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Pfizer's Xtandi Sales Disappoint But Likely A Temporary Issue

JESSICA MERRILL jessica.merrill@informa.com

Pfizer Inc. paid a sweet premium to buy **Medivation Inc.** last year for $14bn, an amount that surpassed even the high estimates of pharma analysts and left some investors questioning the value of the deal. Now, during Pfizer's first quarter sales and earnings call May 2, management admitted the primary driver behind the deal, the prostate cancer drug *Xtandi* (enzalutamide), performed below expectations.

Xtandi's US net sales declined 11%, due to an increased use of patient assistance programs, Pfizer reported. Demand for Xtandi grew, however, up 13%, group president-Pfizer innovative health Albert Bourla added.

Pfizer reported $131m in Xtandi alliance revenues in the quarter. The drug is partnered with the Japanese pharma **Astellas Pharma Inc.** and under the arrangement, the companies jointly commercialize Xtandi in the US and share sales and profits, while Astellas is responsible for marketing the drug outside the US and pays a royalty on sales to Pfizer.

Bourla reassured investors that the issue is a temporary one, likely the result of dislocation in the reimbursement market.

"We believe that the demand for patient assistance as a percentage of total demand will stabilize, moderate gradually through 2017 and over time, resolve," he said.

But Bourla also admitted that the issue was unexpected and was not built into the company's plans for growing the market-leading androgen receptor inhibitor. "This was not anticipated," he said when pressed by an analyst. "Today, Xtandi is performing below our expectations in the US."

Nonetheless, the thesis behind growing Xtandi – expanding its use to earlier, non-metastatic lines of therapy and broadening the prescriber base – remain intact, he insisted.

"We remain confident in achieving both of these initiatives going forward," he said. Pfizer and Astellas have several late-stage studies underway exploring Xtandi in non-metastatic prostate cancer, in hormone-sensitive prostate cancer and other types of cancer, including breast cancer.

The sale of Medivation was a competitive process, one in which Pfizer outbid rivals including **Sanofi**. But some industry watchers wondered at the time if winning Medivation at such a high premium would still be considered a win long-term.

BIG M&A ON THE BACK BURNER – FOR NOW

Investors are already wondering what Pfizer's next big M&A move will be now that the company announced a decision not to pursue a break-up last year and as new headwinds approach, including the loss of *Viagra* in late 2017 and *Lyrica* in 2018 to generics. *(Also see "Stronger Together: Pfizer Decides Against A Split" - Scrip, 26 Sep, 2016.)***Bristol-Myers Squibb Co.** has been floated as a potential acquisition target for Pfizer, with the company's stock price under pressure due to missteps in immuno-oncology.

The field is one Pfizer is also investing heavily in. The company's first immuno-oncology drug, the PD-L1 inhibitor *Bavencio*

CONTINUED ON PAGE 7

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

from the editor

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We're well into the fifth month of 2017 and big-ticket M&A remains a very rare beast, as it has been pretty much since former US President Obama effectively closed off the tax inversion opportunity for US-based big pharma. There's no single definition of "big-ticket", but it's reasonable to argue that apart from Johnson & Johnson, with its $30bn deal for Actelion, big pharma has designed no serious raid on its collective piggy bank so far this year.

Market sentiment appears to be that it is a question of "when" not "if" serious big pharma deal-making will get going again. Consolidation is still touted as an eventual remedy for Pfizer's perpetual organic sustainability challenge, even as the company fails to deliver on previous acquisition investment (see cover story). To judge from the CEO's pronouncements, the hold-up seems to be global political and fiscal uncertainties rather than any fundamental doubt over whether occasionally gobbling a colossally large meal is a suitable diet for healthy growth. Gilead is another bloated fish that needs to figure out a way to maintain its size, and again, there is speculation not quashed by management that M&A will provide a solution (see p10).

And yet, despite expectations that President Trump would implement reforms to effectively free up the cash held overseas by US corporations, clarity on exactly how that would work, and when it might happen, is still lacking. Predictions made in January that biopharma deal-making would reach new heights in 2017 might require reassessment.

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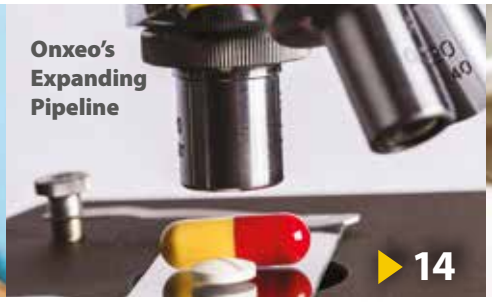

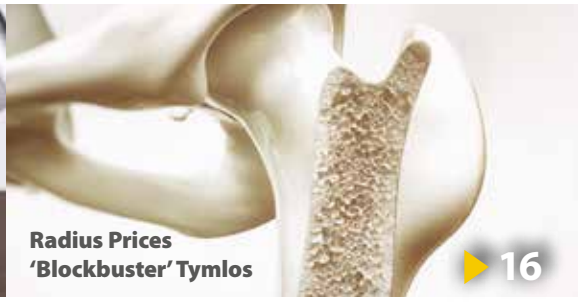

exclusive online content

Catabasis Pursues Bifunctional Mutation-Agnostic Approach To DMD

http://bit.ly/2pqDQZb

Using its safely metabolized and rationally targeted (SMART) linker platform, Catabasis has identified a NF-κB inhibitor – edasalonexent – as a potential Duchenne muscular dystrophy (DMD) treatment. Speaking at the 2017 Biotech Showcase, Dr Jill Milne, co-founder, president and CEO of Catabasis, describes the company's ambitions to pursue a pivotal Phase III trial this year.

Chinese Capital Accesses Western Innovation To Create Homegrown Industry

http://bit.ly/2pmi1JE

With the Chinese market growing at 10-15% a year, it is poised to be world's largest by 2026. Tony Chu, co-founder and managing partner at consultants TPP Healthcare, explains how Chinese capital is accessing Western innovation to build a PRC pharma industry.

Corporate VCs Wade In With Funds To Pursue Gene Therapy For Wilson Disease

http://bit.ly/2pmnznl

Rare copper-overload disorder Wilson disease is seeing a surge of interest: one new copper chelator recently garnered a CHMP recommendation, a novel copper modulator has had promising Phase II data, and French biotech Vivet has secured significant funds to pursue a gene therapy approach to the disease.

Deal Watch: Seattle Genetics' Controversial Collaboration With Immunomedics Topples

http://bit.ly/2qlH5PS

A licensing deal between the two cancer-focused biotechs falls apart amidst investor unrest at Immunomedics. Novartis opts to license Conatus' Phase II NASH candidate and picks up a CAR-T candidate from Celyad, while Shire adds to its dry eye franchise in deal with Parion.

NeRRe: Advancing Neurokinin Receptor Antagonists

http://bit.ly/2pmuz3C

Starting the year with a cash injection of £23m, 2012 GSK spin-out NeRRe Therapeutics intends to advance its neurokinin receptor antagonist pipeline towards late-stage clinical development. CEO Mary Kerr spoke to *Scrip*'s Mike Ward at the 2017 Biotech Showcase in San Francisco.

inside:

Novartis's Rydapt: Two Indications, Two Prices

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Novartis AG's *Rydapt* (midostaurin) has been approved in the US for two different indications and will carry two different prices, one that appears more in line with typical targeted oncology medicines and the other that is in line with drugs for ultra-rare diseases.

In both instances, Rydapt appears to be an important new treatment option. The drug was approved by FDA April 28 for a subset of patients with acute myeloid leukemia (AML), an aggressive blood cancer that has seen few therapeutic advancements in the last decade. In AML, it was approved in combination with chemotherapy for newly diagnosed patients whose cancer tests positive for FMS-like tyrosine kinase 3 (FLT-3) mutations.

About one-third of AML patients are estimated to have the mutation, or roughly 7,000 of the estimated 21,000 people likely to be diagnosed with AML in the US in 2017, according to Novartis. Rydapt is the only targeted therapy approved for FLT-3 mutated AML, which is associated with a poor prognosis.

Rydapt was also approved for a second indication for adults with advanced systemic mastocytosis (SM), which includes aggressive systemic mastocytosis (ASM), systemic mastocytosis with associated hematological neoplasm (SM-AHN) and mast cell leukemia, an indication for which there are no approved treatments. Advanced SM, the drug will be priced differently.

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> For advanced SM, the dose is higher and so is the price, more than $366,179 for a median course of treatment, which Novartis said is in line with drugs for ultra-rare diseases

Advanced SM is a rare blood disorder characterized by uncontrolled growth and accumulation of mast cells, the mediators of allergic responses, in one or more organs. They can accumulate in such high quantities that they cause organ damage. Median survival is less than six months for mast cell leukemia, two years for SM-AHN and 3.5 years for ASM, according to Novartis.

The drug became available commercially May 1 at a wholesale acquisition cost of $7,495 for a 14-day package and $14,990 for a 28-day package in the AML indication. In the Phase III clinical trial supporting the FDA approval, patients received 50 mg of Rydapt twice daily for 14 days (days eight to 21) during the induction phase, in combination with the chemotherapies cytarabine and daunorubicin; and for 14 days (days eight to 21 of each cycle) during the consolidation phase in combination with high-dose cytarabine.

For patients who remained in remission, treatment with Rydapt was continued twice daily as a single agent for up to 12 cycles. Median duration of treatment in the trial was 1.4 months (42 days), representing a WAC of $22,485. Some patients did remain on treatment longer and receive up to 12 cycles.

