the US under an accelerated procedure for use in combination with doxorubicin, for the treatment of adult patients with soft tissue sarcoma with a histologic subtype for which an anthracycline-containing regimen is appropriate and which is not amenable to curative treatment with radiotherapy or surgery.

Lilly has not given up on the drug, however. It has trials ongoing in advanced or metastatic soft tissue sarcoma including a study testing it in combination use with Merck & Co. Inc.'s Keytruda, and it is also testing it in a Phase I/II trial in combination with nab-paclitaxel and gemcitabine in first-line metastatic pancreatic cancer.

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Five Companies To Watch This ASCO

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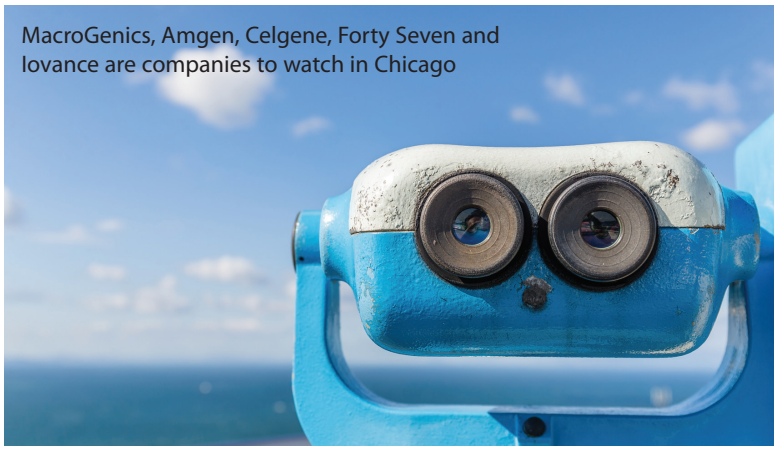
The ASCO abstract drop on 15 May gives a heads up as to which companies will be attracting attention at the meeting in Chicago from 31 May to 4 June. Here we take a look at five firms highlighted by Biomedtracker and Datamonitor Healthcare as being the ones to watch.



MacroGenics, Amgen, Celgene, Forty Seven and Iovance are companies to watch in Chicago

MACROGENICS PHASE III SOPHIA STUDY OF MARGETUXIMAB IN BREAST CANCER

The extent of the benefit given by MacroGenics Inc.'s investigational, immune-enhancing monoclonal antibody margetuximab in heavily pre-treated HER2+ breast cancer patients in the Phase III SOPHIA study is getting a largely positive response.

Expectations had been high following the company's announcement in February of a significant 24% reduction in risk for progression or death, with a trend in favor of overall survival (OS) progression-free survival (PFS) data in SOPHIA, which tested margetuximab with chemo versus Roche's pioneering HER2 therapy Herceptin (trastuzumab) with chemo in women who already had been treated with Herceptin, as well as Roche's other HER2-targeted therapies Perjeta (pertuzumab) and Kadcyla (ado-trastuzumab emtansine). The Rockville, MD-based firm's share price on the NASDAQ shot up by 130% at the time as a major overhang on the stock was lifted.

MacroGenics said it recently had a pre-BLA meeting regarding margetuximab with the US Food and Drug Administration (FDA). The company plans to submit a US biologics license application (BLA) in the second half of 2019.

The fuller data to be presented at ASCO show the median PFS of patients treated with margetuximab and chemotherapy was 5.8 months compared with 4.9 months in patients treated with trastuzumab and chemotherapy (hazard ratio [HR]=0.76; 95% CI: 0.59-0.98; p=0.033).

But the product looks much more effective in approximately 85% of patients carrying the CD16A 158F allele, a pre-specified exploratory subpopulation in the study. Here PFS was prolonged by 1.8 months in the margetuximab arm compared with the trastuzumab arm (6.9 months versus 5.1 months; HR=0.68; 95% CI: 0.52-0.90; p=0.005).

The objective response rate (ORR), a secondary endpoint, was 22% for margetuximab (95% CI: 17.3-27.7%) compared with 16% for trastuzumab (95% CI: 11.8-21.0%).

At the time of the primary PFS analysis (data cut off 10 October 2018), OS data based on 158 events were immature. The median OS at that time was prolonged by 1.7 months in patients treated with margetuximab and chemotherapy compared with patients treated with trastuzumab and chemotherapy.

For the exploratory CD16A 158F allele subpopulation, the median OS was prolonged by 6.8 months in the margetuximab arm compared to the trastuzumab arm, a "whopping improvement", BTIG analysts said in a 15 May analyst note.

