



Array's Three Value Drivers Align With Pfizer's Three Oncology Pillars In \$11.4bn Deal

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The three main value drivers behind Pfizer Inc.'s \$11.4bn purchase of Array BioPharma Inc. appear to align well with the three pillars the big pharma recently outlined for its mid- to long-term strategy in oncology, with Array's BRAF/MEK inhibitor combination Braftovi/Mektovi immediately contributing a small, but growing source of new revenue.

The deal announced on 17 June "makes sense to us as Pfizer works to further boost its innovative core," Credit Suisse analyst Vamil Divan said in his same-day note about the transaction. Meanwhile, Jefferies analyst Eun Yang pointed out that Array is being acquired

at a "healthy premium" based on data for the Braftovi (encorafenib)/Mektovi (binimetinib) combination to date in its approved melanoma indication and in colorectal cancer – both in tumors with hard-to-treat BRAF mutations.

"This proposed acquisition strengthens our innovative biopharmaceutical business and is expected to accelerate its growth trajectory, particularly in the long term. We have the rare opportunity to advance our oncology strategy and to augment our business with three value drivers," Pfizer's Andy Schmeltz, president of the company's US oncology business unit, said during a 17 June conference call

to outline the benefits of the deal with investors and analysts.

Pfizer sees Braftovi/Mektovi as the first value driver, following its June 2018 approval to treat unresectable or metastatic melanoma patients with a BRAFV600E or BRAFV600K mutation as well as its potential next indication in second-line and third-line BRAF-mutated metastatic colorectal cancer based on its use in combination with Eli Lilly & Co.'s EGFR inhibitor Erbitux (cetuximab) in the Phase III BEACON clinical trial. (Also see "Array Raring To Go Commercially With First Approval – Mektovi/Braftovi" - Scrip, 27 Jun, 2018.) and (Also see "Array Celebrates BEACON Of Hope For Anti-BRAF/MEK/EGFR Triplet In Colorectal Cancer" - Scrip, 25 Jun, 2018.)

Schmeltz also cited Array's large portfolio of out-licensed cancer drug candidates as a significant driver of long-term value as well as its research and development platform for targeted therapies, including several attractive – yet undisclosed – preclinical programs in cancer and rare diseases. Array has said previously that it expects to take one new cancer drug into the clinic each year from its preclinical pipeline.

"The deal is a little larger than what we were expecting next from Pfizer, but the price paid appears reasonable when compared to recent deals in the space and it fits well with Pfizer's overall strategic priorities as they look to boost their innovative pipeline with assets that can help drive mid- to long-term growth," Credit Suisse's Divan wrote.

At \$48 per share, the transaction represents a 62% premium over Array's 14 June closing stock price of \$29.59. In that respect, the deal has a slightly lower premium than another big tar-

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from the editor

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The announcement of the cost of bluebird bio's Zynteglo gene therapy for transfusion-dependent beta-thalassemia has been received as relatively restrained, and the plan to spread payment over five years and attach it to treatment success has helped temper the headlines (see p5).

It's been tough for early gene therapy pioneers to see their breakthrough treatments lambasted across the media as egregiously expensive, while their extraordinary promise in offering a one-time cure for devastating illnesses is side-lined as less noteworthy than their price. In fact, the rarity and severity of the conditions for which these advanced therapies have been approved, and the cost of not having them, mean that their purchase is not really placing an undue burden on society, at least compared with some apparently cheaper drugs.

Granted, indication expansion for gene therapies will place a more burdensome demand on payer resources: while Zynteglo's approved indication is small, bluebird is developing the technology also for sickle cell disease. In the meantime, other gene therapies will reach the market over time for a wider range of conditions.

Even so, high-priced gene therapies like Zynteglo and Novartis's Zolgensma will have to work hard to reach blockbuster sales status, given their limited patient pools. While they may be the costliest drugs, they won't come close to rivaling pharma's really big cash cows. In 2018, just 10 drugs generated global revenues of \$87bn, and most of these were monoclonal antibodies costing less than \$150,000 a year but targeting broader patient populations. Gene therapy is a long way from incursion into that territory.

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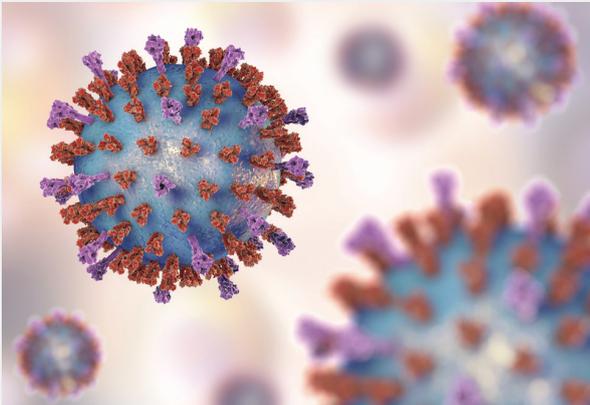
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Enanta Hopes To Succeed In RSV With N-Protein Inhibition Approach

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Enanta Pharmaceuticals Inc.'s EDP-938 hit both the primary and secondary endpoints in a Phase IIa study in respiratory syncytial virus (RSV), but a greater test likely awaits when the Boston-area firm seeks to repeat that success in a real-world setting.

Unlike many pipeline candidates for RSV, which seek to prevent infections with fusion protein inhibitor therapy, Enanta's candidate is a therapeutic N-protein inhibitor. The biotech believes this approach can treat the virus after infection by targeting the RSV replication process; it also says the drug has demonstrated high barriers to resistance in *in vivo* testing.

Enanta presented top-line data during an investor call on 14 June from its Phase IIa challenge study of EDP-938 in adults, revealing that two doses met statistical significance for the primary endpoint of reduction in viral load and a secondary endpoint of total symptom score (TSS). As a challenge study, adult volunteers were exposed to RSV in a controlled setting and then tested twice-daily for infection, with infected patients then being randomized to either a treatment arm or a placebo group.

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geted cancer drug firm buyout this year. Lilly's \$8bn purchase of Loxo Oncology Inc. at \$235 per share was a 68% premium to Loxo's closing stock price prior to the deal announcement. (Also see "Lift-Off For Lilly In Cancer Genetics With Loxo Buy" - *Scrip*, 7 Jan, 2019.)

Array has a stake in the Lilly/Loxo transaction as well. (Also see "Loxo Links And Colorectal Cancer Data Put Array In M&A Spotlight" - *Scrip*, 15 Jan, 2019.) Loxo's two TRK inhibitors – the approved drug Vitrakvi (larotrectinib), which is now wholly owned by co-developer Bayer AG, and the Phase I/II candidate LOXO-195 – were discovered with Array's technology platform. (Also see "Bayer Bags Full Vitrakvi Rights As Lilly Signs Off Loxo Buy" - *Scrip*, 18 Feb, 2019.)

FITTING WITH PFIZER'S THREE PILLARS

The three most valuable aspects of the Array acquisition look like they may strengthen the three pillars of Pfizer's oncology strategy as the big pharma described it during a media briefing in May.

The first part of that strategy is to extend the reach of Pfizer's existing oncology brands, such as the CDK4/6 inhibitor Ibrance (palbociclib) for metastatic breast cancer, the androgen receptor inhibitor Xtandi (enzalutamide) and the PD-L1 inhibitor Bavencio (avelumab). The company said last month that it intends to add indications to its cancer drugs' labels, including through combinations with other novel therapies.

Now, with the acquisition of Array that's expected to close in the second half of 2019, Pfizer intends to test its approved and pipeline therapies in combination with Array's Braftovi/Mektovi and its preclinical drug candidates.

The second pillar in Pfizer's oncology strategy is to develop precision medicines for lung cancer and hematologic malignancies. In addition to combinations with the undisclosed preclinical candidates of interest, some patients with lung cancer have BRAF mutations, so Braftovi and Mektovi could be developed for a targeted population in that indication as well.

The next wave of immuno-oncology is the third part of Pfizer's oncology strategy, including combination regimens that improve the efficacy of known IO mechanisms, such as PD-1/L1 inhibition. The company said in May that it intends to test Bavencio in combination with various targeted therapies, which now will include Braftovi/Mektovi and Array's preclinical assets.

Overarching the three pillars of the company's oncology strategy is a focus on first-in-class and best-in-class drugs – a goal that Array's therapeutic candidates and drug discovery platform also may support.

"Braftovi and Mektovi are being investigated as a potential first-in-class combination for certain patients with metastatic colorectal cancer and have the opportunity to treat earlier stages of the disease," Schmeltz said during Pfizer's call to review the Array deal. "Through the proposed acquisition of Array, Pfizer will set the stage to establish an industry leading colorectal franchise with a potentially first- and best-in-class combination that could have blockbuster revenue potential. This will further augment our existing leading positions in both breast cancer and prostate cancer."

PURSUING A BEST-IN-CLASS BRAF/MEK STRATEGY

While Braftovi/Mektovi was a third-to-market BRAF/MEK inhibitor combination in melanoma, Morningstar analyst Damien Conover said in a 17 June note that "the clinical data from Array's drugs looks better from a cross-trial comparison."

Braftovi and Mektovi face competition from the Merck & Co. Inc. and Bristol-Myers Squibb Co. PD-1 inhibitors Keytruda (pembrolizumab) and Opdivo (nivolumab), respectively, in melanoma, but Conover wrote that "outside of melanoma, the Braftovi-Mektovi combination showed excellent data in BRAF mutated colorectal cancer (10%-15% of colorectal cancer), setting up a potential first-mover advantage in that area. Also, PD-1 drugs haven't shown as compelling data in colorectal cancer." (Also see "Will Pierre Fabre and Array Have Best-In-Class MEK/BRAF Inhibitor?" - *Scrip*, 6 Jun, 2018.)

Sales for Braftovi/Mektovi in melanoma totaled \$35m in Array's most recent quarter, but Pfizer sees a bigger opportunity in colorectal cancer.

But Credit Suisse's Divan noted that commercial performance will be a bigger determinant of the value of Pfizer's Array acquisition than the company's data.

To that point, Mikael Dolsten, Pfizer's president of worldwide R&D, said during the company's call that sales for Braftovi/Mektovi in melanoma totaled \$35m in Array's most recent quarter, but indicated there's a bigger opportunity for the combination in colorectal cancer.

By Pfizer's estimates, Braftovi/Mektovi is being prescribed for about a third of metastatic melanoma patients with a BRAF mutation. However, while about 45% of the 30,000 melanoma patients diagnosed annually in the developed world have a BRAF mutation, 10%-15% of the 200,000 patients diagnosed each year with colorectal cancer have a BRAF mutation. Beyond those two initial cancers, Braftovi and Mektovi are being tested in more than 30 clinical trials across a variety of BRAF-mutated solid tumors.

Jefferies analyst Yang forecast \$1bn in peak US sales for Braftovi/Mektovi in melanoma and colorectal cancer with total revenue for the combination in those indications estimated at \$1.2bn, including royalties from ex-US markets.

Array earns a 20%-35% royalty on the combination's sales in Europe, most of Asia and Latin America from partner Pierre Fabre Group; it receives a 22-25% royalty from sales in Japan and South Korea from Ono Pharmaceutical Co. Ltd.

THE PIPELINE BEYOND BRAFTOVI/MEKTOVI

Pfizer's Schmeltz pointed out that "scientists from Array were responsible for the discovery of various breakthrough therapies that are now out-licensed to a number of high-quality biopharmaceutical companies. Royalties from this portfolio are expected

to continue to drive additional substantial value over time.” He praised the efforts of Array’s R&D team for the discovery of several promising targeted cancer therapies for its own and its partners’ pipelines, and noted that Pfizer will keep that approximately 100-person R&D group intact at Array’s research center in Boulder, CO. That site will compliment Pfizer’s oncology R&D sites in San Diego and in Pearl River, NY.

Pfizer’s investment in Array will not have a significant immediate impact, according to chief financial officer Frank D’Amelio, who said during the company’s call that “this proposed acquisition is primarily targeted to help strengthen our financial growth profile during the mid-term with a potential for meaningful value creation during the mid-2020s.”