The recommended dose for advanced SM is higher than the dosing for AML, 100 mg twice daily. The wholesale acquisition cost is $32,121 for 30 days of treatment, which Novartis said is in line with drugs for other ultra-rare conditions. The median duration of treatment in clinical trials was 11.4 months, putting the total cost for the median treatment at $366,179.

The company said it has initiated an "innovative" indication-based rebate offer to payers for the SM indication to further reduce the net cost of the drug, but additional details were not immediately available.

NOVARTIS STAYS ON TOP OF TARGETED THERAPIES

While many big pharma leaders working in cancer have turned their focus almost exclusively to immuno-oncology and combinations, Novartis has continued to invest behind novel targeted therapies. The company's other targeted therapy, a CDK4/6 inhibitor *Kisqali* (ribociclib), was approved by FDA in March for certain breast cancer patients. *(Also see "Novartis Sets 'Flexible Pricing' For Kisqali To Compete Against Pfizer's Ibrance" - Scrip, 14 Mar, 2017.)*

Novartis has taken heat from investors for falling behind competitors in immuno-oncology, where it failed to invest early in immune checkpoint inhibitors like PD-1/L1. The company was an early backer in a different IO approach, however, chimeric antigen receptor T-cell (CAR-T) therapy, which has shown promise in blood cancers but also presents manufacturing and admin-

istrative challenges for broad-scale production because of the individualized nature of the treatment. Novartis announced in April that its BLA for the CAR-T therapy CTL019 (tisagenlecleucel-T) was accepted by FDA for B-cell acute lymphoblastic leukemia. *(Also see "BLA Accepted: Novartis Inches Ahead In CAR-T Race With Kite" - Scrip, 29 Mar, 2017.)*

Novartis needs new growth drivers in oncology to make up ground lost by generic competition to its blockbuster *Gleevec* (imatinib). *(Also see "Novartis Claims New Drugs, Pipeline Will Fuel Growth, Not M&A" - Scrip, 25 Apr, 2017.)* The company became an industry leader in blood cancer on the back of Gleevec.

While Kisqali is entering a blockbuster category, Rydapt will target a more niche subset of patients. Jeffries analyst Jeffrey Holford forecast in an April 26 research report that Rydapt will generate $319m in sales in 2019, whereas Kisquali is expected to generate $1bn in sales in the same year.

RYDAPT ADDRESSES DEMAND IN AML

For patients, however, the launch is important in a category that has seen little in the way of breakthroughs. The five-year survival rate in AML is only 26%, and the standard of care – chemotherapy – has been the same for decades. In the pivotal Phase III trial testing Rydapt, treatment resulted in a survival advantage.

"The availability of midostaurin now helps to establish a new standard of care in this high-risk patient population," said chief of staff and director of the Adult Leukemia program at Dana-Farber Cancer Institute Richard Stone in a statement. Stone was also the study chair for the RATIFY trial.

In the AML patients, the FLT3 gene mutation can result in faster disease progression, higher relapse rates and lower rates of survival than other forms of AML.

The Phase III trial, RATIFY, patients who received Rydapt plus chemotherapy experienced a significant improvement in overall survival with a 23% reduction in the risk of death compared to chemotherapy alone. Event-free survival (defined as no complete remission within 60 days of the start of induction therapy, relapse or death) was significantly higher for those treated with Rydapt and chemotherapy versus chemotherapy alone, a median of 8.2 months versus three months. The trial screened 3,279 patients for FLT3-mutation status and enrolled 717 patients.

Adverse reactions to the combination arm included neutropenia, nausea, vomiting, mucositis, headache and infection.

Several competitors are also working to develop new options for patients, and data on several potential new drugs for AML was presented at the American Society of Hematology meeting in December. *(Also see "New Drugs Aim To Move Needle In Tough-to-Treat Acute Myeloid Leukemia" - Scrip, 4 Dec, 2016.)*

FDA simultaneously approved a companion diagnostic to monitor for the FLT3 mutation, Invivoscribe Technologies, Inc.'s LeukoStrat DCx FLT3 Mutation Assay.

The approval in SM was based on two single-arm open-label multicenter trials, including the Phase II CPKC412D2201 study, the largest and longest running prospective trial conducted in the ultra-rare disorder.

Rydapt was granted breakthrough therapy designation by FDA, as well as orphan drug designation and priority review.

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Pfizer's Xeljanz: The Slow Road To Blockbuster Status

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It has been almost five years since **Pfizer Inc.**'s *Xeljanz* (tofacitinib) was approved by the US FDA for rheumatoid arthritis, and the drug is just finally reaching the blockbuster-level sales investors had been hoping for years ago.

Xeljanz' long road to blockbuster status points to the challenges new drugs face in competitive therapeutic categories like rheumatoid arthritis, even when they offer a valuable benefit to patients. In the case of Xeljanz, the drug was a first-in-class JAK inhibitor and the first new oral option in a category dominated by injectable tumor necrosis factor inhibitors like **AbbVie Inc.**'s *Humira* (adalimumab) and **Amgen Inc.**'s *Enbrel* (etanercept), which Pfizer shared rights to, but there were also safety concerns related to infections and cancer. *(Also see "Pfizer's Tofacitinib Clears FDA Without Limited Indication" - Pink Sheet, 6 Nov, 2012.)*

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Lately, Xeljanz is gaining momentum as physician, patient and payer experience with the product has grown. Sales of the drug grew 27% in the first quarter to $250m, putting it on track to cross the $1bn sales threshold for the first time in 2017. That performance comes on top of 77% growth in 2016. At a press briefing last year, the Pfizer's Immunology & Inflammation management team attributed the growth to improved market access and increasing physician comfort with the treatment.

Pfizer now has new opportunities for growing the brand further, though Xeljanz will also face more competition from new oral options and injectable biosimilars. The development plan nonetheless was scaled back from the original plan, when Pfizer deprioritized development in psoriasis, ankylosing spondylitis and Crohn's disease. *(Also see "Xeljanz Development Plans Scaled Back By Pfizer" - Pink Sheet, 27 Oct, 2015.)*

The company is pushing to add two new indications to labeling for Xeljanz – psoriatic arthritis and ulcerative colitis – and is expanding the brand geographically. In March, the European Commission approved Xeljanz for the treatment of moderate to severe RA. *(Also see "Pfizer's Xeljanz Set To Lag Lilly's Olumiant In Europe Following Past Rebuffs" - Scrip, 27 Jan, 2017.)* The vast majority of Xeljanz sales come from the US, about 88% in 2016.

During Pfizer's first quarter sales and earnings call May 2, CEO Ian Read said Pfizer is "very enthusiastic" about Xeljanz. "We have an opportunity to be the JAK in the marketplace for rheumatoid arthritis…so we see this position existing for some time in the US," he said.

NEW DATA AND A NEW FDA ACTION DATE

FDA announced May 3 that FDA has accepted two sNDAs for Xeljanz for the treatment of patients with active psoriatic arthritis, one for both the 5 mg twice daily dose and the extended-release 11 mg dose. The filing is based on the results of the OPAL clinical development program, including two pivotal trials and a long-term extension study. The FDA action date is set for December 2017.

The results of the Phase III OCTAVE clinical program testing Xeljanz in ulcerative colitis were published in *The New England Journal of Medicine* (NEJM) May 4. Pfizer previously announced positive results in 2015 from two identical induction studies, OCTAVE Induction 1 and OCTAVE Induction 2, testing Xeljanz versus placebo. *(Also see "Pfizer Eyes Xeljanz Expansion To Ulcerative Colitis" - Pink Sheet, 21 Sep, 2015.)* The company had been waiting the results of a third maintenance trial before filing the drug for FDA approval.

Now, Pfizer said it is preparing to file Xeljanz for ulcerative colitis in the first half of the year. If it is approved, it will join several anti-TNFs that also carry indications for treating ulcerative colitis. The drug could be a new oral option. OCTAVE Sustain, testing Xeljanz versus placebo as a maintenance therapy in patients with moderate to severe UC, enrolled 593 patients who received the tofacitinib 5 mg, tofactinib 10 mg or placebo for 52 weeks. Results showed 34.3% and 40.6% of patients achieved remission at Week 52 with the two doses of Xeljanz, respectively, compared to 11.1% taking placebo. Both treatment doses also met the key secondary endpoints of the study: mucosal healing and sustained steroid-free remission among baseline remitters.

Pfizer has gotten a small reprieve in 2017 with Xeljanz in RA. The company was expecting to face new competition in the oral market with the launch of **Eli Lilly & Co./Incyte Corp.**'s JAK1/2 inhibitor baricitinib. The Lilly drug demonstrated strong efficacy in clinical trials, but FDA issued a complete response for baricitinib in April, setting back the launch timeline, citing concerns about the appropriate dose and safety. *(Also see "Baricitinib Complete Response May Put Lilly/Incyte Behind IL-6 Blockers In RA" - Scrip, 14 Apr, 2017.)*

Two other IL-6 inhibitors, injectable drugs, are also pending at FDA for RA, **GlaxoSmithKline PLC/Johnson & Johnson**'s sirukumab and **Sanofi/Regeneron Pharmaceuticals Inc.**'s sarilumab.