A second pre-specified interim OS analysis based on 270 events is due to be conducted in the second half of this year, with the final pre-specified OS analysis planned after 385 events have accrued, which is projected to be completed in 2020.

"The OS effect could fluctuate, but based on landmark trials like CLEOPATRA (Perjeta + Herceptin vs. Herceptin in earlier mBC), a greater than two-fold effect in OS vs PFS seems reasonable," the BTIG analysts continued.

Biomedtracker/Datamonitor analysts agreed these were encouraging updated results. "Although the absolute benefit may seem minimal, the relative improvement in PFS and trending OS increase are decidedly positive given there are no standard regimens for these patients and a Herceptin retreatment comparator is a good approximation for real-world treatment practice."

However, they note that there is competition on the horizon. "This lack of available treatments may not last too much longer, however. AstraZeneca PLC and Daiichi Sankyo Co. Ltd. are moving toward regulatory submission of their HER2-targeted ADC, trastuzumab deruxtecan, after it met its primary endpoint in the Phase II DESTINY-Breast01 trial, although the full dataset was not disclosed."

But other analysts were less enthused with the SOPHIA data. Those at Credit Suisse said in a 15 May investor note that the abstract "served up more questions than answers." The analysts said the less than one month PFS improvement over Herceptin in the overall population was "weaker than anticipated"; they had been hopeful before the abstract drop of a net mPFS benefit slightly below two months. "Physician experts with whom we have been consulting were hoping for a benefit of at least two months compared to Herceptin, which they would consider practice changing in this third-line setting of patients who progressed on Herceptin/Perjeta/Kadcyla."

They acknowledged that the CD16A 158F data were "more intriguing … suggesting that CD16A 158F could be a biomarker of significant importance for pretreated HER2+ patients." However, there is not yet a commercializable form of the diagnostic test.

FIRST CLINICAL DATA FOR AMGEN'S AMG-510

Amgen Inc. is revealing the first in-human data for its small-molecule inhibitor of KRASG12C, dubbed AMG-510, in patients with locally-advanced or metastatic KRASG12C mutant solid tumors.

AMG-510 has been well tolerated at the dose levels tested and has shown antitumor activity when administered as monotherapy to patients with advanced KRASG12C mutant solid tumors. Maximum tolerated dose has not been determined, and enrollment into the dose exploration cohort is ongoing.

The specific KRASG12C mutation accounts for approximately 12% of all KRAS mutations across tumor type, Amgen said, and it is exploring the potential of KRASG12C inhibition across a broad variety of tumor types.

"While it may be too early to fully put these results into context, the first-in-human data for AMG 510 shown here are noteworthy given the high unmet need for effective targeted agents for KRAS mutant patients," said the Biomedtracker/Datamonitor analysts. KRAS mutations are one of the most frequently observed aberrations in NSCLC and colorectal cancer, but efforts to specifically target mutant KRAS have not yielded an approved KRAS-targeted agent to date.

"We believe that two out of six NSCLC patients experiencing a partial response is encouraging, given that most patients (17/22) enrolled in the study so far were treated with more than three prior lines of therapy. However, we are cautious about over-interpreting the response rate so far given the small number of patients evaluated and the fact that the maximum tolerated dose was not determined at the time of the data cut off."

The analysts said they would now watch for any changes to the efficacy signal, as well as further details on the safety of the drug at the recommended Phase II dose. Amgen disclosed that it was able to determine a target dose, and will move forward with additional trials, including a study in combination with a checkpoint inhibitor.

Morgan Stanley analysts added in a 15 May research note, "While we acknowledge that the data is early, we find it encouraging that there appears to be a signal in NSCLC at the low doses evaluated in the initial dose cohorts. The initial safety profile also appears clean…"

Amgen is also presenting additional early-stage pipeline data for its bispecific T-cell engager (BiTE) across hematologic malignancies and solid tumors, including the first look in prostate cancer. Updated results will also be presented from a Phase I dose escalation study evaluating investigational AMG 420, a B-cell maturation antigen (BCMA)-targeting BiTE molecule, in patients with relapsed or refractory multiple myeloma.

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CONTINUED FROM PAGE 16

CELGENE'S NEW THALIDOMIDE ANALOG IN MULTIPLE MYELOMA

Celgene Corp. is to present the first positive results for the orally-available thalidomide analog (IMiD) cereblon modulator, iberdomide (CC-220), in relapsed/refractory multiple myeloma in combination with dexamethasone. Together the drugs showed favorable efficacy and safety in heavily pretreated patients who had failed multiple prior therapies.