“Given that context, we expect the deal to be approximately \$0.04 to \$0.05 dilutive to adjusted diluted earnings per share (EPS) in each of 2019 and 2020, neutral in 2021 and accretive beginning in 2022, with increasing accretion anticipated thereafter,” D’Amelio continued. He said Pfizer’s \$11.4bn expenditure for Array also won’t prohibit additional business development or tie up cash intended for stock repurchases and dividends, because “we expect to finance a significant majority of the deal with new debt and the remainder to finance with existing balance sheet cash.”

D’Amelio said Pfizer will continue to execute bolt-on transactions rather than larger mergers and acquisitions. The focus is on early- and mid-stage drug candidates that may be able to make up for revenue declines as the company’s approved products lose patent exclusivity. The Braftovi/Mektovi combination has patent protection until 2031.

Pfizer closed up 0.3% at \$42.88 per share after initially falling on 17 June as investors considered the Array acquisition. Array spiked 57% to close at \$46.44 based on the premium Pfizer’s paying in the deal. 🌟

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Bluebird Pushes For Zynteglo Pricing Of Five €315K Annual Installments

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Bluebird bio Inc. is resolute in its determination to negotiate a five-year €315,000 (\$356,000) annual payment model for its new gene therapy Zynteglo in Europe. The company laid out the price of the one-time gene therapy on 14 June in a strategy meant to manage some of the sticker shock associated with a seven-figure drug price by balancing the cost with a risk-based model annuitized over five years.

The price of Zynteglo is set at €1.575m (\$1.78m) over the five years, if the treatment is successful, based on a reduction in the number of blood transfusions. Zynteglo (autologous CD34+ cells encoding β A-T87Q-globin gene) was granted European marketing authorization on 3 June after a positive recommendation by the Committee for Medicinal Products for Human Use (CHMP) in March. (Also see “Bluebird Bio’s Zynteglo Flies Through Its CHMP Review” - *Scrip*, 29 Mar, 2019.)

It is approved for an ultra-rare indication in patients 12 and older with transfusion-dependent beta-thalassemia (TDT), a genetic disorder that results in absent or reduced hemoglobin, resulting in chronic blood transfusions every two to four weeks, organ failure and a potentially shortened life span.

CEO Nick Leschly floated a price ceiling of \$2.1m for the product in January at the J.P. Morgan Healthcare Conference, setting the tone for discussions with payers and patients, but the company had not yet revealed the price. (Also see “J.P. Morgan Notebook Day 2: Biogen, GSK, Bluebird, Roche, Amgen, Biohaven, Lilly And FDA’s Gottlieb” - *Scrip*, 9 Jan, 2019.)



“This is the model. We are not offering up any other model.” - Nick Leschly

Leschly talked to *Scrip* in an interview about the Zynteglo pricing model and the company’s commitment to paving the way for a new payment model for expensive gene therapies. Other early gene therapy developers, namely Spark Therapeutics Inc. and Novartis AG, also are offering flexible payment options in addition to a one-time up-front payment, but bluebird says the five-year payment plan is the only option for its product.

“This is the model. We are not offering up any other model,” Leschly said. “In order to get access to Zynteglo, this is the approach that we think makes sense, not only for this product, but for subsequent ones.”

EUROPE VERSUS US

Still, Leschly acknowledged there will be some level of negotiation with payers. “Are there going to be puts and takes? I think so. But we certainly are not planning on going to a level that would fundamentally change this, going back to a one-time payment model or something that is dramatically different.”

In contrast, Novartis CEO Vasant Narasimhan has talked about how the company expects limited early uptake of an option of five \$425,000 annual payments for its recently approved Zolgensma, part-

ly due to US regulations that restrict those kinds of agreements, particularly around Medicaid best price.

(Also see *"It's Official: Novartis SMA Gene Therapy Zolgensma Is World's Most Expensive Drug"* - *Scrip*, 24 May, 2019.) He indicated the alternative payment plan might be more attractive to small regional payers.

A big difference for bluebird is that Zynteglo is launching first in Europe with a US regulatory filing expected later this year. (Also see *"Bluebird Lays Some New Eggs, But They'll Take Time To Hatch"* - *Scrip*, 16 May, 2019.) Negotiating with single-payer governments in Europe presents some unique challenges and some advantages. The company expects to launch Zynteglo first in Germany, the UK, France and Italy.

"In the US, to have performance-based [contracts], you have to deal with things like best price and price reporting," Leschly said. But, bluebird hopes to implement a similar model for Zynteglo in the US when it launches there likely in 2020 with the hope that some of the current regulatory burdens may be alleviated by then. "And we maybe also have a stronger will to get to this model," he added.

Bluebird is conscious of how a seven-figure drug price sounds to stakeholders and believes that five €315,000 annual payments for five years certainly may be easier for some to digest.

"From a system point of view, we think it is a very wise investment, but at the same time, it is a big number. We recognize that,"

he said. "The flip side of that is how do we make sure that it is palatable and adopted by the system."

DETERMINING VALUE

To determine a value-based price for Zynteglo, bluebird focused on quality of life and life extension benefits and used standard health outcomes metrics to quantify the savings, resulting in a value of \$2.1m. Adding other benefits like health care cost offsets from current treatments and societal value would have increased the value to \$4m, according to the company.

"We focused on life extension, we focused on quality of life, because those are very real direct patient-oriented costs," Leschly said. Bluebird opted not to include cost offsets from current treatments in the calculus, because they represent inefficiencies in the current treatment system that management felt would be unfair to include. After landing on a value of \$2.1m, the company further discounted the price by 15%, landing on €1.575m (\$1.78m) over five years of successful treatment.

The extra discount was applied to show good faith with payers in negotiations, the company said. "There are a number of things we think about. One is just in terms of showing up and giving something back to the payers that we are sitting across the table from," Chief Commercial Officer Alison Finger added.

The tactic, however, is tried and tested for managing sticker shock when it comes

to the launch playbook for pricey gene therapies. (Also see *"Price 'Anchoring'? Zolgensma And The Art Of Managing Gene Therapy Sticker Shock"* - *Scrip*, 19 Mar, 2019.) For example, Novartis talked about a \$4m-\$5m value for Zolgensma (onasemnogene abeparvovec) before launching at a price of \$2.1m. Spark talked about the value of Luxturna (voretigene neparvovec) for inherited blindness as being over \$1m before launching at a price of \$850,000.

Million-dollar price tags are an easy target for negative publicity, but Leschly fought back against the image. "What I can say for sure is, whether it is this medicine or even the Novartis medicine, it is not even close to the most expensive medicine that is out there. It is apples and oranges," he said.

For example, many drugs for rare diseases, including enzyme replacement therapies, or drugs like Spinraza (nusinersen) or Soliris (eculizumab) cost several hundreds of thousands of dollars a year and are taken chronically.

"We are forced into a price that takes all the entire lifetime costs to the patient into one fell swoop," he added. "That's a little lost on people, and I understand that. Yet, at the end of the day, that's where we feel really strongly about saying we're doing the best we can to figure out how you get all of this lifetime value upfront but are reasonable with the system." 🌟

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Amgen's Oncology Strategy: Building A Pipeline Of Novel Paradigm-Changing Drugs

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Amgen Inc. is starting to reach key value-inflection points in its early-stage cancer drug pipeline as it attempts to develop a portfolio of innovative, differentiated therapies that will be effective on their own and build on the promise of immuno-oncology agents, such as PD-1 inhibitors.

The company has a well-established portfolio of blockbuster supportive care therapies, including the anemia treatment Epogen (epoetin alfa), neutropenia thera-

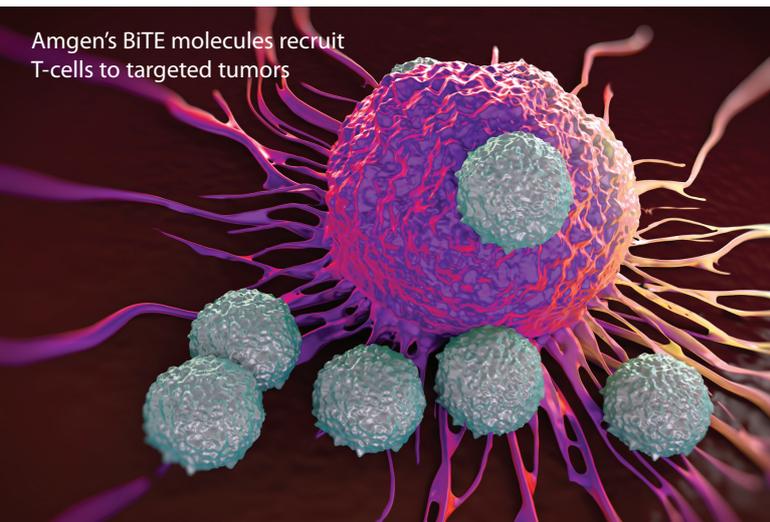
pies Neupogen (filgrastim) and Neulasta (pegfilgrastim), and Xgeva (denosumab) for the prevention of bone breaks in certain cancer patients.

However, Amgen has had some success building a portfolio of anti-cancer agents, including Kyprolis (carfilzomib), Blincyto (blinatumomab), Vectibix (panitumumab) and Imlygic (talimogene laherparepvec), but none have reached blockbuster status. Kyprolis came close in 2018 with \$968m in revenues.

Now, as the big biotech attempts to diversify outside of its mature workhorse brands like Epogen, Neupogen and Neulasta, the company is focused on novel mechanisms and new modalities with the goal of rapidly bringing high-value, first-in-class agents to market that expand its reach in oncology.

"This is our renaissance, where we have all of these new molecules coming through," Amgen vice president of oncology development Greg Friberg told *Scrip*.

Amgen's BiTE molecules recruit T-cells to targeted tumors



ADDING VALUE IN CANCER TREATMENT

When Friberg discusses value, he talks about the value of new medicines to society. A practicing oncologist prior to joining Amgen, Friberg noted in an interview that patients aren't looking for incremental gains from new cancer therapies, but major advances in treatment. That's where Amgen believes its drug candidates – such as the KRAS inhibitor AMG 510 that featured prominently at the recent American Society of Clinical Oncology (ASCO) meeting – can contribute value, he said.

"For some diseases, like even the acute leukemias, 10%-15% complete response rates probably aren't good enough anymore; we need to see something grander," Friberg said. "The blessing and the challenge and the gauntlet being thrown down by immunotherapies is that people are no longer looking for just delayed progression; they're looking for long-term survival – they want to raise the Kaplan-Meier curves."

AMG 510 is generating a lot of attention because of its ability to target the hard-to-reach KRAS oncogene and because of its remarkable efficacy, although in a small group of patients. Amgen reported a 50% response rate and 90% disease-control rate with minimal side effects in 10 evaluable non-small cell lung cancer (NSCLC) patients at ASCO.

The drug, which targets the KRAS G12C mutation, has moved from dose escalation into multiple dose-expansion cohorts in a Phase I solid tumor study, including a cohort testing the oral small molecule combined with Merck & Co. Inc.'s PD-1 inhibitor Keytruda (pembrolizumab). Amgen has not indicated whether it may be possible to seek accelerated approval for AMG 510 based on the dose-expansion cohorts in its ongoing trial or whether an additional Phase II study will be needed, but the company has said that it will provide more information about the path forward for the KRAS G12C inhibitor later this year.

"We still need more clarity on whether Amgen will need to include the lung expansion cohort (n=40) or run a larger trial to gain approval," Credit Suisse analyst Evan Seigerman noted in a 4 June report.

"The typical response rate (RR) in 2L and 3L NSCLC is so low (<10%) '510 could jump to first choice in 2L considering the 50% RR seen in the 10 patients reported," Seigerman speculated.

While it's unclear if the 40-patient lung cancer dose-expansion cohort could serve as a pivotal study for accelerated approval, Jef-

feries analyst Michael Yee predicted in a 3 June report that Amgen will move very quickly to talk with the US Food and Drug Administration about a rapid endorsement.

"We believe breakthrough therapy designation seems very possible and they could expand to say 80-plus patients and get accelerated approval," Yee added. "Previously, management has mentioned to us that a Xalkori ALK-like study could potentially be run for a relatively quick approval."