Pfizer, meanwhile, is working to build an entire Inflammation & Immunology business unit focused in rheumatology, gastroenterology and dermatology, with Xeljanz as an anchor and next-generation JAKs in development. The company has launched a new dermatology-focused commercial team to execute on the launch of *Eucrisa* (crisaborole) in atopic dermatitis. *(Also see "Pfizer Assembling New Commercial Team For Move Into Dermatology" - Scrip, 19 Oct, 2016.)* Interestingly, the company is also competing in the space in the area of biosimilars, and launched *Inflectra*, the first biosimilar version of Remicade in November. *(Also see "Pfizer Will Support Inflectra Launch With Dedicated Sales Force" - Scrip, 14 Nov, 2016.)*

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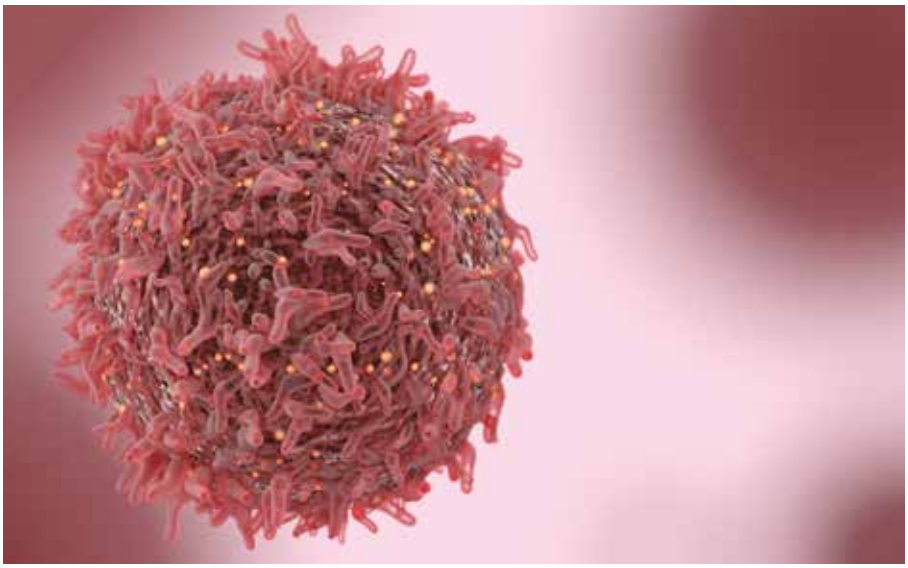
CONTINUED FROM COVER

(avelumab), partnered with **Merck KGAA**, was approved by FDA in March for Merkel cell carcinoma, although the company also announced a major setback in lung cancer, revealing that it's Phase III trial was pushed back until 2019 due to a protocol change. *(Also see "Pfizer's Avelumab Makes Its Debut, In Rare Form Of Skin Cancer" - Scrip, 23 Mar, 2017.)*



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President-worldwide R&D Mikael Dolsten said during the conference call that Pfizer has 30 clinical programs underway involving avelumab, including nine registrational trials. The company also initiated its first triple combination program testing avelumab in combination with investigational drugs targeting 4-1BB and OX40.

Analysts pressed management about their commitment to avelumab and the Merck partnership, attempting to tease out any information about how seriously they should be thinking about a Bristol buyout. But CEO Ian Read didn't offer much to fan the speculation. He insisted the company remains committed to avelumab, though he did say in regards to the Merck deal, "I don't think that any type of breakup fee would be material compared to the size of a large deal."

Pfizer will remain focused on business development, Read said, but he acknowledged uncertainties in the political and healthcare arena that are giving the big pharma pause.

"Pfizer has been and I expect will continue to be active industry consolidators," Read said. "However, there is a lack of clarity on potential tax reform, health care policies of the US and uncertainties in the European markets both with the French election and the UK snap election."

"We never say never, but I believe the current environment needs to stabilize in order to be an advantageous market for big deals," he added.

> 'We never say never, but I believe the current environment needs to stabilize in order to be an advantageous market for big deals'

Pfizer's first quarter sales were lackluster. Revenues declined 2% to $12.78bn, while net income grew 3% to $3.12bn. The big bright spot for Pfizer has been the breast cancer drug *Ibrance* (palbociclib), which has become Pfizer's top-selling oncology drug; Ibrance generated $679m in sales in the quarter, reflecting a 58% jump. But Ibrance no longer has the CDK4/6 inhibitor market to itself now that **Novartis AG**'s *Kisqali* (ribociclib) was approved by FDA. *(Also see "Novartis Sets 'Flexible Pricing' For Kisqali To Compete Against Pfizer's Ibrance" - Scrip, 14 Mar, 2017.)*

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Encouraging HIV 'Cure' Data Strengthen Abivax

Data supporting the potential for a functional cure for HIV, albeit in a small number of patients for a short amount of time, has been enough for French biotech **Abivax** to turn its stock price slump around.

Abivax is not the first company to pursue the holy grail of an HIV cure.

Norwegian biotech **Bionor Pharma** ASA, which was being led by ex-Zealand Pharma CEO David Solomon, had promising Phase I/II data suggesting its Vacc-4x vaccine component could potentially form part of a functional cure for HIV. *(Also see "Bionor Readies Key Trial To Prove 'Shock And Kill' Could Lead To Functional HIV Cure" - Scrip, 21 Dec, 2015.)*

Further clinical testing, dependent on a fundraising, was planned. Solomon left the company at the end of last year, and new CEO Andreas Martinussen was installed. At the start of this year, Bionor said that the Research Council of Norway would give the company NOK 10.3m ($1.2m) to partially fund further testing, but as yet no trial is listed as ongoing in clinicaltrials.gov.

HIV patients are well treated with antiretrovirals, but one of the main obstacles to developing a 'cure' is that the HIV virus hides in 'reservoirs' which are found in various parts of the body. These reservoirs empty the virus back into the blood if antiretroviral treatment is stopped.

Bionor's strategy was to blast out the virus from the reservoirs using HDAC inhibitors such as Celgene's romidepsin, and then use Vacc-4x to clear the virus from the blood.

Abivax's ABX464 inhibits the formation of viral RNA required for the replication of the HIV virus, a mechanism of action never explored before, according to Abivax.

sukaina.virji@informa.com, 5 May 2017

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Merck Confident About Keytruda/Chemo Combo May Date With FDA

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Merck & Co. Inc. is confident in the combination of its PD-1 inhibitor *Keytruda* with chemotherapy ahead of the US FDA's May 10 user fee date for accelerated approval in first-line lung cancer even after a tough quarter marked by sales below consensus for a number of key products and major patent losses.

Keytruda (pembrolizumab) currently is approved as a monotherapy in first-line non-small lung cancer (NSCLC) with high PD-L1 expression, second-line NSCLC with at least 1% PD-L1 expression, refractory classical Hodgkin lymphoma and second-line head & neck cancer. But even with a triple-digit increase in the drug's sales in the first quarter, Merck's PD-1 inhibitor didn't meet analyst expectations for growth.

The company reported on May 2 that it had $584m in Keytruda sales for the first quarter, which was up 170% year-over-year and 30% quarter-over-quarter, but below a consensus estimate of $615m. That contrasts with performance by **Bristol-Myers Squibb Co.**'s competing PD-1 inhibitor *Opdivo* (nivolumab), which had sales of $1.12bn in the first quarter and beat expectations. Opdivo is approved for second-line NSCLC at all levels of PD-L1 expression, as well as a range of other indications including melanoma, kidney cancer and classical Hodgkin lymphoma.

FDA approval of the Keytruda/chemo combination in first-line non-squamous NSCLC would solidify Merck's lung cancer labeling lead over Bristol and is very eagerly awaited. Merck's filing was supported by data from the Phase II "G" cohort of the KEYNOTE-021 study, which tested Keytruda with **Eli Lilly & Co.**'s *Alimta* (pemetrexed) and carboplatin. Results from the Phase III KEYNOTE-089 study of Keytruda with chemo in first-line NSCLC are due in the fourth quarter.

Executives were asked during Merck's first-quarter earnings call on May 2 about prospects for a positive decision from FDA by May 10. Merck has been working closely with the agency and there has been "good dialogue on the results and analysis," Merck Research Laboratories president Roger Perlmutter said.

"I will not predict what FDA will do on the PDUFA date. They need to make their own decisions, but I would say that we have a very strong dataset that stands on its own. There's every reason to expect that based on our discussions with them that they'll be able to see their way clear for that," Perlmutter said.

Updated results from the KEYNOTE-021 G cohort will be presented at the American Society of Clinical Oncology meeting in June.

Analysts have speculated that the agency might delay a decision on the '021 filing for the Keytruda/chemo combo until the Phase III '089 first-line lung cancer data are ready. The company clarified that FDA will not have early private access to the '089 data to help in the review of the '021 data but that the filing can stand on its own. Merck also noted that it has not internally reviewed any data from the '089 study yet.

LUNG CANCER DOMINATES KEYTRUDA SALES

Keytruda monotherapy secured its first-line lung cancer approval in October 2016. About 40% of US sales of the drug in the first quarter derived from lung cancer, 30% from melanoma, 15% from head and neck, and 15% from other utilization, Adam Schechter, President-Global Human Health, said during the call.

Furthermore, 75% to 80% of NSCLC patients in the US are being tested for PD-L1 expression.

"In the United States, Keytruda growth was driven by the launch in first-line lung, as well as the rapid penetration of head and neck cancer and continued strength in melanoma. After seeing a significant increase in PD-L1 testing following our first-line lung approval in the fourth quarter, we are starting to see that translate into demand. In fact, the vast majority of patients as defined by our label are already being prescribed Keytruda," Schechter said.

The exec added that IMS data for new patients on branded drugs indicate Keytruda is the most prescribed product in the first-line lung cancer setting in the US. Meanwhile, the drug's second-line share "has been relatively stable."