Iberdomide, an immunomodulatory compound, is also under development for systemic lupus erythematosus (SLE). Like Celgene's older products lenalidomide (Revlimid) and pomalidomide (Pomalyst), iberdomide binds to cereblon but with a higher affinity. Data from a Phase IIa trial were disclosed in 2017 for SLE, but these are the first data for multiple myeloma. *(Also see "Celgene's Terrie Curran On Building, Broadening The I&I Franchise" - Scrip, 4 Apr, 2018.)*

"The 31% overall response rate in this dose escalation trial matches the response rate seen for NIMBUS, a pivotal Phase III trial that evaluated Pomalyst combined with low dose dexamethasone in patients with refractory multiple-myeloma who have failed at least two prior therapies with both bortezomib and lenalidomide," the Biomedtracker/Datamonitor analysts said.

The safety profile at this point seems more favorable than that reported for Pomalyst in the NIMBUS trial with regards to grade 3/4 neutropenia (26% vs 48%), thrombocytopenia (11% vs 22%), and fatigue (0% vs 5%). "Both Revlimid and Pomalyst carry black box warnings on their labels for venous thromboembolism, a larger trial will be required to determine if this is also seen with iberdomide."

Celgene is also down to present the first efficacy results for liso-cabtagene maraleucel (liso-cel) in mantle cell lymphoma from the Phase I TRANSCEND NHL 001 study, which the Biomedtracker/Datamonitor analysts concluded showed tolerable toxicity and had clinical activity.

Celgene is due to file a BLA with the FDA for liso-cel as a treatment for relapsed or refractory diffuse large B-cell lymphoma (DLBCL) in the second half of 2019. *(Also see "Celgene Gives Reassurances That Key Products And Programs Remain On Track" - Scrip, 31 Jan, 2019.)*

FORTY SEVEN'S "NEXT-GENERATION" IO LOOKS PROMISING

The Menlo Park, CA-based Forty Seven Inc., which is developing "next-generation" IO treatments, is to present promising initial data from its first-in-class anti-CD47 antibody Hu5F9-G4 (also called 5F9) as a monotherapy and in combination with azacitidine for the treatment of acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS).

The early results for the anti-CD47 antibody Hu5F9-G4 combined with azacitidine in newly diagnosed AML not suitable for intensive chemotherapy are encouraging. "With 50% of AML patients (5 of 10) achieving a CR/CRi response, this compares to recently approved Venclexta which reported a 66% CR/CRi response rate when combined with azacitidine in the same AML setting," said Biomedtrakcer/Datamonitor Healthcare analysts. "This is the second Hu5F9-G4 trial to show signs of efficacy; at ASCO 2018, Forty Seven presented encouraging results for Hu5F9-G4 combined with rituximab in DLBCL."

Initial data from 10 relapsed/refractory AML/MDS patients and 24 naive patients are included in the abstract. One of the 10 patients had a response to monotherapy in the refractory setting while five had a CR/CRi with 5F9 combined with azacitidine in AML and three of five had a CR/CRi in MDS.

"Given that azacitidine monotherapy has a typical response rate of 15-25% in naïve patients, we view the 50-60% response rate achieved for the combination as encouraging," Morgan Stanley analysts said in a 15 May research note. "The fact that there is also some monotherapy activity is also important."

IOVANCE BIOTHERAPEUTICS INFILTRATING CERVICAL CANCER

An update to Iovance Biotherapeutics Inc.'s ongoing Phase II study C-145-04 (innovaTIL-04) of LN-145 tumor-infiltrating lymphocyte (TIL) therapy in patients with advanced cervical cancer who have undergone at least one prior line of chemotherapy showed an ORR of 44% (one complete response, nine partial responses and two unconfirmed partial responses) and a disease control rate of 89%.

At 3.5-month median study follow-up, 11 out of 12 patients maintained a response.

Despite the small sample size, these early results show promising signs of efficacy for LN-145 in cervical cancer, according to the Biomedtracker/Datamonitor Healthcare analysts. "The 44% ORR is a large improvement over an earlier data cut from October 2018 and now compares well to historical response rates for approved therapies Avastin and Keytruda."

Jefferies analysts agreed. "The data are significantly better than those reported in the Keytruda Phase II trial where 14% ORR was observed in only PD-L1+ patients. Furthermore, the Keytruda trial enrolled a less sick patient population with a median of one-to-two prior lines of therapy," they said. "We believe this improved response rate in cervical trial is partially contributed by Iovance's Gen2 manufacturing process, which presumably produces younger T-cell phenotype through shorter culture time."

Iovance expects to meet the FDA later this year to discuss a regulatory path forward for LN-145.