The US FDA granted accelerated approval for Pfizer Inc.'s ALK inhibitor Xalkori (crizotinib) for locally advanced or metastatic NSCLC in 2011 based on data from 255 patients with ALK mutations in two single-arm studies. (Also see "Pfizer granted accelerated OK for Xalkori in NSCLC ahead of schedule" - *Scrip*, 29 Aug, 2011.)

AMG 420, AMG 212 ALSO HIGHLIGHTED AT ASCO

Analysts were less enthusiastic and more cautious about Amgen's other oncology programs presented at ASCO – AMG 420 for multiple myeloma and AMG 212 for prostate cancer, which use the same bispecific T-cell engager (BiTE) technology as Blincyto.

The company has been ramping up development efforts using its BiTE platform for the past few years, including its first-generation continuously infused molecules and its less frequently dosed next-generation half-life extended (HLE) BiTEs.

Now, Amgen is beginning to report data that may demonstrate the value envisioned when it bought the technology's originator Micromet Inc. for \$1.16bn in 2012, but analysts view the HLE molecules – with initial data expected for those next-generation BiTEs later this year – as the potentially more valuable part of the BiTE proposition. (Also see "Amgen to swallow \$1.16B Micromet in one BiTE, like a cytotoxic T cell on a tumour" - *Scrip*, 27 Jan, 2012.)

"Overall, the reported data [for continuously infused AMG 420 and AMG 212] re-confirms the therapeutic potential of this platform and these programs, but also highlights their liabilities as well (continuous infusions, infection risks)," SVB Leerink's Geoffrey Porges said in a 4 June note. "In both solid and hematological malignancies, there is a trend toward dose-dependent efficacy, but also safety liabilities. We believe the observed efficacy signals generated at higher doses support further clinical investigation, but still believe that significant commercial opportunity will demand development of the company's emerging half-life extended versions."

Friberg was part of the due diligence team that evaluated Micromet's platform. The technology is used to create bispecific antibodies that target a specific receptor on cancer cells and recruit T-cells to tumors that express the target. He said he was intrigued by "this idea that not only can you look for a flag on the cell to try to use as a target for your warhead, but that warhead is the immune system."

"And there's some profound implications of that," Friberg added. "Unlike with cytotoxins, antibody-drug conjugates or even naked antibodies, the idea that the T-cell would be doing the heavy lifting here means perhaps more deep, long-lasting responses."

BEYOND BLINCYTO: MORE BiTE DATE EMERGES

Blincyto was approved in the US in 2014 for a subpopulation of relapsed or refractory acute lymphoblastic leukemia (ALL), but it has since been approved for a wider relapsed/refractory ALL population. (Also see "Amgen gains early US win for BiTE antibody Blincyto"

to" - *Scrip*, 3 Dec, 2014.) The BiTE also won a supplemental indication in March 2018 for the treatment of ALL patients in first or second complete remission who have minimal residual disease (MRD), becoming the first drug approved to treat MRD.

Blinicyto, which targets CD19, is administered in cycles as a continuous infusion with each cycle consisting of a 28-day infusion period and a 14-day off period for multiple cycles, the number of which depends on the indication and the severity of disease. Hospitalization is recommended during the first few days of treatment to monitor for severe cytokine release syndrome (CRS) or neurotoxicity.

The continuous dosing and recommended hospitalizations to monitor initial treatment side effects contribute to Blinicyto's less-than-blockbuster sales. However, its new MRD indication in ALL – Friberg said about 80% of patients with MRD after chemotherapy achieved MRD-negative status after treatment with Blinicyto in clinical trials – is contributing to major double-digit growth.

Amgen reported \$230m in 2018 sales for Blinicyto, which was up 31% from 2017, helped by 37% growth in the fourth quarter. So far in 2019, the company said sales jumped 41% to \$69m in the first quarter.

Follow-on compounds AMG 420 targeting B-cell maturation antigen (BCMA), AMG 330 targeting CD33 and AMG 212 targeting prostate-specific membrane antigen (PSMA) all use the same continuous infusion BiTE construct as Blinicyto.

Amgen presented data for AMG 420 at the American Society of Hematology (ASH) meeting in December, and confirmed this month at ASCO that five of the six relapsed or refractory multiple myeloma patients who responded to the BiTE and achieved MRD were treated with 400mcg/day – the dose taken into the dose-expansion stage of the company's ongoing Phase I/II clinical trial. Two other patients achieved a very good partial response and a partial response for an overall response rate of 70% (7/10) in the 400mcg/day dose group.

However, 19 out of 42 patients across dosing cohorts in the dose-escalation stage of the trial required hospitalization, including four with prolonged hospitalizations, Amgen reported during its ASCO update for AMG 420. Thirteen patients

experienced serious infections, but there was only one incidence of CRS (grade 3) and there were no grade 3 or 4 central nervous system toxicities.

The company did not provide updated results for AMG 330 in acute myeloid leukemia (AML) at ASCO, but at ASH in December it presented early results from a Phase I dose-escalation study. (Also see "AML Paradigm Shift: Doctors Welcome Many New Approvals And Approaches" - *Scrip*, 6 Dec, 2018.)

SOLID TUMOR, COMBO THERAPY PROMISE

ASCO gave Amgen its first opportunity to report results for a BiTE in a solid tumor, however, with Phase I dose-escalation results for AMG 212 in 16 prostate cancer patients. Responses to treatment based on reductions in prostate-specific antigen (PSA) were dose-dependent with three patients achieving a 50% or greater drop in PSA levels. One long-term responder's soft tissue metastases regressed completely, while his bone metastases showed signs of regression.

Friberg noted that this patient "had been riddled with metastatic tumors, was in a wheelchair and had a very nice response, including a near complete PET response. [The individual] was able to ski and live their life in ways that they hadn't been able to before."

Serious side effects for AMG 212 included three cases of CRS, two of which were grade 2 while one was a grade 3 case. However, the Phase I study was stopped before a maximum tolerated dose (MTD) was reached when the trial's sponsor – Amgen's partner Bayer AG – shifted its development priorities. Amgen has taken over the program and will advance AMG 212 on its own.

AMG 420, AMG 330 and AMG 212 have sister compounds using Amgen's HLE technology, which allows for weekly or possibly less-frequent dosing rather than continuous infusions. Initial results are expected this year for the HLE BiTE targeting BCMA (AMG 701) in multiple myeloma and may be reported this year for HLE BiTEs targeting CD33 (AMG 673) in AML, PSMA (AMG 160) in prostate cancer and FLT3 (AMG 427) in AML.

New and updated data also will be reported this year for compounds using the

first-generation BiTE technology, including Blinicyto in ALL, AMG 330 in AML and AMG 596, which targets EGFRviii, in glioblastoma.

Friberg said Amgen's BiTE data this year will begin to answer two big questions. First, do the BiTEs work in other diseases, particularly beyond blood cancers? Second, does the half-life extension technology work as well as the continuously infused BiTEs?

"When those cards turn over, we'll have a chance to see just how broadly we can apply some of this technology and which flavor of the technology that we could put out there," he said.

Questions of how broadly the BiTE technology can be applied also will begin to be answered as combination regimens are tested, including with immuno-oncology agents, such as PD-1/L1 inhibitors.

"The opportunity then in solid tumors – prostate cancer, glioblastoma – to try and sweep away residual disease that might be left over after ... surgery or chemotherapy or targeted therapy, it's an exciting prospect to me, because I just see it as an arrow from an entirely different quiver," Friberg said. "As you think of cancer as this complex beast where you want to take your best shots, but do it in a rational and sequential way, I'm excited that we've got, potentially, this whole new class of arrows to grab for. That's the promise. Now, they have to work."

NEXT NOVEL ONCOLOGY DRUGS: MCL-1 INHIBITORS

The next targeted Amgen cancer therapies with their first clinical date in 2019 will be myeloid cell leukemia sequence-1 (MCL-1) inhibitors, including the intravenously dosed AMG 176 and oral drug AMG 397. The company plans to report results this year in multiple myeloma and AML; another study is ongoing for AMG 397 in non-Hodgkin's lymphoma.

Targeting MCL-1 "has a lot of promise preclinically and now we're just trying to get a handle on its clinical profile," Friberg said. He noted that MCL-1 is a cousin of BCL2 – the target for AbbVie Inc./Genentech Inc.'s leukemia drug Venclexta (venetoclax).

MCL-1 and BCL2 "have sort of similar stories where these are signals that keep cells from dying in the face of stresses or these

signaling pathways,” Friberg explained. “Much like KRAS, it has been difficult to drug MCL-1, a little bit for a different reason, because it’s a protein-protein interaction as opposed to a kinase. But we seem to have a molecule that can interfere with this protein-protein interaction and pre-clinically we’re excited about what we see.”

Amgen anticipates that MCL-1 inhibitors will be effective as monotherapy and in combination with other agents. And as is the case with its KRAS inhibitor AMG 510, the company’s MCL-1 inhibitors may produce first-in-class clinical data. Only two other MCL-1 inhibitors are in the clinic, according to Biomedtracker – AstraZeneca PLC’s Phase I asset AZD5991 and the Phase I drug MIK665 developed by Servier SA and Novartis AG.

EXPANDING THE USE OF BLINCYTO, KYPROLIS

In addition to data for its early-stage molecules, Amgen continues to expand the use of its approved anticancer agents, including Blinicyto in ALL and the proteasome inhibitor Kyprolis for multiple myeloma.

Studies are ongoing for Blinicyto in first-line ALL and for a subcutaneous formulation of the BiTE.

Kyprolis, which was acquired in the \$10.4bn purchase of Onyx Pharmaceuticals Inc. in 2013, is approved in combination with dexamethasone and in combination with Celgene Corp.’s immunomodulatory agent Revlimid (lenalidomide) plus dexamethasone for relapsed or refractory multiple myeloma patients whose disease has progressed after one to three prior treatment regimens.

“Kyprolis has settled as what we like to think of as a best-in-class proteasome inhibitor for relapsed/refractory disease,” Friberg said. “From that standpoint, what we want to make sure of is that we have the right data for folks in the relevant combinations that are moving forward.”

That includes in combination with CD38 inhibitors, which have become an important new drug class in multiple myeloma. Johnson & Johnson’s CD38-targeting therapy Darzalex (daratumumab) “has just changed the landscape for multiple myeloma, so our big next card turning over is

a combination of Kyprolis with dexamethasone (Kd) with or without daratumumab.”

Results from the Phase III CANDOR study of Kd versus Kd with Darzalex are expected this year.

And in addition to US FDA approval for once-weekly dosing of Kyprolis, Amgen is pursuing approvals for the less-frequent dosing regimen globally. The drug’s original dosing regimen was twice-weekly.

“The third major pillar is that we’re collecting data [and] continuing to share not only the efficacy profile [of Kyprolis] in different settings and subsets,” Friberg said. “We want to get that story out there and the fortunate aspect is – that we’ve seen in our large randomized studies – that the benefits of Kyprolis seem to be there across all these different subsets [regardless of] renal dysfunction or age.”

In addition to Amgen’s ongoing efforts to broaden the use of its approved products, 2019 and 2020 may reveal whether the company’s investments in building out its oncology pipeline with novel molecules will pay off. 🌟

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Sobi Realigns Focus On Late-Stage Hematology & Immunology Assets

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Swedish Orphan Biovitrum AB, the Solna, Sweden-based speciality pharma company, is ramping up its immunology focus to build a second significant pillar alongside its hemophilia franchise. Adding to its growing Kineret (anakinra) business and the November 2018 acquisition of US rights to commercialize Synagis (palivizumab) from AstraZeneca PLC, Sobi has now exercised its option to acquire Gamifant (emapalumab) from Novimmune SA (Also see “Novimmune Sells Gamifant And IO Assets To Sobi” - *Scrip*, 14 Jun, 2019.) (Also see “Sobi Advances Growth Strategy With Gamifant Launch In Early 2019 For Primary HLH” - *Scrip*, 20 Nov, 2018.), as well as employees involved in the clinical and biopharmaceutical development of the program. The consideration is CHF515m (\$519m), of which CHF400m had already been committed in the license agreement.

Concurrently, the company has announced that it intends to look for additional on-market and late stage assets, discontinue and divest discovery and early research programs and reallocate R&D resources to late-stage development. The two early stage programs it is looking to divest are SOBI006, a pre-clinical anti-IL-1 product, and SOBI003, a chemically modified recombinant human sulfamidase to treat metabolic disease

mucopolysaccharidosis type IIIA (MPS IIIA), also known as Sanfilippo syndrome, an inherited lysosomal storage disease, which is in Phase I testing.