Approval of the Keytruda plus chemotherapy filing on May 10 would expand the market opportunity in non-squamous NSCLC to include all patients with low or

Merck: 1Q Sales Vs. Consensus Estimate

PRODUCT	1Q ACTUAL SALES	CONSENSUS ESTIMATE
PRODUCT SALES BELOW CONSENSUS		
Januvia/Janumet	$1,335m	$1,390m
Keytruda	$584m	$615m
Zetia	$334m	$366m
Isentress	$305m	$319m
Vytorin	$241m	$263m
Remicade	$229m	$255m
Singulair	$186m	$207m
Cubicin	$96m	$98m
PRODUCT SALES AT OR ABOVE CONSENSUS		
Gardasil	$532m	$377m
Zepatier (HCV Combo)	$378m	$290m
Zostavax	$154m	$136m
Nasonex	$139m	$126m
Cozaar/ Hyzaar	$112m	$112m

Source: Jeffrey Holford, Jefferies, May 2 note

no expression of PD-L1. But since the drug was studied in combination with Alimta, Merck expects that early adoption will be in settings where physicians are already using Alimta, Schechter said.

Melanoma continues to drive the majority of Keytruda sales outside of the US, but the company said it is working through the reimbursement process for first-line and second-line lung cancer. Schechter said Merck expects lung cancer to become a much larger contributor outside of the US as the year progresses.

TOUGH QUARTER ACROSS THE PORTFOLIO

The first quarter was in some respects tough on Merck. The company reported total quarterly revenue of $9.4bn, up by 1% year-over-year and 2% higher than consensus of $9.23bn.

Chief financial officer Robert Davis noted that strength in its launches and solid performance of its in-line businesses helped offset significant headwinds in the first quarter, as some key products faced generic competition – *Zetia* (ezetimibe), *Cubicin* (daptomycin) and *Nasonex* (mometasone furoate) in the US and *Remicade* (infliximab) in Europe.

Schechter noted that the company had to contend with a nearly $700m decline in sales related to patent losses.

"We anticipate further erosion from these products in 2017, but as we did in the first quarter, we will continue to look for opportunities to offset these losses with strength from across our broad portfolio of products and from our multiple new product launches, which are each off to a very strong start," he said.

Jefferies analyst Jeffrey Holford pointed out in a May 2 note that first quarter sales for a number of key drugs were below consensus, including Keytruda and the DPP-4 inhibitor *Januvia/Janumet* (sitagliptin) for diabetes. Merck reported about $1.3bn in sales for Januvia/Janumet, down by 5% from the first quarter of 2016, largely due to US performance.

"Januvia continues to maintain DPP-4 leadership with more than a 70% market share in the US and a 65% market share globally," Schechter said.

Merck remains confident in its diabetes franchise and executives said the company looks forward to expanding it.

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Sosei Backs RNA Activation Through Sizeable Equity And Option Deal

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Robert Habib

RNA technology has failed to live up to its early drug discovery potential, but Sosei believes MiNA Therapeutics "activating" RNA approach could change all that.

Sosei has agreed to make a strategic investment of £35m into MiNA Therapeutics in return for a 25.6% equity share and an exclusive option to potentially acquire the London-based biotech company in full.

The option agreement has a further two stages, linked to two more equity stakes, which together would result in 100% ownership of MiNA for a further £140m. In addition, if Sosei fully exercises its option, MiNA shareholders could receive another £240m contingent on achieving certain development and regulatory milestones and including potential royalties on any products emanating from MiNA's RNA activation platform.

MiNA was founded on the discovery that the Argonaute family of proteins, which have been known for some time to play a central role in how RNA silences gene expression (RNA interference) through their activity in the cytosol of cells, can also be responsible for gene activation. The 'activation' activity occurs through the action of Argonaute proteins located in the nucleus of cells, MiNA CEO Robert Habib told *Scrip*.

MiNA's lead RNA activation program is already in clinical testing. The Phase I/IIa OUTREACH study is currently ongoing with MTL-CEBPA in advanced liver cancer patients.

MiRNA has a library of "millions" of RNAs targeting genes. Its lead program was selected using a number of criteria, most notably unmet need and ease of delivery. "There is a lot of room for improvement on standard of care – *Nexavar* (sorafenib) – in hepatocellular carcinoma," said Habib. With regards to delivery of RNA, it is better understood in certain tissue types, liver cells being one. "We started off with a gene target that was a master regulator of liver function but also a tumor suppressor," explained Habib. "Liver cancer is two diseases in one: 90% of patients have cirrhosis," and a significant proportion of liver cirrhosis patients have NASH (nonalcoholic steatohepatitis), currently a particularly hot area of drug development focus.

Clinical read-outs from OUTREACH are expected during 2018. "We expect that in 12-18 months we will be able to more fully analyze the asset and make a decision on how we proceed," Sosei CEO Peter Bains told *Scrip*. However, he sees the program as having "clear 'go-to-market' potential for Sosei."

But the excitement is not just about the lead program. "If you think about the bigger picture potential when it comes to RNA activation: this is a huge strategic, scalable opportunity," he said.

MiNA and its technology is a strong fit with Sosei's vision to become a global biotechnology company. "This inorganic strategy is complementary to Sosei's organic strategy, which is focused on advancing a growing pipeline of drug candidates from Heptares." Bains said it was too early to speculate on whether there would be any crossover between Heptares and MiNA's technology.

MiNA CEO Habib is clear what his hopes are for the future. "This is a good deal for MiNA. Sosei is a great partner for now – the capital allows us to progress and grow – but also for the future. A big selling point for us is the relationship Sosei has with Heptares. That company has continued to flourish and innovate with Sosei."

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Gilead's CEO Gives Glimpse Of Strategic Opportunities As HCV Sales Slide Continues

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Expectations were low in regard to sales of **Gilead Sciences Inc.**'s hepatitis C drugs and the company's dealmaking activity going into its first quarter earnings conference call on May 2 – and from that perspective, Gilead did not disappoint, though CEO John Milligan did pull back the curtain a little bit in regard to the company's strategy under pressure from an analyst.

Gilead reported $6.5bn in first quarter revenue, down 17% from $7.8bn in the same period of 2016; revenue from treatments for the hepatitis C virus (HCV) were down 40% at $2.58bn. Sales of HIV drugs rose 13% to $3.27bn, but the $376m increase was just a fraction of the $1.72bn in lost HCV sales. That's why analysts and investors continue to look for hints about Gilead's strategy for boosting revenue over the short and long term, including through significant merger or acquisition deals.

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Milligan said the company continues to pursue both licensing deals and M&A, and again noted some of Gilead's internal investments that are designed to support dealmaking activity, such as the January hiring of former **Novartis AG** executive Alessandro Riva to head up the oncology business. *(Also see "Gilead Cites 'More Sophisticated' Process As Pressure For A Major Deal Increases" - Scrip, 20 Mar, 2017.)*

The CEO noted that the company's executives "are in fact fully engaged with our teams assessing a number of different opportunities, which we think could play out over the coming year as we start to make progress in getting partnerships and potential acquisitions together."

But in terms of whether or not tax reform in the US and abroad could support increased dealmaking activity, Milligan said his teams will "focus on what is right for Gilead, try to ignore the noise globally in terms of tax reform, and do the best thing for the company and for the shareholders in the long-term."

PRESSED FOR DETAILS, MILLIGAN OFFERS STRATEGIC INSIGHTS

When pressed by Cowen analyst Phil Nadeau about a more detailed explanation of Gilead's strategy, the CEO outlined some ongoing actions and a few new opportunities that may help the company return to an extended period of overall revenue growth:

- The company continues to work on stabilizing its HCV revenue and introducing its final hepatitis C drug to the market – the three-drug combination pill containing *Sovaldi* (sofosbuvir), velpatasvir and voxilaprevir (GS-9857), which has been submitted for approval to the US FDA and European Medicines Agency (EMA) with an FDA decision expected by August 8. *(Also see "Gilead Coming To The End Of HCV Road With Triple-Drug Regimen" - Scrip, 2 Nov, 2016.)*
- In HIV, Gilead launched its antiviral therapies containing tenofovir alafenamide (TAF) to maintain its HIV market share in the face of generic competition that will hit *Viread* (tenofovir disoproxil) sales in the EU this year and in the US next year. (*Also see "Gilead HIV Sales Getting Boost From Switches To TAF-Based Combos" - Scrip, 2 Nov, 2016.) Genvoya* (elvitegravir/cobicistat/emtricitabine/TAF) was the most-prescribed HIV drug in the US and the fourth most-prescribed therapy for treatment-naïve patients in the top five European markets at the end of 2016. Sales of Gilead's TAF-containing HIV drugs increased from $169m in the first quarter of last year to $1.25bn in the first quarter of 2017.
- Separately, the TAF formulation *Vemlidy* was approved in November in the US and EU, which is expected to stabilize the company's hepatitis B sales. *(Also see "US, EU Nods For Gilead's Vemlidy To Enter Saturated Hep B Market" - Scrip, 11 Nov, 2016.)*
- Gilead continues to advance its portfolio of acquired compounds for non-alcoholic steatohepatitis (NASH) and could beat **Intercept Pharmaceuticals Inc.** to the market if that company's Phase III program continues to be delayed by slow patient enrollment. *(Also see "Intercept's NASH Phase III Enrolling Slowly; Gilead Could Gain Ground" - Scrip, 13 Jan, 2017.)* Gilead executive vice president of research and development and chief scientific officer Norbert Bischofberger said during the company's earnings call that it's too early to say definitively that its NASH trials aren't slowed by enrollment issues, but Gilead may benefit from working with clinical trial sites that participated in the company's HCV trials.
- In Gilead's nascent inflammation portfolio, the company and its partner **Galapagos NV** for the development of the JAK1 inhibitor filgotinib – in Phase III for ulcerative colitis and in Phase II for rheumatoid arthritis (RA), ankylosing spondylitis and psoriatic arthritis – may benefit now that the **Eli Lilly & Co.** and **Incyte Corp.** JAK1/2 inhibitor baricitinib has been delayed by an FDA rejection. *(Also see "Filgotinib Progress At Higher Dose Justifies Gilead's Gamble" - Scrip, 25 May, 2016.)* "I think we have

a really great opportunity with filgotinib to accelerate the clinical development timelines now that baricitinib seems to have a setback, which could provide greater upside for us as well if that is significantly delayed," Milligan said. *(Also see "Baricitinib Complete Response May Put Lilly/Incyte Behind IL-6 Blockers In RA" - Scrip, 14 Apr, 2017.)*

- The CEO also said in regard to other therapeutic areas that, "I think it's pretty clear we're looking for another avenue to increase our opportunity for revenue, and also for helping patients with the considerable resources that we have, and it's clear we've been focusing on oncology" with the Riva hire supporting that element of Gilead's strategy.