"In our view, this dataset should enable a regulatory path of single-arm design for pivotal trial. If FDA allows a single arm trial, IOVA could be submitting regulatory approval for two indications – melanoma and cervical cancer – by year end '20, which is a probability that the market is significantly discounting," the Jeffries analysts said in a 15 May research note.

Also significant for the product and the company is that in another study in melanoma, innovaTIL-01, no responders have progressed since the last update at the Society for Immunotherapy of Cancer meeting last November, they added.

"We think the ASCO update suggests Iovance's TIL therapy could open the door for cell therapy in lucrative solid-tumor market.".

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Merck KGaA Keen To Remain Key Player In MS Now And In Future

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Merck KGaA is confident that it can continue to grow in the multiple sclerosis space, with Mavenclad and evobrutinib hopefully filling the revenue gap created by the continued decline of Rebif sales.

The German group has unveiled a reasonable set of financials for the first quarter with healthcare sales rising 3.2% to €1.48bn. However Rebif (interferon beta-1a), still easily the biggest earner for division, saw sales fall 16% to €299m.

Merck's pharma chief Belén Garijo said on a conference call that Rebif's market share was stable "within the declining interferon class" but the drug lost yet more ground against Roche's disease-modifying agent Ocrevus (ocrelizumab). The latter, which the Swiss major has touted as the best launch in the company's history, had first-quarter sales of CHF836m ($829m), well ahead of consensus forecasts.

Nevertheless, Merck believes it can compete with Ocrevus with Mavenclad (cladribine). First-quarter sales of the latter were €43m, up from €13m in the like, year-earlier period. The Darmstadt-headquartered company noted that the drug had now been approved in 55 countries and reimbursed in 50% of markets it has been launched in; for the full year, it is forecasting sales in the mid-triple-digits.

The company secured a thumbs-up from the US Food and Drug Administration at the end of March this year and attained coverage by leading US pharmacy benefits manager Express Scripts within just one week of approval. In Europe, Garijo stressed that it was achieving an increase in market share despite growing competition – up 5% on the first quarter of 2018 to 17% in Germany – and up 13% to 21% in the UK, boosted by an outcomes-based reimbursement deal inked with NHS England.

Merck is now looking at global peak sales of €1-1.4bn for Mavenclad, split fairly evenly between the US and Europe.

The company hopes that its MS franchise will soon be complemented by its investigational Bruton's tyrosine kinase (BTK) inhibitor evobrutinib. Last week, Merck presented updated Phase II data at the American Academy of Neurology meeting in Philadelphia, with simultaneous publication in the *New England Journal of Medicine*, which demonstrated that the drug is the first oral BTK inhibitor to show clinical proof of concept in relapsing MS.

The data showed that the reduction in lesions detected using the contrast agent gadolinium was maintained after 48 weeks using both daily and twice daily doses of evobrutinib 75mg. Safety-wise there were no treatment associated infections, infestations, or lymphopenia observed and no new safety signals were identified over 52 weeks.

Phase III trials of evobrutinib in MS will start in the second half of 2019 and commenting on the data in an investor note (13 May), Hugo Solvet, an analyst at Bryan Garnier, wrote that while he believed the drug "might be a nice fit within Merck's portfolio, allowing it to leverage its Mavenclad sales force, we doubt that the profile of the drug will enable a multi-blockbuster status." Phase II readouts of the drug in rheumatoid arthritis and systemic lupus erythematosus are scheduled for the first quarter of 2020.

> Merck KGaA is not looking to partner evobrutinib for MS but is keeping its options open in the arthritis and lupus indications.

Garijo confirmed that since Merck linked up with GlaxoSmithKline PLC earlier this year, with the UK major making a €300m upfront payment to get access to the bifunctional immunotherapy M7824 (bintrafusp alfa), the company could take a more flexible approach to partnering evobrutinib. The company is not looking to partner the drug for MS but is keeping its options open in the arthritis and lupus indications.

Outside of MS, Merck noted that its Pfizer Inc.-partnered checkpoint inhibitor Bavencio (avelumab) contributed €22m to first quarter turnover. Its current commercial value is limited by the small patient population with Merkel cell carcinoma, for which it is approved, but the drug, in combination with Pfizer's tyrosine kinase inhibitor Inlyta (axitinib), is currently under priority review at the FDA for the treatment of advanced renal cell carcinoma, with a decision expected next month *[Update: the FDA approved Bavencio/Inlyta hours after the conference call (14 May), weeks earlier than expected.]* .

However, the Bavencio/Inlyta combo will face fierce competition from the combination of Merck & Co. Inc.'s PD-1 inhibitor Keytruda (pembrolizumab) with Inlyta which was approved last month as a first-line treatment of kidney cancer. Garijo was bullish on the call, saying that the company and Pfizer were confident of its potential based on the promising results of the JAVELIN Renal 101 study.