TWO CENTERS OF EXCELLENCE

The intended reorganization will see the company establish two centers of excellence: one for hematology in Sweden and another for immunology in Switzerland. Anticipated annual savings from the R&D reorganization, estimated at SEK200-300m (\$21-32m), will be reallocated to late stage development initiatives. Costs of around SEK100-200m, relating to the reorganization and redundancies, will be charged in 2019. The business development priority in the next 24 months will be to acquire more on-market products, one or two Phase III assets and possibly an option in a Phase II asset if it was core to the company’s strategy (Also see “New CEO Revamps Top Team, Specialty Care Business At Sobi” - *Scrip*, 25 Oct, 2017.).

In 2018, Sobi posted a 40% year-on-year increase in revenues, totaling SEK9.14bn (up from SEK6.5bn), with its hemophilia franchise accounting for nearly two thirds the number. Hemophilia product sales more than doubled from SEK1.9bn

to SEK4.2bn while royalty and manufacturing revenues associated with Refacto pushed the franchise contribution from SEK3.7bn to SEK6.0bn. The company's heavy reliance on hemophilia is already diminishing.

The company's immunology-focused franchise contributed SEK1.2bn to total 2018 revenues but the recent acquisition of Synagis, a humanized mAb against respiratory syncytial virus (RSV) F protein, for RSV infection, is already having a transformational impact on the company. Although the acquisition was only completed on 23 January 2019, towards the end of the RSV season, the product posted revenues of SEK665m in the first quarter of 2019. Indeed, alongside Kineret revenues of SEK346m and Gamifant revenues of SEK89m, immunology accounted for just over one third the company's first-quarter revenues of SEK3.3bn, a 66% year-on-year surge.

SOBI'S STRATEGY

Sobi acquired US rights to Synagis in a deal that saw the Swedish company pay AstraZeneca \$1.5bn up front – \$1bn in cash and \$500m in shares (which represented about 8% of the company) – and up to \$470m in milestones related to Synagis sales (*Also see "Sobi Taps AstraZeneca's RSV Therapies, Both Current And Future, For US Expansion" - Scrip, 13 Nov, 2018.*). The deal also involved about 130 AstraZeneca employees and rights to half of future US earnings of MEDI8897, a second monoclonal antibody targeting RSV. The MEDI8897 component of the deal included a commitment by Sobi to pay AstraZeneca \$175m after BLA submission plus \$160m in total non-contingent payments during 2019-2021.

A key pillar to Sobi's strategy is to take on-market products and run targeted life cycle management programs including the opening up of new indications. Sobi acquired full rights to Kineret from Amgen Inc. in 2013 after amending a 2008 deal that gave the Swedish company worldwide rights to the IL-1 receptor antagonist to treat rheumatoid arthritis and four orphan indications. In 2008, Kineret was only approved in the US and EU to treat rheumatoid arthritis. Since then, Sobi has secured approvals to treat neonatal-onset multisystem inflammatory disease (NOMID), cryopyrin-associated periodic syndrome (CAPS) and Still's Disease in the EU, an indication which is in Phase III trials in the US. Additional indications for Kineret being explored by Sobi include idiopathic recurrent pericarditis, pancreatic ductal adenocarcinoma and chimeric antigen receptor T-cell therapy toxicities.

With sales of key hemophilia products Elocta and Alprolix also making progress in the first quarter – Elocta saw sales rise 53% year-on-year to SEK991m and Elocta advanced 120% to SEK337m over the same timeframe – Sobi is forecasting that revenues could reach SEK12.5bn to SEK13.0bn in 2019; a 2.5 times multiple on the SEK5.2bn revenues posted in 2016. 🌟

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Analysts Impressed By Safety Profile Of Oral Semaglutide

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Novo Nordisk AS's investigational oral version of its GLP-1 agonist semaglutide is safe in patients with type 2 diabetes at high cardiovascular risk, according to full results from the PIONEER 6 study released at the American Diabetes Association (ADA) on 11 June, which showed a non-significant 21% reduction in major adverse cardiac events (MACE).

Full results of PIONEER 6, topline data from which was released last November, showed the trial met the primary objective of demonstrating non-inferiority to placebo in the incidence of major adverse CV events (MACE), which is a composite of CV death, non-fatal heart attack or non-fatal stroke.

Semaglutide is Novo Nordisk's ground-breaking oral GLP-1 diabetes therapy. It is the first oral formulation of a glucagon-like peptide-1 (GLP-1) receptor agonist developed for the treatment of type 2 diabetes. The Danish group hopes to launch the drug next year.

Summarizing the trial's main message, Mansoor Husain, PIONEER 6 investigator and lead author of the *NEJM* publication of the study, said: "The PIONEER 6 trial demonstrates that oral semaglutide does not increase the risk of major adverse cardiovascular events while providing further evidence for the overall cardiovascular profile of semaglutide."

The study is part of Novo Nordisk's PIONEER clinical development program, which is composed of 10 evaluations of its oral GLP-1 semaglutide as a diabetes treatment.

PIONEER 6 was designed to assess the cardiovascular safety of oral semaglutide, which is awaiting approval in the US, compared with placebo in a type 2 diabetes patient population at high risk of CV events.

PIONEER 6 had a relatively short duration of follow-up of just under 16 months.

It also had a relatively small number of patients. Just 3,183 patients were enrolled in PIONEER 6, whereas patient numbers have been far higher in other CV outcomes trials for this drug class such as REWIND with Eli Lilly & Co.'s Trulicity (dulaglutide), and LEADER, assessing Novo Nordisk's injectable Victoza (liraglutide), which each included around 9,000 patients.

Although a relatively small trial designed to show non-inferiority, analysts said there was a clear trend towards benefit on the primary composite endpoint of CV death,

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“It will be interesting to see if oral semaglutide is able to receive a CV claim in its label.” - Credit Suisse

non-fatal heart attack or non-fatal stroke. Bryan, Garnier and Co in a reaction note to investors on 12 June called the full PIONEER 6 results “very impressive”, adding that “the magnitude of the benefit after only 16 months was a very positive surprise, particularly as 85% of participants had CV or chronic kidney disease.”

Credit Suisse noted that the overall hazard ratio was 0.79, “suggesting a 21% risk reduction with oral semaglutide, although the 95% confidence interval of 0.57-1.11 crossed 1.0 and thus did not allow for the results to be considered statistically superior.”

Analysts generally expect the FDA to approve oral semaglutide by September.

Novo Nordisk expects the Food and Drug Administration to decide by early next year on whether the drug maker can sell its diabetes injection version Ozempic and the oral formulation as protective of heart health. Neither of the two drug versions have completed long-term cardiovascular outcomes studies on the scale of their main competitor, Eli Lilly’s Trulicity.

“Given differences in performance for oral semaglutide in PIONEER 6 and injectable semaglutide in SUSTAIN 6 on some of the individual components of the composite endpoint, it will be interesting to see if oral semaglutide is able to receive a CV claim in its label early next year, or if the FDA will want to wait for the results of the larger SOUL trial that is starting now,” analysts at Credit Suisse said.

Injectable semaglutide-treated patients in the SUSTAIN 6 trial had a significant 26% lower risk of the composite outcome of death from cardiovascular causes, nonfatal myocardial infarction or nonfatal stroke than those receiving placebo.

Some analysts believe use of existing GLP-1 agonist drugs will be limited by the fact they need to be injected.

But an orally administered GLP-1 agonist such as semaglutide will also have its challenges.

“It will be very important to see how the product performs in the real world, given the need to take the medication by mouth every day on an empty stomach with up to 4 ounces of water and then having to wait at least 30 minutes before eating, drinking or taking any other oral medication,” analysts at Credit Suisse said.

“How the product is priced relative to other oral products and injectable GLP-1s will also obviously play a role in the commercial impact the product has,” they added. ✨

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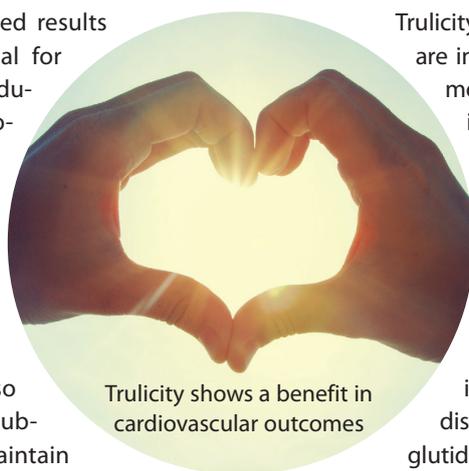
Lilly’s Trulicity Shows Unique Cardiovascular Outcomes Benefit, Albeit A Modest One

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Eli Lilly & Co. reported the first detailed results from a cardiovascular outcomes trial for the GLP-1 receptor agonist Trulicity (dulaglutide) at the American Diabetes Association’s annual meeting on 9 June in San Francisco, showing treatment with Trulicity resulted in a significant 12% reduction in major cardiovascular events in a uniquely broad patient population. But the results were more modest than some investors had expected.

Trulicity competes in a crowded class, so it’s unclear if the data will give Trulicity a substantial commercial boost as it works to maintain its market-leading position against competition from Novo Nordisk AS’s Ozempic (semaglutide), which has shown a bigger benefit on cardiovascular outcomes but in a narrower patient population.

Lilly released positive top-line results from REWIND in November without providing any details, but it set investor expectations high. (Also see “Lilly’s CVOT Success With Trulicity Causes Bullish Outlook For Diabetes Franchise” - Scrip, 6 Nov, 2018.)



Trulicity shows a benefit in cardiovascular outcomes

Trulicity and Ozempic are both GLP-1 agonists that are injected once a week, but Lilly will face even more competition from Novo Nordisk because it has already filed the first oral GLP-1 agonist, an oral version of semaglutide, which is pending at the US FDA with approval expected later this year.

Lilly’s cardiovascular outcomes trial for Trulicity enrolled patients with or without established cardiovascular disease, whereas Novo’s CVOT for Ozempic was conducted in patients with established cardiovascular disease, where the benefit was bigger. Semaglutide-treated patients in the SUSTAIN-6 trial had a significant 26% lower risk of the composite outcome of death from cardiovascular causes, nonfatal myocardial infarction or nonfatal stroke than those receiving placebo.

Lilly’s Trulicity is the first type 2 diabetes medicine to significantly reduce major adverse CV events (MACE 3) in a study population where the majority of participants had CV risk factors without established CV disease. Lilly confirmed that it has filed the REWIND data with regulators in Europe and the US, and is expecting ap-

proval of a cardiovascular risk-reduction claim in 2020.

"We expect the Trulicity label to align with the REWIND cardiovascular outcomes study population," VP-US diabetes Ilya Yuffa said in a 10 June conference call.

STAKING A CLAIM IN A COMPETITIVE MARKET

Nonetheless, Morgan Stanley analyst David Risinger said in a 10 June research note that the Trulicity data were disappointing. The modest results may not move the commercial needle, he noted, because while the benefit in REWIND was in a broader patient population – patients with or without established cardiovascular disease – Ozempic showed a greater risk reduction in a more targeted patient population.

"We believe that doctors are likely to view CV risk reduction as a GLP-1 class effect regardless of established CV disease," he said. "Therefore, physicians concerned about patient CV risk may prefer Ozempic over Trulicity even if Ozempic receives a narrower indication for established CV disease in 2020."

Biomedtracker analysts attending ADA said key opinion leaders found the data underwhelming. "While the data in those without CV disease were novel and could impact guidelines, the CV benefit did not really appear any stronger than other GLP-1 agonists that have had positive CVOTs," they said. "KOLs and investigators we spoke with [are] fairly confident that the difference in primary prevention patients was just due to differences in the trial designs."

Novo Nordisk filed a supplemental new drug application (sNDA) with the FDA for once-weekly Ozempic in March to expand labeling to include an indication for reduction in the risk of major adverse cardiovascular events (MACE) such as heart attack, stroke or death in patients with type 2 diabetes and established cardiovascular disease, based on the results of SUSTAIN-6. The filing coincided with Novo Nordisk's regulatory filings for oral semaglutide for cardiovascular risk reduction and blood sugar control.