"I feel very good that we've got a number of different ways to accelerate growth for the company in the future, so that a decade from now we're a very different company, having reinvented ourselves beyond antivirals into a really multi-therapeutic area company. I feel very good about where we are and we'll continue to try to enhance that as well," Milligan said.

HCV WEIGHS ON FUTURE EARNINGS

The HCV portfolio will continue to weigh on Gilead's earnings in the meantime with new challenges – on top of the ongoing decline in the number of patients receiving treatment – expected over the next several months.

"Gilead still has a dominant hold on the HCV market, but I'm expecting falling patient numbers, continued pricing competition and the late 2017 launch of **AbbVie Inc.**'s rival pan-genotypic regimen, glecaprevir/pibrentasvir (G/P), to shrink Gilead's HCV revenues going forward," Datamonitor Michael Haydock said, noting that most of the company's already declining hepatitis C drug sales can be attributed to large drops in patient numbers with some revenue lost to competing therapies launched at aggressively discounted prices.

"I think glecaprevir/pibrentasvir is currently an underappreciated threat to *Epclusa*, given its pan-genotypic efficacy and its anticipated approval as an eight-week regimen in non-cirrhotic patients and 12 weeks in cirrhotic patients – (pan-genotypic) Epclusa is 12 weeks across the board," Haydock said. AbbVie's two-drug combination product could become the new standard of care for non-cirrhotic patients with genotypes 2 through 6 HCV, he said, and could be a fierce competitor for Gilead's eight-week therapy *Harvoni* (sofosbuvir and ledipasvir) in non-cirrhotic genotype 1 HCV, especially if AbbVie is willing to offer payers deep discounts.

The Datamonitor analyst noted that Gilead has had the upper hand compared with its competitors in terms of negotiating agreements with payers – offering higher Epclusa (sofosbuvir and velpatasvir) discounts for payers that exclusively list Harvoni on their formularies for genotype 1 patients. Conversely, payers that exclusively cover AbbVie's *Viekira Pak* (dasabuvir, ombitasvir, paritaprevir and ritonavir) or **Merck & Co. Inc.**'s *Zepatier* (elbasvir and grazoprevir) may face higher pricing for Epclusa to treat genotypes 2 and 3.

"Once approved, G/P will provide payers with another option for genotype 2/3 patients and will weaken Gilead's bargaining position in payer negotiations," Haydock said.

Mizuho Securities analyst Salim Syed noted in a May 2 report after speaking with Gilead's management team that the company sees AbbVie's latest HCV combo regimen as a competitive threat, but it believes that it has better data for Epclusa in genotype 3 cirrhotic patients. "The company noted that it is not sure exactly what impact AbbVie's regimen would have on either price or volume, but that it is monitoring it closely," Syed wrote.

GOING DIRECT TO PATIENTS TO BOOST HCV SALES

With HCV sales already declining and more competition on the way, Gilead is running two direct-to-consumer (DTC) advertising campaigns aimed at boosting the number of people seeking HCV treatment.

"The first launched in late 2016 with the goal of increasing screening among Baby Boomers. We are pleased to see that this campaign, along with the efforts of organizations like the [Centers for Disease Control and Prevention (CDC)], had an immediate effect with a 24% increase in HCV antibody testing among undiagnosed baby boomers over the first two months of implementation," Gilead executive vice president of commercial operations James Meyers said during the company's earning call. "The second campaign launched in March, and is directed towards diagnosed patients with a goal of encouraging them to seek treatment with Harvoni."

Meyers added: "It's important to remember that while the timeline for a patient to go from entering care to initiating therapy has lengthened and is more variable, there are still nearly three million people with HCV infection in the US, only half of whom are diagnosed."

HCV treatment initiations totaled 154,000 patients in the US in 2014 when Sovaldi and Harvoni launched with 256,000 patients starts in 2015 and 231,000 in 2016. Gilead still expects to grab a large share of those patients; based on its first quarter sales the company maintained its full-year 2017 guidance of $7.5bn to $9bn in HCV drug sales and $15bn to $15.5bn in non-HCV product sales.

"First-quarter total HCV sales of $2.58bn were shy of expectations of $2.61bn; however, the downward trajectory is consistent with 2017 financial guidance provided by the company last quarter," William Blair analyst John Sonnier wrote in a May 2 report. "We reiterate our position that the difficulty in accurately forecasting the HCV market is extremely high and note that a contributing factor is likely the shifting patient profile to a healthier population with perhaps a lower sense of urgency to seek care. Nonetheless, the underlying prevalence of the disease remains unchanged, and we estimate that millions of patients globally remain untreated to date."

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AstraZeneca's Imfinzi Debuts In Bladder Cancer

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Approval of the anti-PD-L1 *Imfinzi* (durvalumab) for second-line bladder cancer represents a major milestone for **AstraZeneca PLC** in immuno-oncology, but the modest market is very competitive and the drug likely will have to face competition from four other members of its checkpoint family for this indication by the end of the year.

FDA announced accelerated approval for second-line bladder cancer on May 1, six weeks before the drug's user fee date. The approval covers use in patients with locally advanced or metastatic urothelial cancer who progress after platinum-based chemotherapy or who have progression 12 months after treatment with platinum-based chemo in the neoadjuvant or adjuvant setting.

The agency also approved a complementary diagnostic from **Ventana Medical Systems Inc.** for PD-L1 expression – the Ventana PD-L1 (SP263) assay – but testing is not required for use. Labeling reflects that patients with higher PD-L1 expression had an overall response rate of 26.3% in the pivotal single-arm study, compared with 4.1% for patients with no or low PD-L1 expression. The overall ORR in the 182-patient study was 17%.

Bladder cancer is a modest market compared to other indications targeted for checkpoint inhibitors – Morningstar Research expects peak worldwide sales of $3bn for the indication in 2022, of which AstraZeneca would get a 20% share. The American Cancer Society estimates that some 76,000 people in the US were diagnosed with bladder cancer in 2016, 11% of whom were in advanced stages.

A CROWDED MARKET

Imfinzi is the fifth member of the PD-1/L1 checkpoint inhibitor family to secure approval in the US, after two PD-1 inhibitors – **Bristol-Myers Squibb Co.**'s *Opdivo* (nivolumab) and **Merck & Co. Inc.**'s *Keytruda* (pembrolizumab) – and two PD-L1 inhibitors – **Roche**'s *Tecentriq* (atezolizumab) and **Merck KGAA**/**Pfizer Inc.**'s *Bavencio* (avelumab). Imfinzi's average monthly wholesale acquisition cost (WAC) is $15,000. "Importantly, the WAC price is rarely the price paid by an individual patient," AstraZeneca told *Scrip*.

The list price is a bit higher than the other drugs in the class. Opdivo's average list price is now $13,280 per month and Keytruda and Bavencio both have a list price of about $13,000 a month. Tecentriq's list price is $12,500 per month.

Tecentriq was the first to get a bladder cancer indication with accelerated approval in May 2016 in second-line disease, followed up by a first-line clearance in April. Approval was supported by a study in which the drug demonstrated a 14.8% ORR.

Bristol's Opdivo won accelerated approval for second-line bladder cancer in February. Opdivo was associated with a 19.6% ORR in a single-arm study in bladder cancer.

Tecentriq and Opdivo compete directly with Imfinzi in the second-line setting, and will likely serve as barriers to market entry, due to physician comfort and familiarity, Datamonitor Healthcare analyst Dustin Phan commented.

And yet more checkpoint competition is on the way. Merck announced in February that FDA has accepted filings for Keytruda in first-line urothelial cancer patients ineligible for cisplatin-containing therapy and for second-line cancer after disease progression following platinum-based therapy. Decisions are expected on these filings by June 14.

"Importantly, Keytruda's [second-line] indication could be a full approval based on the improvement in overall survival (OS) seen in the Keynote-045 trial," Leerink Swann analyst Seamus Fernandez wrote in a May 1 note. Overall survival data is not yet available for any of the other drugs.

Merck KgAA/Pfizer's Bavencio is under review for accelerated approval in second-line bladder cancer, with an Aug. 27 user fee date.

Tecentriq currently has the first-to-market advantage in the lucrative treatment-naïve population, Phan noted.

Imfinzi is also in development for first-line bladder cancer – the Phase III DANUBE study includes a monotherapy cohort and an arm that combines Imfinzi with the company's CTLA-4 inhibitor tremeliumumab.

The study has an estimated primary completion date of April 2018, with data release and submission for regulatory approval expected soon after. Bristol is positioning its combination of Opdivo with the CTLA-4 inhibitor *Yervoy* (ipilimumab) in the same setting, but is further behind.