Bernstein analyst Wimal Kapadia issued a note saying that Merck's mature pharma products such as the diabetes drug Glucophage (metformin) and infertility treatment Gonal-F (follitropin alfa) continue to outperform and are offsetting the decline of Rebif, while the company will benefit from one-offs, eg €100m annually from GSK until 2021 at a minimum. However, on Bavencio and Mavenclad, "we are increasingly unconvinced by the €2bn in pipeline sales guidance to 2022," he wrote.

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Merck & Co And The 'Strange Business' Of Antibiotics

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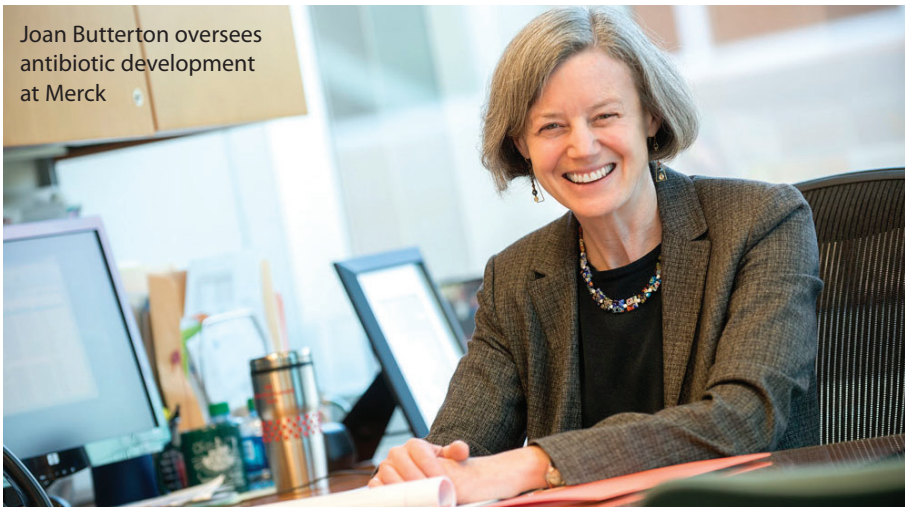
Having one of the industry's largest portfolios of anti-infective drugs allows Merck & Co. Inc. to weather the various storms within this sector of the biopharmaceutical industry, where there is a major need for new medicines to combat antimicrobial resistance (AMR), but where stewardship is required to make sure overuse doesn't worsen the AMR crisis.



Joan Butterton oversees antibiotic development at Merck

Merck has a long history of developing antibiotics and antifungals, and has stuck with the challenging therapeutic area because of the immense public health need, noted Joan Butterton, associate vice president in the infectious disease group at Merck Research Laboratories. Butterton spoke with *Scrip* as the company prepares to add a new indication and a new product to its blockbuster anti-infective portfolio.

A supplemental new drug application (sNDA) seeking an additional indication for the five-year-old antibiotic Zerbaxa (ceftolozane/tazobactam), a cephalosporin combined with a beta-lactamase inhibitor, is under consideration at the US FDA. The agency is also considering an NDA in support of a first-ever indication for another antibiotic combination therapy that pairs the beta-lactamase inhibitor relebactam with Primaxin (imipenem/cilastatin), a carbapenem combined with a dehydropeptidase inhibitor.

Butterton acknowledged the complex development path for antibiotics and the difficulty in selling enough novel drugs in this space to justify the investment without worsening the AMR crisis. "It's a strange business to be in – to make products that cost so much to make, and take so much time to make, when you don't want people to use them," Butterton said. "Because the more you use any antibiotic, the more that resistance will develop, and then you won't have a drug that you can use anymore. And for stewardship purposes, you really want to be able to appropriately limit the use to where it's really needed. That's a strange model for any company."

Merck has successfully built a portfolio that's large enough to balance out the rough waters of anti-infective development and commercialization, which starts with high-cost preclinical studies and clinical trial programs and ends with a slow period of building a market for new antibiotics and antifungals. Some key products in this part of the company's overall portfolio are losing patent exclusivity, but a new indication for Zerbaxa and the new relebactam/Primaxin combination should add to Merck's antibiotics revenue stream.