REWIND enrolled 9,901 adults with type 2 diabetes and compared a 1.5mg dose of Trulicity versus placebo, in addition to standard of care, on the risk of MACE 3. The trial was the longest CVOT trial in the GLP-1 agonist class (median 5.4 years) and consisted primarily of people without established CV disease. While all participants had CV risk factors, only 31% of study participants had established CV disease. The trial results were simultaneously published in *The Lancet*.

Lilly is running a Phase III trial testing two higher doses of Trulicity, a 3mg dose and 4.5mg dose, which could show a greater benefit on blood-sugar reduction and weight loss.

"If successful, this would provide more options for patients to stay on Trulicity and gain further clinical benefits," Yuffa said.

Lilly also presented more Phase II data its dual GIP/GLP-1 receptor agonist tirzepatide in patients with type 2 diabetes. (Also see "Questions Persist On Lilly's Tirzepatide And Tolerability" - *Scrip*, 10 Jun, 2019.)

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AZ's Farxiga Fillip As Drug Reduces Renal Disease Risk In Type 2 Diabetics

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Having already shown that its blockbuster Farxiga can reduce cardiovascular events in diabetes patients, AstraZeneca PLC has presented data which shows that the drug can also cut the risk of kidney disease or renal death, giving the firm a boost in its battle to maintain market share in the fiercely competitive SGLT2 inhibitor class.

The company has presented a pre-specified analysis from the Phase III 17,160-patient DECLARE-TIMI 58 cardiovascular outcomes trial at the American Diabetes Association meeting in San Francisco which showed a 47% reduction in kidney function decline, end-stage renal disease (ERSD) or renal death for Farxiga/Forxiga (dapagliflozin) compared with placebo. The drug also reduced the relative risk of a cardio-renal composite of kidney function decline, ESRD, or renal or cardiovascular death by 24% compared with placebo.

OVERLOOKED PROBLEMS

Elisabeth Björk, head of AstraZeneca's head of late-stage development at the firm's cardiovascular, renal and metabolism (CVRM) unit, told *Scrip* that heart failure and renal complications are among the earliest problems of patients with type 2 diabetes and are often overlooked. "The fact that we are able to reduce them

in this broad patient population, one that is representative of the patients that are seen by the primary care physician is very important, very striking."

Joris Silon, senior vice president of CVRM, added that real world evidence showed that heart failure and chronic kidney disease were the first and the most prevalent complications seen in quite healthy diabetes patients and "preventing these cardio and renal events are what really matter for patients and for the healthcare system at large. It is very costly to treat these patients so preventing the complication makes a lot of difference." People with diabetes have a six-to-twelve times higher risk of developing ESRD and are twice as likely to develop chronic kidney disease (CKD) than those without, the company noted.

The renal analysis comes six months after AstraZeneca presented primary results from DECLARE at the American Heart Association meeting in Chicago showing that Farxiga could cut hospitalizations for heart failure or cardiovascular death hospitalization for heart failure or CV death in a broad patient population by 17% against placebo. (Also see "AstraZeneca: DECLARE-TIMI Outcomes May Support Competitive Claim For Farxiga In Heart Failure" - *Scrip*, 13 Nov, 2018.)

In another sub-analysis of the study presented at the American College of Cardiology meeting in New Orleans in March this year, Farxiga reduced the risk of major adverse cardiovascular events (MACE) by 16% compared with placebo in diabetics who had a prior heart attack and also cut hospitalization rates for heart failure regardless of ejection fraction status, a measurement of the percentage of blood leaving the heart with each contraction.

Björk stressed that the population in DECLARE was broader than that studied by AstraZeneca's rivals in the SGLT2 space. Johnson & Johnson's Invokana (canagliflozin) which has fallen behind Farxiga and Boehringer Ingelheim GmbH/Eli Lilly & Co.'s market leader Jardiance over amputation concerns, showed positive renal disease results in April from the CREDENCE study at the International Society of Nephrology meeting in Melbourne but in sicker patients than those studied in the AstraZeneca trials; based on CREDENCE, the US Food and Drug Administration granted a priority review of Invokana for chronic kidney disease in patients with type 2 diabetes last month.

As for Jardiance, a kidney disease sub-group analysis from the landmark 7,000-patient EMPA-REG cardiovascular trial has been encouraging and last year BI began the EMPA-KIDNEY program in partnership with Lilly, Oxford University, Duke University and others to study Jardiance in patients with chronic renal disease, evaluating 5,000 diabetic and non-diabetic patients. (Also see "BI Bets On Expanding Jardiance As Diabetes Drug Sales Soar" - *Scrip*, 18 Apr, 2019.)

Farxiga, which was approved in Europe and Japan earlier this year for type 1 diabetes as well, is already a big earner for AstraZeneca with first quarter sales up 17% to \$349m. The data from the renal sub-analysis will be shared with regulators, Björk noted, adding that next year would see a read-out from the Dapa-CKD trial of Farxiga in patients with and without diabetes, which will include sicker patients than those in DECLARE. (Also see "AZ's Forxiga Gets Type 1 Diabetes EU Okay As Sanofi Suffers US Setback" - *Scrip*, 25 Mar, 2019.)

Silon told *Scrip* that patients with renal disease, diabetic or not, "have maybe been left in the cold a little bit, even though the medical need is high. If you have declining kidney function, there is not so much out there, so we really are trying to do more." He noted that later this week at the European Renal Association and European Dialysis and Transplant Association (ERA-EDTA) meeting in Budapest, Hungary, AstraZeneca will be presenting data on the company's potassium binder Lokelma (sodium zirconium) "where we will hopefully be able to show that we can help patients on dialysis with the complications of hypokalemia."

The company's other big hope in the renal space is roxadustat, a first-in-class oral inhibitor of hypoxia inducible factor-prolyl hydroxylase (HIF-PHI) which is partnered with FibroGen Inc. and was approved in China in December to treat anemia in chronic kidney disease patients on dialysis. However, confusion over top-line pooled cardiovascular Phase III safety data on roxadustat caused shares in both AstraZeneca and FibroGen to slide when unveiled on 9 May this year. (Also see "AstraZeneca, FibroGen Plan New Roxadustat Filings, But CV Data Confuse Investors" - *Scrip*, 10 May, 2019.) (Also see "First Approval For AZ's Roxadustat With China Green Light" - *Scrip*, 18 Dec, 2018.) 🌟

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Provention Bio Soars On Hopes Teplizumab Is Type 1 Diabetes Game Changer

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Provention Bio Inc.'s market value soared on Monday after news the US-based biotech's investigational anti-CD3 monoclonal antibody teplizumab delayed the onset of type 1 diabetes (T1D) in people at high risk – the first time a drug has been able to delay or prevent the disease.

Results from the study, presented at the American Diabetes Association meeting in San Francisco at the weekend, showed that a single 14-day course of teplizumab, or PRV-031, significantly delayed the onset and diagnosis of clinical T1D, compared with placebo, by a median of two years in children and adults considered to be at high risk.

The median time to clinical diagnosis of T1D for placebo participants was just over 24 months. In comparison, the median time for teplizumab-treated participants to clinical diagnosis of T1D was just over 48 months ($p=0.006$).

During the trial, 72% in the placebo group developed clinical diabetes compared with only 43% of the teplizumab group. Teplizumab was well tolerated and the safety data were consistent with prior studies in newly diagnosed patients.

Type 1 diabetes is the second most common disease in children, after asthma, according to Disruptive Tech Research.

POSSIBLE PARADIGM SHIFT

"This ground-breaking study demonstrates that we can use immunotherapy, specifically PRV-031 (teplizumab), to prevent or significantly delay the onset of clinical type 1 diabetes by at least two years in individuals who will almost certainly progress to clinical disease," Eleanor Ramos, Provention's chief medical officer and chief operating officer, told analysts on a webcast held by the company on 10 June.

"We view this as a major paradigm shift," she added.

The long-running study was conducted by the Type 1 Diabetes TrialNet, an international collaboration aimed at discovering ways to delay or prevent T1D.

Its purpose was to evaluate Provention Bio's PRV-031 (teplizumab) for the prevention or delay of clinical T1D in relatives of type 1 diabetics at high-risk of developing the disease.

NASDAQ-listed Provention Bio acquired all rights to teplizumab, a 33-year-old drug, in May 2018 from MacroGenics Inc., which along with Eli Lilly & Co. had previously tried to develop the compound under a 2007 partnership but then abandoned the anti-CD3 monoclonal antibody after it failed in a trial to lower subjects' overall daily insulin usage and HbA1c level at 12 months.

Explaining Provention's thinking at the time, Ramos last May said: "Data from previous clinical studies of PRV-031 have indicated the drug's potential to intercept the progression of recently-diagnosed type 1 diabetes by resetting the immune system and stopping the immunologic attack on the beta cells of the

pancreas, as measured by C-peptide levels." Provention Bio will now seek breakthrough therapy designation for teplizumab in treating at risk T1D patients as well as exploring other possibilities for the compound.

Kevan Herold, a professor of immunobiology and internal medicine at Yale University and lead author of the study told the analysts call that "this is the first trial to successfully delay diagnosis of T1D in at-risk individuals."

"This begins to speak to the question about prevention: will this actually prevent the onset of diabetes? I would say from these data that we don't know yet, but there certainly are very exciting findings here to suggest that the effect could even be long lasting," Herold added.

Ashleigh Palmer, Provention Bio's CEO, told the analyst call that "based on the 'at risk' study's remarkable result, we plan to expand our clinical development program for teplizumab to address the continuum of T1D."

"Our initial focus with teplizumab has been intercepting T1D within six weeks of diagnosis. Consistent with this effort, in April we initiated a Phase III pivotal study – the PROTECT Study – in patients recently diagnosed with clinical T1D."

The CEO added, "With the 'at risk' study in hand we have also initiated discussions with the FDA to determine the regulatory path forward in preventing or delaying onset of clinical stage disease in at risk individuals. To facilitate this process, we will be pursuing breakthrough therapy designation for teplizumab."

BULLISH ANALYSTS

Analysts and investors responded enthusiastically on Monday to teplizumab's prospects and implications for Provention Bio as an investment.

Analysts at Disruptive Tech Research urged investors to buy the biotech's stock immediately.

"A drug with the potential to generate billions directly from T1D and tens of billions of dollars if it expands into other autoimmune diseases is worth at least \$1 billion in market capitalization. That would translate into roughly \$26 per share. Hence, the suggestion to buy shares today up to almost any price," they said in a note to investors. 🌟

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AbbVie Ups The Ante For Upadacitinib At EULAR

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With approvals for upadacitinib expected in the coming months, AbbVie Inc. has been making the case for its closely watched JAK1 inhibitor with long-term data demonstrating that the drug works better than its own mega-blockbuster Humira in keeping rheumatoid arthritis patients in clinical remission as well as improving their symptoms.

The US major presented new results from the SELECT-EARLY and SELECT-COMPARE Phase III trials at the European League Against Rheumatism congress in Madrid which show that over 48 weeks "a significantly higher proportion of patients" treated with once-daily upadacitinib monotherapy or in combination with methotrexate stayed in clinical remission, compared with those treated with methotrexate alone or a combination of the latter and Humira (adalimumab). AbbVie also noted that the oral treatment improved signs and symptoms of rheumatoid arthritis, as evaluated by the American College of Rheumatology (ACR) 20 and 50 measure.

Aileen Pangan, executive medical director at AbbVie's immunology unit, told *Scrip* that sustained remission, defined as lasting six months or more, is the primary treatment goal according to the American College of Rheumatology and EULAR recommendations but some 70% of treated patients are not achieving it. She added that "to really know if we're delivering innovation in the clinic," it was crucial to test upadacitinib against Humira, a leader of the anti-TNF class which has become a standard of care in RA, and to demonstrate the new drug's superiority in terms of both clinical responses and remission.

Putting together clinical packages for approval has become increasingly complex. "We're constantly trying to evaluate how we're doing things so that we can adjust because we're no longer doing Humira trials from 15 years ago. That was a very different time," said Pangan. The bar for demonstrating levels of efficacy is higher



Aileen Pangan

nowadays, and she noted that while AbbVie still measures ACR20 as a primary endpoint, "because it was required by the US Food and Drug Administration," it has set itself the more stringent goals of ACR50 and 70, as well as a range of remission endpoints.