"If successful, this will place AstraZeneca's PD-L1/CTLA-4 immune checkpoint combination ahead of Opdivo plus Yervoy, which is not expected to complete Phase III studies until [the third quarter of] 2020," Phan commented.

Michelle Werner, vice president of oncology, told *Scrip* that one unique aspect of the launch is that the company is offering a program called Lighthouse to educate physicians and patients about preventing and managing immune-mediated adverse events, which occur with all cancer immunotherapies, but are worse with CTLA-4 inhibitors than PD-1/L1 inhibitors.

PAVING WAY FOR LUNG SBLA

Although the bladder cancer indication is a "relatively small opportunity" for AstraZeneca, "the approval will allow the agent to become more familiar with oncologists and should help facilitate future sBLAs," Leerink's Fernandez observed.

Analysts are most eager to see progression-free survival results in the middle of this year from the Phase III MYSTIC study, which tests the drug as a monotherapy and with tremelimumab in first-line non-small cell lung cancer (NSCLC). The company has changed the design of the study to have more of a focus on Imfinzi as a monotherapy and to stress different endpoints, which caused a delay to the readout.

Investors are a bit nervous about prospects for PD-1/CTLA-4 combinations in light of the changes to MYSTIC design and Bristol's decision not to file its PD-1/CTLA-4 combination Opdivo/Yervoy for accelerated approval in first-line NSCLC this year, instead waiting for the readout of CheckMate 227 in 2018. This has given Merck the lead in first-line NSCLC, with approval already for Keytruda monotherapy and a filing for Keytruda with chemotherapy combination with FDA with a May 10 user fee date.

AstraZeneca notes that it is running a total of 19 late-stage trials with durvalumab in 8,000 patients, including 13 IO/IO combination studies.

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Incyte Eyes Big Phase III IDO Expansion, NewLink Plans First Pivotal Trial

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First-quarter earnings calls on May 4 provided an opportunity for **Incyte Corp.** to highlight the breadth of the multi-tumor registrational program for its leading IDO inhibitor epacadostat and for **NewLink Genetics Corp.** to share its plans to test its IDO pathway inhibitor indoximod in a pivotal melanoma study, which is set to kick off by the end of the year.

Incyte Corp's epacadostat is the most advanced candidate for one of the hottest new immunotherapy targets in development: indoleamine 2,3-dioxygenase 1 (IDO1). After early data were reported for the drug in combination with **Merck & Co. Inc.**'s PD-1 inhibitor *Keytruda* (pembrolizumab) in melanoma, the combination jumped straight to Phase III for that indication. *(Also see "J.P. Morgan Notebook Day 1: PCSK9 Face-Off, Teva's Slowed Growth, Merck's Keytruda Wins, Lilly's CDK4/6 Hopes And More" - Scrip, 10 Jan, 2017.)*

Epacadostat is a direct inhibitor of IDO, whereas indoximod – the second-most advanced IDO drug – works on the IDO pathway.

NewLink plans to start a large study testing indoximod with a PD-1 inhibitor in melanoma by the end of the year and the company believes this might be enough to support a regulatory filing. NewLink would like to assess the drug in metastatic melanoma patients who are treatment-naïve, aside from use of BRAF inhibitors in BRAF-mutant patients, but its plans are subject to regulatory review, CEO Chuck Link explained to *Scrip*. A new formulation and dosing for indoximod will be evaluated in the first part of the trial, with an adaptive design.

Currently, aside from BRAF inhibitors, PD-1 inhibitors are approved for frontline melanoma as is the combination of **Bristol-Myers Squibb Co.**'s PD-1 inhibitor *Opdivo* (nivolumab) and CTLA-4 inhibitor *Yervoy* (ipilimumab). Older treatment options that have been surpassed by the new checkpoint inhibitors include dacarbazine (DTIC) chemotherapy and IL-2 immunotherapy.

NewLink is currently going it alone on development and is able to finance a large Phase III study. The company ended the first quarter with $118.2m in cash and plans to end 2017 with $75m in cash, excluding financing and milestones.

NewLink presented Phase II data for indoximod and Keytruda at the American Association for Cancer Research (AACR) meeting in April. *(Also see "AACR In Review: IDO Pushes Ahead, CTLA-4 Combo Lags Behind" - Scrip, 12 Apr, 2017.)* In the study, the combination demonstrated a 59% objective response rate and a complete response rate of 12% in patients with non-ocular melanoma, and was well tolerated.

Chief medical officer Nicholas Vahanian said during NewLink's May 4 investor call that the company's "top priority is to bring indoximod to market as quickly as possible."

One study may be enough to support approval, but the company will need regulators to weigh in on this plan, Link said.

In melanoma, Incyte is running just one pivotal study of its epacadostat with Keytruda.

NewLink execs also pointed out that indoximod is in multiple Phase II trials, including in prostate cancer, pancreatic cancer and acute myeloid leukemia. Data (Abstract #3066) will be presented at the American Society of Clinical Oncology (ASCO) annual meeting in June on use in prostate cancer in combination with *Provenge* (sipuleucel-T), the first cancer vaccine, which now is owned by **Valeant Pharmaceuticals International Inc.** but is set to be sold to the **Sanpower Group** in China. Phase Ib data for NewLink's direct IDO inhibitor navoximod (GDC-0919), which is partnered with **Roche**, in combination with Roche's PD-L1 inhibitor *Tecentriq* (atezolizumab) in multiple tumor types will also be featured at ASCO (Abstract #105). Phase II data for indoximod in pancreatic cancer and AML will be presented later this year after ASCO.

NewLink also plans to put a next-generation candidate for indoximod in the clinic by the end of the third quarter.

> The company's 'top priority is to bring indoximod to market as quickly as possible.' One study may be enough to support approval, but the company will need regulators to weigh in on this plan

INCYTE STEPS ON THE IDO GAS

Meanwhile, Incyte is building on its big lead in the IDO space, having started its Phase III ECHO-301 melanoma study of epacadostat and Keytruda about one year ago.

During the company's earnings call, chief medical officer Steven Stein said the trial has been recruiting very well.

"The collaborative effort with Merck has been very successful and enrollment target numbers for ECHO-301 have recently been reached at most investigator sites. Sites in Japan remain open for recruitment in that portion of the study," Stein said.

Around the time of the AACR meeting, the company announced plans to start two Phase III studies of epacadostat with Bristol's Opdivo, one in first-line non-small cell lung cancer (all levels of PD-L1 expression) and one in first-line head and neck cancer. *(Also see "Deal Watch: Merck, Incyte Double Down On Keytruda/Epacadostat Collaboration" - Scrip, 31 Mar, 2017.)* Previously it announced that in partnership with Merck, it will soon be starting six pivotal trials beyond melanoma: two in non-small cell lung cancer, one in first-line kidney cancer, one in squamous cell cancer of the head and neck and two in bladder cancer (first-line and second-line).

Incyte hopes that these studies will start by the end of the year.

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The company clarified during the call that there is no agreement for exclusivity with Bristol. With Merck, there's a 15-month exclusivity agreement around the ability to test the same clinical question – but a different clinical question could be tested with another partner.

CEO Hervé Hoppenot said the company is looking forward to showing the data driving the go-forward decisions at the ASCO meeting.

Poster presentations related to IDO at the ASCO meeting include Phase I/II results from the ECHO-202/KEYNOTE-037 study of epacadostat with Merck's Keytruda in non-small cell lung cancer (Abstract #9014), renal cell carcinoma (Abstract #4515) and triple negative breast cancer (Abstract #1103). There also will be separate oral presentations for the combination in urothelial carcinoma (Abstract #4505) and squamous cell cancer of the head and neck (Abstract #6010).

ASCO also will feature oral presentations of Phase I/II data for epacadostat with Bristol's Opdivo in the ECHO-204 study of advanced solid tumors (Abstract #3003). Stein said the data from the ECHO trials will include about 30 to 40 patients per tumor type.

IDO represents a big bright spot for Incyte following the US FDA's complete response letter in April for its rheumatoid arthritis drug baricitinib, which is partnered with **Eli Lilly & Co.***(Also see "Baricitinib Complete Response May Put Lilly/Incyte Behind IL-6 Blockers In RA" - Scrip, 14 Apr, 2017.)*

Incyte declined to comment about the CRL during its call, aside from saying that "Lilly will now engage with the FDA to discuss the agency's concern and determine the potential path forward."

In February, baricitinib was approved in Europe, where it has been launched under the brand name *Olumiant*. Incyte reported $400,000 in royalties related to Olumiant from Lilly in the first quarter.

In the first quarter, Incyte reported $384m in revenue from about $265m in product revenue, $30m in royalties and $90m in contract revenue. For the same period in 2016, Incyte reported about $263m. The company's JAK inhibitor *Jakafi/Jakavi* (ruxolitinib) performed well, with $251m in sales (up 37% year-over-year) in the US and $29m in ex-US royalties from partner **Novartis AG**.

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Onxeo Seeks Partner For Its Expanding Oncology Pipeline

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Onxeo SA's CEO Judith Greciet outlines the company's business goals for 2017 and its plans to secure a partner for its lead product *Livatag* (doxorubicin Transdrug), for which a Phase III trial is expected to complete soon in second-line hepatocellular carcinoma (HCC).

Spectrum Pharmaceuticals Inc.. Onxeo now plans to move Beleodaq into Phase III trials for first-line treatment of PTCL, in combination with chemotherapy. Greciet added that the company plans to develop Beleodaq as an oral formulation, in combination with other anti-cancer

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The French company needs a partner for Livatag to help successfully commercialize and promote the product if it is approved by regulators. As an R&D development company rather than a commercial business, Onxeo does not have the infrastructure or experience to launch a new medicine solo.