13 APPROVED PRODUCTS, BUT GENERIC FLOOD KICKS IN

Merck has 13 approved antibiotics and antifungals, including drugs that have gone generic, but does not report individual sales for all of those products. Sales for many of them are included in the "Other Pharmaceutical" line item in the company's earnings reports, such as Zerbaxa and the antibiotic Sivextro (tedizolid), both of which were acquired in the $9.5bn purchase of Cubist Pharmaceuticals Inc. in 2014. *(Also see "Merck's $9.5bn Cubist buy overshadowed by court decision" - Scrip, 9 Dec, 2014.)*

Sivextro, approved for skin and skin structure infections in 2014 and now in Phase III for pneumonia, was developed by Trius Therapeutics Inc., which Cubist bought for up to $818m in 2013. The lipopeptide antibiotic Cubicin (daptomycin) also came to Merck via Cubist.

Merck reports sales for the antibiotics Primaxin, Cubicin and Invanz (ertapenem), and for the antifungals Noxafil (posaconazole) and Cancidas (caspofungin), as part of its Hospital Acute Care business. The five drugs delivered $2.2bn in sales in 2018, but sales for four of the products declined by double-digit percentages in the first quarter of this year for a Q1 total of $470m (*see table below*). Invanz, Cancidas, Primaxin and recently Cubicin have gone generic.

REINVESTING IN PORTFOLIO GROWTH, PUBLIC HEALTH NEED

This revenue supports Merck's ongoing research and development in the anti-infective space, including new indica-

Merck First Quarter Antibiotic And Antifungal Sales

DRUG	Q1 2019	Q1 2018	Q1 DIFFERENCE	FULL YEAR 2018
Noxafil	$190m	$176m	8%	$742m
Cubicin	$88m	$98m	-10%	$367m
Invanz	$72m	$151m	-53%	$496m
Cancidas	$61m	$91m	-33%	$326m
Primaxin	$59m	$72m	-19%	$265m

Source: Merck & Co. Inc.

tions for approved products – Sivextro, for instance, is in Phase III for pneumonia – and novel drugs. The company's Early Discovery Centers continue to do R&D in the antimicrobial space, Butterton said.

The executive, an infectious disease doctor with a master's degree in the history of medicine, noted that "when you think about the history of Merck, it's quite clear that anti-infective drug development and research has been a core mission for the company."

Merck has been making small molecule anti-infectives for more than 80 years – and has introduced "at least a couple of new antimicrobials every decade" since the late 1930s, Butterton said.

"This type of research and development is really difficult," she explained. "The bacteria have very small genomes, they only make a limited number of targets for us to attack, all of the easy ones have already been explored, so it's hard to come up with new ways to treat these infections [and] it takes a lot of time. And then the clinical trial programs are time-consuming, expensive and difficult, so it takes a lot of expertise to be able to do this."

DOUBLING THE ZERBAXA DOSE FOR A CRITICAL NEED

Zerbaxa originally was designed to be a potent anti-Pseudomonas drug with the goal of eventually delivering enough of the antibiotic to the lungs for critically ill patients with pneumonia caused by *Pseudomonas*, Butterton explained. Its first indications were in complicated urinary tract infections (cUTI) and complicated intra-abdominal infections (cIAI). The approved dose was doubled to test it in nosocomial pneumonia, including hospital-acquired bacterial pneumonia (HABP) and ventilator-associated bacterial pneumonia (VABP), which is the indication now awaiting FDA approval.

"The initial studies in patients over 18 years were conducted using a 1.5g dose of Zerbaxa (ceftolozane 1g and tazobactam 0.5g) given every eight hours in cUTI and cIAI, as these are common infections and there is a well-defined regulatory pathway for potential approval," Butterton explained.

"While these studies were ongoing, further studies were conducted, first in healthy volunteers and then in patients on a mechanical ventilator, to evaluate the optimal dose to use in pneumonia," she said. "These studies found that doubling the dose to 3g (ceftolozane 2g and tazobactam 1g) every eight hours attained the necessary exposure targets in the lung, and this dose was subsequently employed in the Phase III ASPECT-NP HABP/VABP study."

ASPECT-NP enrolled 726 critically ill patients, all of whom were hospitalized and on mechanical ventilation for nosocomial pneumonia, and showed Zerbaxa 3g administered intravenously every eight hours was non-inferior to meropenem (1g given intravenously every eight hours) for eight to 14 days. *(Also see "Merck Looks To Add Pneumonia To Zerbaxa Label; Market Value Not Clear" - Scrip, 12 Sep, 2018.)*

The sNDA for Zerbaxa in the treatment of nosocomial pneumonia in adults has a 3 June review date with the FDA. *(Also see "Merck & Co's Frazier: International Business Is Only Scratching The Surface" - Scrip, 30 Apr, 2019.)* The product also is under review by the European Medicines Agency for this indication. In the US, it has a qualified infectious disease product (QIDP) designation from the FDA for HABP/VABP infections.