Additionally, AbbVie presented data from an integrated analysis across five Phase III SELECT clinical trials which showed that treatment with upadacitinib in patients with moderately to severely active rheumatoid arthritis demonstrated "a consistent safety profile." The latter is under particular scrutiny for drugs in this class, especially as the FDA approved a 2 mg daily dose of Eli Lilly's oral JAK1/2 inhibitor Olumiant (baricitinib) a year ago for rheumatoid arthritis but turned down the 4 mg version over concerns about thrombosis – one of multiple risks flagged in a boxed warning on Olumiant's label. (Also see "Lilly Prices Olumiant For JAK Battle, But Misses Approval For Higher Dose" - *Scrip*, 2 Jun, 2018.)

Pangan told *Scrip* that across all the five pivotal studies, "we're not seeing anything unexpected." She noted that serious infection rates are higher than placebo but are similar to those seen with Humira – "but I think it adds value when you just don't have placebo, but you have a long-

term active comparator, and you are able to show the rates are comparable, because physicians are very familiar with methotrexate and Humira." (Also see "AbbVie Soothes Safety Fears With More Upadacitinib RA Data" - *Scrip*, 7 Jun, 2018.)

Upadacitinib has been filed on both sides of the Atlantic and AbbVie used a priority review voucher to speed up evaluation of the drug at the FDA. The company expects a decision from the agency in the third quarter and the firm will be hoping that it will soon start helping to soften the blow of the rapid erosion in sales that Humira is experiencing in Europe as a result of biosimilar competition – the \$20bn blockbuster is protected in the US until 2023.

ECONOMIC ARGUMENT

One of the challenges AbbVie will have in Europe, if upadacitinib is approved, will be to convince doctors to prescribe it given the availability of Humira biosimilars and off-patent versions of other anti-TNFs such as Amgen/Pfizer's Enbrel (etanercept) and Johnson & Johnson/MSD's Remicade (infliximab). Key to meeting that challenge will be the remission data and at an event on the sidelines of the EULAR meeting, Louis Bessette, a professor from Laval University in Canada put forward an economic as well as clinical case for drugs that do better on the remissions front than the older biologics.

He cited an analysis of over 4,500 older patients from Corrona, the world's largest real-world registry of rheumatoid arthritis patients, which revealed that those in remission had the lowest an-

nual medical costs (about \$11,000), while those with high disease activity had the highest (over \$20,000). The difference between remission and moderate disease activity was about \$6,500 a year, and unsurprisingly, higher rates of hospitalization (and higher costs) occurred as disease activity increased.

Bessette told *Scrip* that when patients have achieved remission for a year or so, physicians can look at drug tapering, dose reductions and discontinuation, a factor for payers to consider. That is before the direct and indirect costs of uncontrolled rheumatoid arthritis, such as impaired work productivity and absenteeism, are taken into consideration, he added.

As for upadacitinib's prospects in other areas, Pangan noted that Phase III trials in psoriatic arthritis, Crohn's disease, atopic dermatitis and ulcerative colitis are ongoing and it is also being investigated to treat ankylosing spondylitis and giant cell arteritis. She also highlighted ABBV-599, a combination of upadacitinib and the BTK inhibitor ABBV-105, which is in Phase II.

Pangan acknowledged that when a lot of companies try to do trials in the same diseases, patient enrolment can be an issue, and this is the case in the immunology space at the moment. However, "AbbVie has had many years of experience doing this and we understand what our investigators need and we understand the countries where we do our studies. We are experts in immunology and know what we need to do to get our programs moving forward." 🌟

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Novartis MAXIMISEs Cosentyx PsA Position

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As rival companies prepared to present data at the European League Against Rheumatism (EULAR) congress on their drugs for psoriatic arthritis (PsA) and related diseases, Novartis AG kicked off the Madrid meeting with a study of its blockbuster Cosentyx which the Swiss firm believes will consolidate its market-leading position.

The Basel-headquartered major has presented new data from the MAXIMISE trial evaluating Cosentyx (secukinumab), in the management of axial manifestations of PsA. The ongoing 52-week Phase IIIb trial met both its primary and key secondary endpoint with 63.1% of Cosentyx 300mg and 66.3% of 150mg patients achieving a 20% improvement in the Assessment of Spondyloarthritis International Society (ASAS20) measure at week 12 versus 31.3% for placebo.

Commenting on the results, Antonio Mera Varela, head of rheumatology at the University of Santiago de Compostela, Spain, said, "This is the first time we've seen the efficacy of a biologic in the axial manifestations of PsA at 12 weeks. It's highly important that there is something that can help manage all aspects of my patients' PsA."

In an interview with *Scrip*, Eric Hughes, global development head of immunology, hepatology and dermatology, said MAXIMISE was "a pretty robust study of 498 patients looking at an endpoint that people have really neglected before in PsA." He noted that PsA was "a complex disease and has lots of manifestations

"It's highly important that there is something that can help manage all aspects of my patients' PsA." –

Antonio Mera Varela

including joint pain, enthesitis, dactylitis and psoriasis of the skin and nails but two-thirds of patients actually have inflammatory backpain as well and we're really excited to be leading this area."

Hughes added: "It is a curious thing that traditionally, we've always thought of just ankylosing spondylitis (AS) in terms of axial inflammatory back pain but the measures that we use to determine the effectiveness of drugs in this area, American College of Rheumatology (ACR) scores, actually don't include back pain in the assessment. So even though we know two-thirds of PsA patients have inflammatory back pain, we haven't been measuring it. Novartis is leading the charge showing that Cosentyx has activity against it, it comes on quickly and we hope to show that it lasts."

The MAXIMISE data will be useful for physicians and Hughes also hopes that they will be considered for the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) guidelines

in the US. "The group has been struggling with this because no one's had a great dataset to look at. Now for the first time, we have a large randomized control study with a primary endpoint, which will help them develop and update their guidelines."

Cosentyx, which is approved for psoriasis, AS and PsA, is Novartis' best-selling drug, and first-quarter 2019 sales came in at \$791m, a 36% rise on the like, year-earlier period. There are other interleukin-17 inhibitors playing catch-up – Eli Lilly & Co's Taltz (ixekizumab), and Valeant/Leo Pharma AS's Siliq/Kyntheumin (brodalumab) – but Novartis believes the scale and quality of data it has generated, with three five-year Phase III extension studies in psoriasis, PsA and AS and having more than 200,000 patients treated with Cosentyx since launch just over four years ago, will keep the drug at the top of the class.

At EULAR, Novartis also presented new data from the 996-patient randomized FUTURE 5 trial showing no radiographic progression in almost 90% of PsA patients treated with Cosentyx 300 mg over two years. Additionally, the study showed that 77% of patients achieved ACR20 and 51.9% reached ACR50, with 70.1% getting a Psoriasis Area and Severity Index (PASI) score of 90; 49.5% had PASI 100, or completely clear skin.

Significant results were also achieved at the lower 150mg dose (79.4% ACR20, 52.6% ACR50, 59.2% PASI 90 and 44.2% PASI 100). Cosentyx "is an amazing molecule and its durability is fantastic," Hughes concluded, claiming the data generated shows that IL-17A "really is the key cytokine of the inflammatory process" for psoriasis, PsA and AS. 🌟

Published online 13 June 2019

Aurobindo Upbeat On Outlook As It Moves To Close Sandoz Deal

PENELOPE MACRAE

Aurobindo Pharma Ltd. said it expects to close its big-ticket purchase of Sandoz International GMBH's US dermatology business and general oral solids portfolio within eight to 12 weeks, as it reported an 11% jump in quarterly profit to INR5.85bn (\$84.3m) from a year earlier.

Aurobindo added the acquisition, which plugs key product gaps and includes three manufacturing plants, may give sales a bigger than expected boost despite ongoing US pricing pressures.

The Indian firm said it has done its sums and that the Sandoz deal could beat its earlier expectations for the acquisition, which that will make it the second-largest US prescription generic player, up from fifth. The purchase will also vault the company to second spot in the dermatological drugs segment.

Aurobindo will pay \$900m upfront to Sandoz' parent, Basel-based Novartis AG, which is pivoting to higher-growth areas like more complex generics, followed by \$100m in performance-based payments.

"The Sandoz acquisition is adding almost 300 products to the portfolio, apart from a certain number of products in the pipeline, so just the combination of the business growth, plus the opportunity to grow in terms of specific launches...is what will really fuel the

growth," Aurobindo managing director N. Govindarajan told analysts in an earnings conference call.

The Indian company has been hit by a rash of US regulatory bad news recently, along with US lawsuits alleging price-fixing by Aurobindo and other Indian generic drug makers, and the firm's shares have shed INR130 in the past month to hit INR619.50 on 7 June.

But analysts believe the Hyderabad-based firm offers far more positives than negatives, and 15 out of 19 Indian brokerages have "buy" recommendations for Aurobindo shares, underpinned by high expectations for the Sandoz acquisition.

IMPACT FROM REGULATORY ISSUES?

In mid-May, Aurobindo announced the US FDA had classed three of its plants which export to the US as "official action indicated," meaning the company can't win US regulatory approval for products until compliance problems are fixed. Aurobindo gave no timeline for expected resolution of the agency's complaints but told analysts it is confident the regulatory notice won't disrupt supplies or revenue from operations.

Investors' concerns about these regulatory problems "are misplaced as only five-six products (out of 100-plus pending) are

dependent on these plants," noted Indian brokerage HDFC analyst Amey Chalke.

Fresh legal troubles for Aurobindo surfaced just recently when a bankrupt US generic drug distributor, Aceto Corp, filed lawsuit against Aurobindo and founder P V Ramprasad Reddy, accusing them of waging a "systematic scheme to destroy" the company's business. Aceto alleges Aurobindo failed to supply multiple drug orders, leading to revenue losses that caused its bankruptcy.

Aurobindo, which like several other Indian generic firms is facing US lawsuits alleging price-fixing, said it "vigorously denies" the allegations. (*Also see "Aceto Claims Aurobindo Caused Its Collapse" - Scrip, 6 Jun, 2019.*)

Despite the regulatory and legal issues, Aurobindo remained upbeat on its prospects. At the time of the Sandoz deal announcement, "we'd made some estimates, factored in certain variables such as competition and pricing. At this point of time, we're fairly optimistic we would beat our expectation," North America chief financial officer Swami Sambamurty Iyer said in the conference call.

In any event, "we feel reasonably optimistic that what we predicted, we'll be able to achieve," Swami told analysts. Aurobindo forecast in announcing the deal that the acquired Sandoz portfolio would

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notch \$900m in sales in the first 12 months after the transaction's completion.

That \$900m revenue projection was lower than the \$1.2bn in sales the acquired Sandoz portfolio racked up in 2017, and highlights the fierce generic drug competition in the US that has forced down prices - although some companies now report some stability may be returning to the market.

But analysts are looking to Aurobindo's vertical integration and strong cost-competitiveness to make a success of the Sandoz acquisition. They see the company as being able to squeeze cost synergies from the acquisition through its strong manufacturing base. "Its vertically integrated model with huge capacity [is] unmatched by most peers," noted ICICI analysts Siddhant Khandekar and Mitesh Shah.

Other analysts say Aurobindo is emerging as an important consolidator in the generics space as other branded companies like Novartis look to rationalize their portfolios. Also, expectations for the positive effects of the acquisition were fueled when Sandoz' US business's operating margin of 25% beat forecasts of 20% for the March quarter.

'LAST LEG' OF SANDOZ TRANSACTION

The Sandoz transaction is waiting to receive US Federal Trade Commission clearance, which is subject to the divestment of overlapping assets, and analysts are anxious this process not be delayed. As the acquired Sandoz businesses includes some "rapidly declining" opportunities, timely completion is critical, analysts caution.

"We're in the last leg of this [acquisition] process," Aurobindo chief operating officer Sanjeev Indravadan Dani said during the conference call. "It's our own estimate it [the FTC approval] could be anywhere between eight to 12 weeks," he said. Novartis said separately on 1 May it expected the sale to be completed in the third quarter. (Also see "Slowing Biopharmaceuticals Puts A Dent In Sandoz' Sales" - *Generics Bulletin*, 1 May, 2019.)