"I believe partnering the compound with a very good commercial partner will give the product a better chance of success and the catalyst for that partnering is, of course, the availability of the data," Greciet said. She also highlighted that the compound has potential as part of a combination first-line treatment for other solid cancers. However, this is all still in the preclinical stage and relies on the results from the Phase III Livatag trial in second-line HCC, for which results will be announced mid-2017.

Meanwhile, Onxeo's histone deactylase inhibitor (HDACi), *Beleodaq* (belinostat), is already on the US market for peripheral T-cell lymphoma (PTCL); the product was promoted and sold by its partner, agents, as it is currently only available intravenously. With a prototype, ready and accepted for clinical development, Onxeo is currently running preclinical assessments and hopes to study the formulation in other solid tumors, aside from PTCL. The outcome of the first preclinical study will be announced this summer.

Last year Onxeo acquired **DNA Therapeutics SA** for its signal interfering DNA repair technology and first-in-class molecule – a move aimed at increasing Onxeo's pipeline options.

The lead molecule from **DNA Therapeutics SA**, AsiDNA (formerly DT01), a first-in-class signal-interfering DNA (siDNA) molecule with potential as a treatment for genetically unstable or resistant types of cancers, is expected to enter the clinic this year.

"For 2017 the key focus will be on Livatag, to make sure the product gets the best value once the clinical data are available, and to take AsiDNA and the Beleodaq combo into clinic by the end of the year," Greciet said.

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Brigatinib Approval Validates Ariad Buy – Can Takeda Carve A Position?

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Takeda Pharmaceutical Co. Ltd. has said that brigatinib was a key value driver behind its $5.2bn acquisition of US oncology specialist **Ariad Pharmaceuticals Inc.**, and the accelerated US FDA approval of the ALK inhibitor as *Alunbrig* last week for second-line non-small cell lung cancer (NSCLC) appears to provide some early validation of this view.

Following the purchase of Ariad, completed only in February, the Japanese company foresees eventual peak annual sales of more than $1bn for the once-daily oral drug, adding to the revenues already coming in from Ariad's only other already marketed product, the leukemia therapy *Iclusig* (ponatinib).

But given that brigatinib is the fourth kinase inhibitor approved in the US for its indication - ALK (anaplastic lymphoma kinase)-positive NSCLC patients progressing after or intolerant of first-line therapy with crizotinib (**Pfizer Inc.**'s ALK inhibitor *Xalkori*) - it will need to carve out a competitive niche.

Two second-generation ALK inhibitors, **Novartis AG**'s *Zykadia* (ceritinib) and **Roche**'s *Alecensa* (alectinib), are already approved in the US (and some other markets) for second-line ALK+ NSCLC.

EFFICACY, METASTASES BENEFITS?

Brigatinib, which holds orphan and breakthrough therapy designation in its initial indication, was granted approval following a rolling NDA submission completed last August, based primarily on tumor response rate and duration of response in the Phase II ALTA trial.

The 222-patient study showed patients receiving 180mg/day plus a seven-day lead-in of 90mg/day achieved a confirmed overall response (OR) as assessed by the independent review committee of 53%. The median duration of response was 13.8 months as assessed by the IRC. *(Also see "Rydapt And Alunbrig Approvals Headline Good Week For Targeted Oncologics At US FDA" - Pink Sheet, 29 Apr, 2017.)*

While other studies have already shown progression-free survival benefits for brigatinib versus Zykadia and Alecensa, the early indications are that it is in the area of brain metastases that Takeda may be looking for other key positioning and differentiation advantages.

Such metastases are common in ALK+ NSCLC patients, occurring in up to 70% of those treated with a first-line ALK inhibitor.

In the ALTA trial, 67% of patients with measurable brain metastases (n=18) achieved a confirmed intracranial overall response by IRC assessment. 78% of those with an intracranial response in the 90mg arm and 68% in the 90-180mg group also maintained a response for at least four months.

In addition to highlighting the median duration of response greater than one year against NSCLC, "importantly, the extent of activity among those with brain metastases was also notable," University of Colorado director of thoracic oncology Dr. D. Ross Camidge emphasized in a Takeda statement on the approval.

At the time of the Ariad acquisition, the company's chief medical and scientific officer Dr. Andrew Plump also stressed that brigatinib is "clearly highly active against brain metastases".

On top of this activity and the convenience of once-daily oral dosing with or without food - Alecensa is twice daily with food and Zykadia once daily on an empty stomach at least two hours after a meal - the other main characteristic Takeda may be looking to emphasize is the drug's broad activity against resistance mutations.

While the initial approval represents only a narrow indication, given that only 2-8% of patients with metastatic NSCLC have ALK rearrangements, Takeda has already said it sees chances for expansion into other genetically defined NSCLC subgroups for the drug given a broad inhibitory profile against various ALK resistance mutants.

It has so far not further elucidated this strategy but this might enable an expansion of the patient population, and despite being a relative latecomer, the company sees best-in-class potential for brigatinib.

While the second-generation ALK inhibitors can overcome secondary mutations (such as the L1196M "gatekeeper" mutation responsible for Xalkori resistance), recipient patients can also acquire further ALK gene mutations that mediate resistance to both Zykadia and Alecensa, so Alunbrig might be able to find a role here.

Camidge also pointed to a continuing need for ALK-targeting agents with a manageable safety profile and that "may address mechanisms of clinical resistance to crizotinib, including progression in the central nervous system."

Serious adverse reactions occurred in 38% of patients in the 90mg group and 40% of those in the 90-180mg group, and fatal adverse reactions including pneumonia occurring in 3.7% of patients.

FIRST-LINE PLANS

Global filings are planned for brigatinib, initially in the second-line ALK+ NSCLC setting, for which a marketing authorization application was filed in the EU in February.

Differentiation is also likely to be particularly critical in the first-line setting, where Zykadia and Alecensa are already jockeying for position and Roche's Phase III ALEX study with Alecensa showed advantages over Xalkori in PFS terms.

Brigatinib is in the ongoing Phase III ALTA 1L trial versus crizotinib to support its planned expansion to the first-line setting in advanced/metastatic ALK+ NSCLC.

Datamonitor Healthcare is forecasting US sales of around $47m for brigatinib in first-line NSCLC in 2023. "Brigatinib will be a key option for patients in later lines of therapy, due to the variety of secondary mutations responsible for resistance to ALK inhibitors, but the drug's late arrival to market [particularly in the more profitable first-line setting] will prevent it from gaining substantial uptake in earlier lines of therapy," Datamonitor states.

However, a partnership - such as that effectively provided by the Takeda acquisition - will help the drug better compete with same-class competitors, Datamonitor predicts.

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From the editors of PharmAsia News.

Radius Prices Osteoporosis 'Blockbuster' Tymlos To Compete, Grow Market

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Radius Health Inc. set a price of $19,500 per year for its newly approved osteoporosis drug *Tymlos* (abaloparatide), which the company believes will improve access to the daily injectable medicine for cost-sensitive patients – and which may help it gain market share from an established product.

Radius CEO Bob Ward is confident that Tymlos, which won US FDA approval on April 28, can achieve blockbuster status. However, with a mechanism that's similar to **Eli Lilly & Co.**'s 15-year-old drug *Forteo* (teriparatide), the company may need to do more than set a wholesale acquisition cost (WAC) that's substantially below the competing product to generate $1bn or more in annual sales. Radius hopes new treatment guidelines for anabolic (bone-building) drugs will help boost sales and the company believes it can increase the number of eligible post-menopausal women getting treatment with injectable drugs.

"We expect Tymlos to enjoy a lengthy branded commercial life and for the brand to achieve blockbuster status," Ward said during a May 1 first quarter earnings call, which was dominated by a discussion of the market prospects and commercial strategy for the drug.

Radius reported a net loss of $56.9m ($1.32 per share) for the January-to-March period compared to a net loss of $40.5m ($0.94 per share) for the same period last year. The company ended the quarter with $282.1m in cash and securities to support the early May launch of Tymlos and its ongoing cancer research and development programs. The osteoporosis drug is a parathyroid hormone-related protein (PTHrP) analog as opposed to.

Radius has hired 230 sales representatives to market the osteoporosis drug, which is an analog of parathyroid hormone-related protein (PTHrP) while Forteo is an analog of parathyroid hormone. The sales team will first target 20,000 endocrinologists and rheumatologists that already prescribe injectable anabolics and who treat a lot of osteoporotic women with a high bone fracture risk. The 200 top prescribers out of that group account for 20% of anabolic drug sales.

"We evaluated the commercial landscape and here in the US there's about 20,000 physicians that represent the greatest opportunity today," Ward said in an interview.

That specialty market size is appropriate for a newly commercial biotechnology company to handle on its own, at least domestically, he said. For first product launches, Radius found that biotech firms were most successful when they worked with a partner in ex-US markets. That's why Radius is talking to partners in Europe ahead of a decision from the European Medicines Agency's (EMA's) Committee for the Human Use of Medicinal Products (CHMP) on Tymlos, which is expected in July.

LARGE MARKET WITH ROOM FOR GREATER USE

The daily injection was approved in the US to treat post-menopausal women with osteoporosis who are at high risk for a fracture due to a previous fracture, who have multiple risk factors or who are intolerant to other osteoporosis therapies.

That covers a market that's quite large, considering 1.4m post-menopausal American women have had at least one osteoporotic fracture, which can be quite expensive for the health care system and payers as well as incapacitating for patients, Radius chief medical officer Lorraine Fitzpatrick noted during the company's earnings conference call.