NEW ANTIBIOTIC NDA CLOSELY FOLLOWS ZERBAXA SNDA

A 16 July FDA action date was granted for the agency's priority review of relebactam plus imipenem/cilastatin for the treatment of cUTI and cIAI caused by certain Gram-negative bacteria in adults with limited or no alternative treatment options. The antibiotic combination pill was comparable to Colistin (colistimethate sodium) and Primaxin in the Phase III RESTORE-IMI 1 trial, but with much lower rates of nephrotoxicity. *(Also see "Keeping Track: CDER Approves Its First Two Novel Agents Of 2019" - Pink Sheet, 10 Feb, 2019.)*

The relebactam and imipenem/cilastatin combination – also known as IMI/REL – received a QIDP designation for cUTI and cIAI as well as HABP/VABP in 2014. *(Also see "Merck's relebactam dubbed qualified infectious disease product " - Scrip, 5 Sep, 2014.)*

Butterton explained that carbapenems, like imipenem, have historically been used for the treatment of patients with serious infections, and in the IMI/REL combination, the novel beta-lactamase inhibitor relebactam restores the activity of imipenem against resistant bacterial pathogens. In addition to the cUTI and cIAI indications, IMI/REL "potentially could be used in the treatment of infections either known or highly suspected to be caused by resistant organisms," she said.

In fact, "IMI/REL has demonstrated activity against *Klebsiella pneumoniae* carbapenemase (KPC)-producing enteric bacteria and carbapenem-resistant (CR) *Pseudomonas*, two of the most commonly encountered CR pathogens," Butterton added.

In terms of balancing the use and sales growth of novel antibiotics with the need for antibiotic stewardship to prevent overuse that could contribute to AMR, she said the "use of any novel agent targeting serious, emerging mechanisms of resistance would typically be restricted in antimicrobial stewardship programs. As is true across the range of antimicrobial agents, use should be determined by local epidemiology and individual patient factors. If approved, IMI/REL should be used in a manner that is consistent with the principles of antimicrobial stewardship."

LIMITED CAPACITY TO INVEST DESPITE AMR CRISIS

Despite Merck's long history, deep expertise and blockbuster revenues in the anti-infective space, no one company has the capacity to invest in every intriguing antibiotic candidate that comes its way, even with the need for new antimicrobial agents to thwart the AMR crisis.

Some smaller companies that have developed effective antibiotics have gone out of business or halted R&D after their antibiotics were approved, because they couldn't generate enough revenue to fund ongoing operations. Achaogen Inc., whose antibiotic Zemdri (plazomicin) was approved in the US last year, revealed in April that it will wind down its business and sell off its assets via Chapter 11 bankruptcy proceedings.

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

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

PIPELINE WATCH, 10–16 MAY 2019

Event Stage	Lead Company/Partner	Drug Name	Indication	Comments	Change To LOA (%)	LOA (%)
Phase III Updated Results	Sesen Bio, Inc.	Vicinium (oportuzumab monatox)	Bladder Cancer	VISTA; Durable Anticancer Activity	0	39
Phase III Updated Results	GenSight Biologics S.A.	GS010	Leber's Hereditary Optic Neuropathy	REVERSE; Durable Responses At Wk 96	0	47
Phase III Updated Results	MacroGenics, Inc.	margetuximab	Breast Cancer, HER2-Positive	SOPHIA; Positive Results	2	45
Phase III Updated Results	AstraZeneca PLC	Imfinzi (durvalumab)	Head and Neck Cancer	EAGLE (+/-tremelimumab); Mixed Results	-1	32
Phase III Updated Results	Actinium Pharmaceuticals, Inc.	Iomab-B plus cell transplant	Acute Myeloid Leukemia	SIERRA; Promising Results	0	37
Phase II/III Updated Results	Geron Corporation	imetelstat	Myelodysplastic Syndrome	Imerge; Durable Transfusion Independence	0	37
Phase II/III Updated Results	BeyondSpring Pharmaceuticals, Inc.	plinabulin	Neutropenia/Leukopenia	Protective-2 (China); Encouraging Results	0	60
Phase III Top-Line Results	Myovant Sciences Ltd.	relugolix	Uterine Fibroids	LIBERTY 1; Met Primary Endpoint	10	78
Phase III Top-Line Results	Zealand Pharma A/S	dasiglucagon	Hypoglycemia In Diabetes	HypoPal; Met All Endpoints	0	68
Phase III Top-Line Results	Pfizer Inc.	abrocitinib	Atopic Dermatitis	JADE Mono-1; Positive Results	2	64
Phase III Top-Line Results	Agios Pharmaceuticals, Inc.	Tibsovo (ivosidenib)	Cholangiocarcinoma, IDH1-Mutant	ClarIDHy; Met Primary Endpoint	3	38
Phase III Top-Line Results	Novartis AG	spartalizumab, anti-PD-1 Mab	Melanoma	COMBI-i (w/dabrafenib and trametinib); Durable Responses	0	35
Phase III Trial Initiation	Rigel Pharmaceuticals	Tavalise (fostamatinib)	Autoimmune Hemolytic Anemia	Warm AIHA; 24 Wk Study	30	61
Phase III Trial Initiation	NatureCell	JointStem cell therapy	Osteoarthritis	In Korea	0	24