Aurobindo's fourth-quarter results to 31 March showed sales increased across all business lines, particularly in the US market, where revenues leaped by more than

31% to \$353m from the same year-earlier period. The US sales, which accounted for 47% of total revenues, were lifted by 86% year-on-year growth in injectable revenues and new business opportunities.

With more than 40 product approvals, integration of the Sandoz portfolio and a ramp-up in injectable revenues, analysts forecast the US segment will notch \$2.3bn in sales by fiscal year 2021 which would equate to 33% CAGR.

"The key driver for APL [Aurobindo Pharma Ltd], henceforth, will be the integration of Sandoz' oral and dermatology business acquisition," said Vishal Manchanda, research analyst at India's Nirmal Bang brokerage. Aurobindo's Europe sales, meanwhile, rose 14% in the quarter while rest of world revenues jumped 38%. EBITDA climbed 32% in the quarter year-over-year to INR10.6bn, and Aurobindo's results were also flattered by a 6-7% fall in the Indian currency against the US dollar.

FOCUSING ON INTEGRATING ACQUIRED BUSINESSES

"Near-term priorities are to integrate the acquired businesses, improve the efficiencies and achieve synergies," managing director Govindarajan told analysts, adding management was pleased with the strong quarter. He predicted "steady progress on our differentiated pipeline during the year coupled with the recent acquisitions will drive the future growth."

The company was busy on the acquisition front during the last financial year. Along with its debt-funded purchase of the Sandoz dermatology and generic business, it bought Canadian generic giant Apotex Inc's businesses in five European countries for €74m (\$83.8m).

In January, Aurobindo announced a deal to buy seven marketed oncology injectable products from US-based Spectrum Pharmaceuticals Inc. for \$300m that included strong marketing infrastructure, giving the company entry to the branded oncology market.

Net debt jumped 49% in the quarter to INR48bn. Still, given Aurobindo's track record of successful acquisitions and "looking at the broader picture of synergy... the company is well poised to manage this added [debt] burden," said brokerage ICICI.

Govindarajan said the Apotex acquisition is already working out well. "We're looking at very good sales synergy after the operations have been streamlined... we'll be economizing on the cost of production. It's a loss-making business as we take over. And I think in about one and a half years, you will see the results," he told analysts.

Govindarajan, who began working for Aurobindo in 2010, has been spearheading a drive to transform the company from what he's described as a "me-too" company producing simple copycat generics to having a differentiated portfolio in higher-margin, more niche areas.

Earnings from acquired operations are expected to drop over time. But analysts say Aurobindo can aggressively invest in restructuring costs to ensure margins remain favorable, while to ensure long-run growth the company said it's continuing to build capabilities in alternate dosage forms like respiratory inhalers, peptides, vaccines and depot injectables.

R&D, BIOSIMILARS

As part of its drive to steer products into more complex areas, Aurobindo spent about 5% of sales this year on R&D and said it would spend 5-6% of its expanded sales base on R&D for next year as its efforts to bring its first biosimilar to market gain momentum.

"Please remember that next year will be more crucial. Because by the time, I think we would get at least Phase I of one biosimilar," said CFO Subramanian.

Aurobindo said in December that it expected its first biosimilar product to receive approval in the US in the next 12-18 months, while in Europe it hopes for a green signal by 2022. It forayed into the biosimilar space when it acquired four cell culture-derived products from Switzerland-based TL Biopharmaceutical AG.

Aurobindo said it launched 15 products including four injectables during the quarter. It received final approval for eight ANDAs during the period, taking the total such approvals for the year to 48.

The company filed 22 ANDAs including six injectable products for the quarter. For the year, ANDA filings totaled 63, including 21 in the rapidly growing injectables segment. 🌟

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ADC Therapeutics Raises \$76m To Keep ADC Development Momentum Going

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Positive data and a drug approval have put antibody-drug conjugates (ADCs) into the spotlight recently and a new \$76m financing announced 12 June by the Swiss firm ADC Therapeutics SARL underscores the field's growing momentum.

Lausanne-based ADC Therapeutics extended its \$200m series E venture capital round, which originally closed in October 2017, to \$276m. The additional cash will fund ongoing and planned pivotal trials for its lead ADC candidates ADCT-402 and ADCT-301, and a biologics license application (BLA) filing for ADCT-402 in relapsed or refractory (R/R) diffuse large B-cell lymphoma (DLBCL) in the second half of 2020, along with continued advancement of earlier-stage programs.

ADC Therapeutics CEO Chris Martin noted that ADCs are complex molecules dependent on the selection of the right target on cancer cells, an appropriate antibody to deliver the molecule, a payload potent enough to kill cancer cells, and effective conjugation that ties the antibody and payload together. Multiple players appear to be getting it right based on newly reported data and the recent US Food and Drug Administration approval of Roche's Polivy (polatuzumab vedotin-piiq) in R/R DLBCL. (Also see "Roche's Polivy ADC Is Approved As Another New Option For R/R DLBCL" - *Scrip*, 11 Jun, 2019.)

The recent American Society of Clinical Oncology meeting also saw multiple standout datasets for ADCs, including early Phase I data in solid tumors for the Daiichi Sankyo Co. Ltd./AstraZeneca PLC candidate DS-1062, which targets TROP2. (Also see "Lung Cancer, Conjugates Emerge As Key Asia Company Themes" - *Scrip*, 4 Jun, 2019.) The Seattle Genetics Inc./Astellas Pharma Inc. ADC enfortumab vedotin also continued to yield positive Phase II results in bladder cancer.

"I think the leading companies working with ADCs have now worked out how to make ADCs which are effective not just in front-line hematological tumors, but in the harder-to-treat patient settings, both in hematological and solid tumor settings," Martin said. He included ADC Therapeutics among the companies getting it right based on results to date for its two lead programs.

USING PBD PAYLOADS TO DIFFERENTIATE

The company's ADCs use second-generation pyrrolobenzodiazepine (PBD) payloads. PBDs offer several advantages over other cytotoxic payloads, including the fact that they're more hydrophilic, or water-soluble, than earlier PBDs, which makes them easier to conjugate and gives ADCs a broader therapeutic index. PBDs also are very potent, but Martin said the biggest advantage is that while they bind with the minor groove of DNA, they do it without disturbing the DNA helix and without recruiting the DNA-repair machinery, which could lead to treatment resistance.

"So, you have these very potent payloads that work both in rapidly dividing and slowly dividing cells and are active in tumors that have become resistant to DNA interactive drugs, so this makes them



"I think the leading companies working with ADCs have now worked out how to make ADCs which are effective not just in front-line hematological tumors, but in the harder-to-treat patient settings." - Chris Martin

particularly suitable for treating patients that are heavily pretreated and relapsed or refractory and you can get durable responses in that relapsed/refractory patient population," Martin said.

The Phase I trial for the CD19-targeting ADCT-402 in R/R B-cell lymphomas is a good example of strong responses to PBD-based ADCs, he said, noting that response rates were positive regardless of genetic status or the number of prior lines of therapy in DLBCL.

"Across all of these hard-to-treat patient categories in diffuse large B-cell lymphoma, we've seen good levels of response with an overall response rate of 42% across all of the patients, both transplant-eligible and transplant-ineligible," the CEO said. "We're also seeing in the Hodgkin lymphoma study [for ADCT-301] in median sixth-line patients in the Phase I study an 86% overall response rate, so a very high response rate in a very hard to treat relapsed/refractory patient population."

ADC Therapeutics will present Phase I data for ADCT-402 (loncastuximab tesirine) in 183 patients with R/R B-cell lymphomas, including 139 with DLBCL, and Phase I results for the CD25-targeting ADCT-301 (camidanlumab tesirine) in 128 patients with R/R Hodgkin and non-Hodgkin lymphoma (NHL) during the International Conference on Malignant Lymphoma (ICML) in Lugano, Switzerland, 18-22 June.

PIVOTAL DATA, RESULTS FROM EARLIER PROGRAMS DUE SOON

ADCT-402 was moved into a Phase II trial in R/R DLBCL based on its Phase I data. The Phase II results are expected in the third quarter and will support a BLA filing in the second half of 2020.

ADC Therapeutics plans to begin a Phase II pivotal trial for ADCT-301 later this summer based on that drug's Phase I data in 77 R/R Hodgkin lymphoma patients.

The company also has Phase Ib trials ongoing for ADCT-401 combinations with the BTK inhibitor Imbruvica (ibrutinib) in R/R DLBCL or mantle cell lymphoma (MCL) and with the PD-L1 inhibitor Imfinzi (durvalumab) in R/R DLBCL, MCL or follicular lymphoma.

Phase I trials are ongoing for ADCT-301 in advanced solid tumors based on its mechanism of action that targets regulatory T-cells, for the CD22-targeting ADCT-602 in acute lymphoblastic leukemia (ALL), and for the AXL-targeting ADCT-601 in solid tumors. Data from those Phase I studies may be reported in late 2019 or early 2020.

ADC Therapeutics also is using its extended series E round to complete invest-

igational new drug (IND) application-enabling studies for DLK1-targeting ADCT-701 and KAAG1-targeting ADCT-901, both of which are being developed to treat solid tumors.

With the potential launch of ADCT-402 in 2021 followed by a possible BLA filing for ADCT-301 and with a full pipeline of additional ADC programs in both solid tumors and hematological malignancies, Martin said the company continues to assess its financing needs and noted that all private and public market funding options remain open.

"I think over the coming years there's going to be a number of important new ADCs coming to market and playing a fulfilling and important role in the treatment paradigms for otherwise hard-to-treat patients," Martin said.

Recent data for its own molecules as well as for the Roche, Daiichi Sankyo and

Seattle Genetics ADCs are "helpful for us and I think it is something that is driven by the underlying science becoming much stronger and the teams developing ADCs becoming considerably more experienced in how to get ADCs to be effective in those patient populations," he added.

The work by ADC Therapeutics in the ADC field has been funded by \$531m in venture capital to date, including the now \$276m Series E round and a \$105m private placement in October 2016. The company raised \$80m in September 2015. (Also see "*\$80m Windfall Will Push 7 ADC Drug Candidates Into Clinic Within Two Years*" - *Scrip*, 2 Sep, 2015.) It launched in 2011 and revealed its first \$50m in funding the following year. (Also see "*Private equity player Celtic bankrolls new Swiss antibody-drug conjugate company*" - *Scrip*, 26 Mar, 2012.) 🌟

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BlackThorn Raises \$76m To Personalize Medicines For Neurobehavioral Disorders

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BlackThorn Therapeutics Inc. put its \$54m in series A venture capital funding to work, emerging with a refined artificial intelligence and machine learning (AI/ML) platform for the development of personalized medicines to treat neurobehavioral disorders and with a drug in the clinic. On 13 June, the company said it has raised \$76m in series B cash to advance its lead drug candidate and take a second program into human studies.

"We have pioneered methodologies using 'explainable AI' to generate predictive models that can be used to inform patient enrichment strategies for clinical development." – Bill Martin

San Francisco-based BlackThorn launched in October 2016 with a \$40m series A round that was expanded a few months later by \$14m. The company's PathFinder platform uses AI/ML to mine its library of phenotyped neurobiological data for new drug targets. The findings also may be used to identify appropriate patients for clinical trials to increase the likelihood of successful outcomes.

Since BlackThorn's series A round, president and chief operating officer Bill Martin told *Scrip*, "we have developed next generation AI technologies to enable a new era of targeted drug discovery; built the leading cloud-based computational psychiatry and clinical neuroscience data platform; advanced our therapeutic pipeline into the clinic; and have built out a highly talented team at the intersection of high tech and the life sciences."

"We have stayed true to our original mission of transforming the way mental health is understood and treated through applying the latest advances in data science and neuroscience across drug discovery and development," he continued. "We are still using AI technologies – what's new is that we have pioneered methodologies using 'explainable AI' (XAI) to generate predictive models that can be used to inform patient enrichment strategies for clinical development. In this way, we can identify patient subgroups using baseline characteristics to predict who is more likely to respond to drug or placebo. This could result in more efficient clinical trials and better patient outcomes."

BlackThorn will use its series B funding to initiate a Phase II trial for BTRX-335140, a kappa opioid receptor antagonist for the treatment of mood disorders, and to take BTRX-323511, a vasopressin 1a receptor antagonist that may be able to treat patients with autism spectrum disorder, into the clinic in 2020. Both candidates came from the company's drug target research collaboration with the Scripps Research Institute in San Diego. Martin noted that in addition to its Scripps collaboration, "we

have multiple discovery programs in which we are generating our own targets and molecules.”

BlackThorn extended a separate agreement last year with Yale School of Medicine’s division of neurocognition, neurocomputation and neurogenetics to understand the neurobiological basis of dysregulated mood and behavior. The company also gained an exclusive license for GEMINI-DOT (Gene Expression Mapping Integrated with Neuro-Imaging for Discovery Of Therapeutics), a technology platform used to bi-directionally map gene expression patterns and neuroimaging features for the identification of drug targets and related patient populations; it was co-developed by BlackThorn and Yale professors Alan Anticevic and John Murray.

BlackThorn will also use its series B financing to continue the development of PathFinder, its own AI/ML-powered technology platform, and to continue advancing drug candidates based on PathFinder-identified targets.

The venture capital round was backed by new investors, including Polaris Partners, Premier Partners, Scripps Research and Vertex Ventures HC, and existing investors Alexandria Venture Investments, Altitude Life Science Ventures, ARCH Venture Partners, Bio-

matics Capital, GV (formerly Google Ventures), Johnson & Johnson Innovation - JJDC Inc. and Mercury Fund.

In addition to BTRX-335140 for mood disorders and BTRX-323511 for autism, BlackThorn launched with BTRX-246040, a Phase II nociceptin receptor (NOPR) antagonist that Eli Lilly & Co. unsuccessfully attempted to develop for major depressive disorder (MDD). BlackThorn has since discontinued development in MDD, but initiated a Phase IIa study last year testing BTRX-246040 in Parkinson’s disease patients with motor fluctuations; it was completed in April, according to clinicaltrials.gov.

“This is a very interesting molecule that has been found well-tolerated in approximately 250 people,” Martin said. “We are continuing to evaluate the appropriate path forward for this program based on the clinical trial results, advances with our computational psychiatry platform and other considerations. We are not able to provide additional details about those next steps at this time, but I am excited for the advances we see overall with our clinical pipeline and PathFinder platform.” 🌟

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Roche’s Polivy Approved As New Option For R/R DLBCL

JESSICA MERRILL jessica.merrill@informa.com

Roche is launching Polivy (polatuzumab vedotin-piiq) for the treatment of adults with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) in the US with an aim to move the first-in-class antibody-drug conjugate (ADC) into the front-line setting.

The anti-CD79b ADC was granted an accelerated approval from the FDA on 10 June based on the results of a Phase Ib/II trial after a swift four-month review, well ahead of the 19 Aug. user fee date. The approval is for use in combination with bendamustine plus Rituxan (rituximab) for the treatment of adults with relapsed or refractory (R/R) DLBCL who have received at least two prior therapies.

It represents a new option for a vulnerable patient population, given that treatment options remain limited for patients who progress on multiple regimens. DLBCL is the most common form of non-Hodgkin’s lymphoma. In the US, nearly 25,000 new cases of DLBCL will be diagnosed in 2019, according to Roche. As many as 40% of patients relapse after treatment after which therapeutic options are limited and survival is short.

Roche’s Rituxan already is the backbone for standard-of-care treatment in the front-line setting in combination with chemotherapy in a regimen known as R-CHOP. Bendamustine plus Rituxan (BR) often is used in refractory patients, as are hematopoietic stem cell transplants. But there have been two recent high-profile approvals for the same setting as Polivy, R/R DLBCL after two or more lines of therapy, the chimeric antigen receptor T-cell (CAR-T) therapies: Gilead Sciences Inc.’s Yescarta (axicabtagene ciloleucel) and Novartis AG’s Kymriah (tisagenlecleucel).

Polivy targets CD79b, a protein expressed in most B-cells, an immune cell impacted in some types of NHL. It binds to CD79b and destroys B-cells through the targeted delivery of a chemotherapy with the aim of minimizing the impact on normal cells. Polivy was developed with ADC technology licensed from Seattle Genetics.

The cost of Polivy will be approximately \$90,000 for a fixed course of approximately four months (every three weeks for six cycles), Roche said. The cost is based on labeled dosing and average patient weight from the Phase Ib/II trial on which the approval was based.

The approval of Polivy was based on the results of a Phase Ib/II study that showed 16, or 40%, of people treated with Polivy plus BR achieved a complete response compared to seven, or 18%, of those treated with BR alone. Of the people treated with Polivy plus BR who achieved a complete or partial response, 64% had a duration of response lasting at least six months compared to 30% of people treated with BR alone. And, 48% of people treated in the Polivy group had a duration of response lasting a year, compared to 20% of those treated with BR alone.

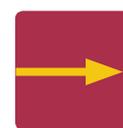
The Phase II portion of the randomized trial enrolled 80 patients with heavily pre-treated R/R DLBCL to receive either BR or BR plus Polivy for a fixed duration of six 21-day cycles.

A Phase III trial is ongoing studying Polivy as a first-line treatment for DLBCL in combination with cyclophosphamide, doxorubicin and prednisone (CHP) chemotherapy. Roche also is studying the ADC in other types of non-Hodgkin’s lymphoma.

Polivy is one of two new oncology drugs Roche plans to launch in the near term. The other is a kinase inhibitor entrectinib, which is pending at the FDA with an 18 Aug. user fee date. The company is seeking approval for a tumor-agnostic indication in patients with neurotrophic tropomyosin receptor kinase (NTRK) fusion-positive, locally advanced or metastatic solid tumors, as well as a second indication in metastatic ROS1-positive non-small cell lung cancer. Given that the drug also has been granted a priority review by FDA, a rapid approval also could be on the horizon. 🌟

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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.



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<http://bit.ly/2mx4jY3>

PIPELINE WATCH, 7-13 JUNE 2019

PHASE III

Event Stage	Lead Company/Partner	Drug Name	Indication	Comments	Change To LOA (%)	LOA (%)
Phase III Updated Results	Eli Lilly & Company	LY900014 (ultra rapid lispro)	Diabetes Type 1	PRONTO-T1D; Met Primary Endpoint	1	64
Phase III Updated Results	Eli Lilly & Company	LY900014 (ultra rapid lispro)	Diabetes Type 2	PRONTO-T2D; Met Primary Endpoint	1	64
Phase III Updated Results	Zealand Pharma A/S	dasiglucagon	Hypoglycemia, Type 1 Diabetes	16137; Confirmed Efficacy	0	68
Phase III Updated Results	Gilead Sciences/Galapagos	filgotinib	Rheumatoid Arthritis	FINCH 1; Improved Symptoms	0	72
Phase II/III Top-Line Results	Savara Inc.	Molgradex (inhaled GM-CSF)	Pulmonary Alveolar Proteinosis	IMPALA; Missed Primary Endpoint	-5	63
Phase III Trial Initiation	Innovate Biopharmaceuticals, Inc.	INN-202	Celiac Disease	Study 3001; First In The Condition	39	54
Phase II/III Trial Announcement	Lysogene/Sarepta Therapeutics	LYS-SAF302, gene therapy	Mucopolysaccharidosis IIIA	AAVance; In Europe And US	0	62

PHASE II

Event Stage	Lead Company/Partner	Drug Name	Indication	Comments	Change To LOA (%)	LOA (%)
Phase IIb Updated Results	Eli Lilly & Company	tirzepatide (LY3298176)	Diabetes Type 2	vs. dulaglutide; Clinical Benefits	0	65
Phase IIb Updated Results	UCB SA	bimekizumab	Psoriatic Arthritis	BE ACTIVE; Improved Outcomes	0	61
Phase II Updated Results	Albireo Pharma, Inc.	odevixibat	Primary Biliary Cholangitis	Pediatric; Reduced Symptoms	0	59
Phase II Updated Results	Albireo Pharma, Inc.	odevixibat	Alagille Syndrome	Pediatric; Reduced Symptoms	0	24
Phase II Updated Results	Zafgen, Inc.	ZGN-1061	Diabetes, Type 2	Improved Insulin Sensitivity	0	21

Source: Biomedtracker | Informa, 2019

Real-World Evidence Sought In Sanofi Pasteur Observational Flu Vaccine Trial

STEN STOVALL sten.stovall@informa.com

Sanofi Pasteur hopes real world evidence produced from an observational clinical trial in the US using data from 1.6 million people and in which its Flublok vaccine will be compared with standard-dose inactivated influenza vaccine can promote the cause of using Big Data.

Through its partnership with Kaiser Permanente of Northern California, an integrated healthcare system, Sanofi Pasteur is backing a real-world evidence study of its egg-free, cell-based influenza vaccine using data generated during post-marketing routine clinical practice with Kaiser Permanente's digitalized patient record system.

David Loew, the head of Sanofi Pasteur, said in an interview that the observational study, which began last September, aims in large part to demonstrate the power that integrated electronic health registries can have on vaccine evaluations.

"It will allow us to get a better understanding of the performance of vaccines in a real world environment, help demonstrate the value of a vaccine, and provide insights for future vaccines development," Loew said during a recent visit to London.

The study's overall objective is to describe the effectiveness of Flublok Quadrivalent vaccine compared with standard dose inactivated influenza vaccine (SD-IIV) in adults 18 to 64 years of age.

The 2018-2019 and 2019-2020 formulations of Flublok Quadrivalent recombinant influenza vaccine and SD-IIV will be evaluated for outcomes including all polymerase chain reaction (PCR)-confirmed influenza, PCR-confirmed hospitalized influenza, hospitalized community-acquired pneumonia and cardio-respiratory events.

Loew said that because the study was conducted by Kaiser Permanente in a routine clinical setting, and due to the controlled na-

ture of the vaccination logistics and the depth of their electronic medical record system, the collection of data would be highly efficient in terms of patient vaccination, identifying influenza events and flu-related complications in outpatient and inpatient facilities.

It may also reduce bias in the analysis.

"This might be something that's really going to change the future of running clinical studies, because having electronic medical records allows you to compare very large sets of data," Loew said. "This real world data setting will allow us to tease out new findings as well."

Loew continued: "Some healthcare systems cannot pick up, for example the correlation between the flu and a cardiovascular event, because they make the wrong diagnosis; they think it's the flu and they try to treat it as if it is the flu but when you are later hospitalized and you have a cardiac arrest, they don't link that scenario. There is increasing evidence where we see a correlation between the two."

He added, "This is a really new model that we're pushing here. These observational studies will allow records to electronically map people from their first vaccination on to when a health issue becomes apparent."

Loew said observational studies like this were opening up an entirely new field of scientific analysis. "And regulators are following this very closely, because if it proves to be a viable model it would allow data for many more people, and done at a fraction of the cost."

The research has wide applicability. "We're working now with governments to see where else we can do these studies in the future," Loew said. "The countries that are best prepared with electronic medical records are going to be able to get involved." 🌟

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APPOINTMENTS

Executive	To Company	New Role	From Company	Previous Role	Effective Date
Vijay Shreedhar	Adamas Pharmaceuticals Inc	Chief Commercial Officer	Amgen Inc	Executive Director and Integrated Commercial Lead	30-May-19
Tariq Kassum	Celsius Therapeutics	Chief Executive Officer and President	Obsidian Therapeutics	Co-Founder, Chief Operating Officer and Head, Corporate Development	11-Jun-19
Raj Kannan	Chiasma Inc	Chief Executive Officer and Director	Kiniksa Pharmaceuticals	Chief Commercial Officer	17-Jun-19
Jeysen Yogarathnam	Eiger BioPharmaceuticals Inc	Vice President, Global Hepatitis Delta Virus (HDV) Clinical Development	Janssen Biopharma	Senior Medical Director	5-Jun-19
Adriana Herrera	Eisai Inc	Senior Vice President, Americas Commercial Oncology	Novartis Oncology	Vice President, Global Disease Lead, Lung Cancer	29-May-19

Click here for all appointments: <https://bit.ly/2oHWRyN>

Source: Medtrack | Informa, 2019

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