Source: Biomedtracker | Informa, 2019

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Zemdri was approved to treat cUTI in patients with limited or no other treatment options, but was rejected for a smaller bloodstream infection indication under the FDA's limited population antibiotic drug (LPAD) pathway. *(Also see "Achaogen Questioning Whether Others Will Pursue LPAD Pathway After Zemdri Misses Out " - Pink Sheet, 26 Jun, 2018.)* The FDA has since acknowledged that the LPAD pathway may have limited use, suggesting additional incentives are needed to help speed new antibiotics to approvals. *(Also see "LPAD Approval Pathway Is Not Saving Antimicrobial Development" - Pink Sheet, 28 Nov, 2018.)*

"I don't think that there's any one-size-fits-all solution and we at Merck think there's going to need to be a suite of incentives to answer all of the market challenges," Butterton said. She noted that different incentives are needed in different parts of the world based on each market's specific characteristics and challenges.

Programs like LPAD and the FDA's QIDP designation have sped candidates through development and approval, helping companies raise funding to develop new drugs. Various efforts like the antibiotic accelerator CARB-X and Novo Holdings' REPAIR Fund also have backed start-ups with novel antibacterial and antifungal drugs. *(Also see "REPAIR Is Trying To Fix The Antibiotic Gap Left By Industry" - Scrip, 12 Sep, 2018.)*

"The problem then is you have a drug on the market, but it's with a limited safety and efficacy database, and it's also been done in an indication, like urinary tract infection, which is really not the key indication for that product," Butterton said. "So, companies are unable to show that they differentiate from a cheaper, potentially generic competitor and they aren't able to show the value of the drug to the market and to health technology assessment groups that value these assets."

Market entry rewards, transferable exclusivity and other types of "pull incentives" can make a difference, she noted, such as a model for paying for new antibiotics in the UK that's based on the value they deliver and not on the number of drugs companies sell. *(Also see "Pharma Welcomes UK Incentive Plan To Tackle AMR" - Scrip, 24 Jan, 2019.)*

"The deeper pockets [of a big pharma company] probably let you ride out the ups and downs of markets and to take some risks that small companies might not be able to make, but even large companies would benefit from pull incentives, because they would have a guaranteed return," Butterton said. "And, honestly, for any company, being able to have some confidence and being able to plan makes an enormous difference in where you invest."

She doesn't fault other big companies for choosing not to invest in antibiotics, however, because "there are a lot of public health challenges in the world and different companies develop different expertise in different areas … We certainly don't want to be incentivizing companies just to dabble in something without making a real commitment to doing it in the way it needs to be done."

However, the increasing attention being paid globally to the AMR crisis does make Butterton hopeful that "there will be more action that will actually lead to incentives that will allow people to stay in this business. There is a lot of great science out there and that's why we have new compounds going forward and people interested in investing in them."

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APPOINTMENTS

Executive	To Company	New Role	From Company	Previous Role	Effective Date
Mark Levick	Alvotech Iceland	Chief Executive Officer	Sandoz	Head, Development, Biopharmaceuticals	9-May-19
Brendan Rae	CytoDyn Inc	Senior Vice President, Business Development	Serina Therapeutics	Chief Business Officer	14-May-19
Carsten Thiel	EUSA Pharma (UK) Ltd	President, Europe	Abeona Therapeutics	Chief Executive Officer	15-May-19
Darrel P. Cohen	EUSA Pharma (UK) Ltd	Head, Clinical Development	Pfizer Oncology	Vice President, Clinical Development Leader	15-May-19
Beth-Anne Lang	LEO Pharma AS	Vice President and Head, Global Regulatory Affairs	Takeda	Vice President, Global Regulatory Affairs, Marketed Products	13-May-19
Lloyd Klickstein	resTORbio Inc	Chief Scientific Officer	Novartis Institutes for Biomedical Research	Global Head, Translational Medicine	14-May-19

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

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