Fitzpatrick said that "major osteoporotic fractures are fractures of a hip, wrist, shoulder, forearm or a clinical spine fracture," which results in "a lot of disability, a lot of lack of mobility for the patient and lack of independence." Radius believes that its data to date on reductions in fracture risk will be important to payers, since fewer fractures mean lower health care costs, she noted.

FDA approval was based on 18-month results from the Phase III ACTIVE clinical trial and initial six-month results from ACTIVExtend, including reductions in vertebral and non-vertebral fractures by 86% and 43%, respectively, versus placebo. Studies also showed increases in bone mineral density (BMD) and markers of bone formation. *(Also see "Will Radius Health's Abaloparatide Data Do The Trick In Osteoporosis?" - Scrip, 18 Aug, 2016.)*

Tymlos was approved two months before the revised June 30 action date that Radius revealed in March and almost three months ahead of the July 19 user fee date for **Amgen Inc.**'s competing osteoporosis therapy, the sclerostin inhibitor *Evenity* (romosozumab). *(Also see "Radius Reveals Abaloparatide Delay, After Playing Up Launch Readiness" - Scrip, 10 Mar, 2017.)*

It remains to be seen how Amgen will try to compete in terms of price with Tymlos, but the big biotech's current osteoporosis blockbuster *Prolia* (denosumab) – which generated $1.64bn in 2016 sales ($1.05bn in the US) – likely will continue to be used ahead of anabolics, given the twice-yearly physician administered injection's WAC price of $1,077.55 per syringe or $2,155.10 annually. Forteo's WAC price is $2,727.84 for 28 days of therapy or $32,734.08 for a year of treatment.

The $19,500 per year price tag for Tymlos, prior to discounts given to payers to win inclusion on formularies, is a bit of a double-edged sword for Radius, because it could mean greater sales volume than projected, but reduced revenue compared with investors' hopes. Indeed, the company's stock price closed down 9.6% at $35.31 on May 1 after Radius reported the drug's list price during its earnings call.

PRICED TO PROVIDE ACCESS, INCREASE MARKET

Ward said the company set its Tymlos price with access to the drug in mind, since two-thirds of women in this post-menopausal treatment group in the US are covered by Medicare and many of the one-third who are covered by private payers have concerns about co-pay requirements for brand-name medicines.

"In terms of enabling patients to get access to appropriate therapeutics, historically price has been a barrier to getting products to patients," the CEO told *Scrip*. "When we look at anabolics access here in the US, for patients in the US, doctors haven't offered them, because they were concerned that patients couldn't afford the out-of-pocket cost."

Jefferies analyst Eun Yang said in a May 1 research note that the number of Tymlos injections sold could rise based on the drug's competitive cost, but with a WAC price about 33% below her expectations, Yang reduced her peak US sales estimate to about $200m. Yang expects Tymlos to capture about 30% of a US anabolic drug market that she estimates to be $585m to $780m in annual sales – based on a declining number of Forteo injection sales – giving the Radius drug a $175m to $234m market share.

Yang said in an April 28 note immediately following Tymlos approval that the drug's label was in line with expectations, including a black box warning regarding a risk of osteosarcoma, which Forteo also has in its label. Even so, the analyst said the Radius drug will face tough competition for market share, since Amgen's Prolia already is used ahead of anabolics, Forteo has a strong presence that will be eroded when biosimilars hit the market – potentially in 2019 – and Amgen may have a second competing osteoporosis therapy within a few months.

However, Radius has high hopes for a growing market for anabolic therapies based on new treatment guidelines that the American Association of Clinical Endocrinologists (AACE) released in September, which recommend first-line treatment with injectable therapies for post-menopausal women with a previous fracture or high fracture risk.

"The is the first time anabolics have been indicated in the first line. Anabolics in the past were recommended for later treatment. This is a change in how people think about managing osteoporosis," Ward said in the interview.

He noted that Radius plans to capture some of the osteoporosis market's potential growth based on the AACE guidelines by offering an option for patients who want to self-inject – a benefit over Prolia, which is physician-administered. The company believes that Tymlos also has a convenience factor in that it doesn't have to be refrigerated after the initial dose – a big benefit for women who like to travel.

Radius already has patient support programs in place to help with questions about the Tymlos injector – a pen loaded with a month's worth of doses – and inquiries about the company's patient assistance program to help with out-of-pocket costs.

MAKING PROGRESS WITH PAYERS

In terms of payer negotiations, Ward told *Scrip* that Radius has seen "openness and enthusiasm" from private payers. He also noted that the timing of FDA approval was positive for the company, because May is when Medicare Part D plans submit recommendations to their formularies.

"We anticipate initial formulary decisions flowing in the coming days and weeks," Radius chief commercial officer David Snow said during the company's earnings call. "The branded osteoporosis treatments all face some type of prior authorization, and we expect that that will continue during the launch phase."

Snow noted that prescriptions for Forteo have gone down as the Lilly drug's pricing has gone up, enabling the big pharma to maintain rising revenue, but lose market share. That's why the lower cost of Tymlos could be a competitive advantage, especially if the market's overall size could be increased.

He noted that most post-menopausal women who are taking injectable therapies are 70 or older and insured by Medicare, but there's potential for growth among commercially insured women in their 50s who've already had a fracture, but aren't being treated with an injectable, and among women in their 60s who have had a fracture and have other risk factors, such as family history and low bone mineral density. The 60-70 age group is covered by a mix of commercial insurance and Medicare.

"Frequently in reviews, conversations and even symposia, clinicians tell us that they desire to use anabolics more frequently, but the out-of-pocket burden was so substantial that they were restricting use and didn't offer it to many appropriate patients," Snow said. "If we're to expand the use to more anabolic-appropriate patients, we have to address this out-of-pocket challenge."

Hence, the $19,500 per year WAC price at a discount to Forteo.

"If the initial comments we've gotten from payers is any indication, we expect to see a very favorable response from clinicians and patients," Snow said. "Our focus is not only on gaining market leadership, but regaining growth in the anabolic class."

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Novo Nordisk Sharpens Its Outlook But Warns Risks Remain Later In 2017

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Novo Nordisk AS delivered a strong start to the year, beating consensus sales and earnings forecasts, driven by demand for its innovative products within diabetes and obesity care as well good cost control - but analysts say the rising sales trend and cost constraints could unravel later in 2017.

The Denmark-based group – which is grappling with increasing competition worldwide and pricing pressures in the US where it generates 40% of its sales – pleased battered shareholders and beat market predictions May 3 by announcing group sales in the first quarter jumped 5% when measured in Danish kroner, its reporting currency.

The strong start gave the Danish group the confidence to say 2017 revenue is now expected to grow 0% to 3%, a tightened range from -1% to 4% in February, but with the mid-range unchanged. "These reflect expectations for continued growth of performance for *Victoza* (liraglutide) and *Tresiba* (insulin degludec) as well as a positive contribution from *Saxenda* (liraglutide for weight loss) and *Xultophy* (insulin degludec and liraglutide)," the group's CFO Jesper Brandgaard said on a call with analysts discussing the quarter.

WELCOME RESPITE FOR NEW CEO

The update is good news for Lars Fruergaard Jørgensen, who took over as Novo Nordisk's CEO in January after a management shake-up. The group in February cut its sales and profit forecast for the fourth time in a year, citing political risks on drug pricing in the US, its biggest market.

Still, most analysts said the strong start felt temporary. One reason is that the company is indicating it will increase investment later in the year. Meanwhile, downward pricing pressures - and rival products that continue to take market share - threaten its sales and profitability prospects.

"Cost control was good, particularly in R&D, which at DKK3.3bn ($480m) was just 11.6% of sales. This is likely a temporary pause, however, as the company is winding down low innovation R&D projects as per its strategy update from October last year," analysts at Berenberg said in a reaction note.

Lars Fruergaard Jørgensen

'When we look at the full year, we see the same landscape as when we announced our full-year results'

Asked on a call with reporters in connection with the update why the guidance was tightened – implying less uncertainty - the group's new CEO replied: "We had anticipated that Q1 was going to be a challenging quarter compared with the year-ago quarter … but we saw sales for the first quarter come in slightly higher than expected, impacted by some one-offs that are not recurring, and we see a slightly higher inventory on Victoza in the US and we have had a credit from wholesalers related to price change on the *NovoLog* insulins franchise, and we also see in Europe some one-offs, that have made Q1 better than originally guided."

But these sales drivers are expected to be countered later this year by an impact from lower realized prices in the US, driven by lower prices in the basal insulin and growth hormone segments, management said.

CEO Fruergaard Jørgensen thus believes the company has little room for maneuver in coming months. "When we look at the full year, we still see the same landscape as when we announced our full-year results in February - but we have lowered the upper end of the range because we see that there's still competition both in our insulin franchise and our GLP-1 franchise, so we do not see that we can overperform or positively drive Victoza or the Tresiba brands beyond what we had planned," Fruergaard Jørgensen said.

"That said, we are now four months into the year and from an overall risk point of view we believe that we have better visibility – also in the political arena. Therefore, there was grounds for "a narrowing of the guidance but with the same mid-point," the CEO said, adding: "We felt it was prudent, as the risk looks lower, but the opportunity is also lower in terms of over-performance."

Analysts at Bernstein said in a note that Novo Nordisk's stock "will likely remain strong until mid-17 data points, adding: "We are now heading into a relatively solid period for the company: Results for 2Q are likely to be decent given that pricing trajectory is unlikely to change; there is potential for positive clinical data in the third quarter of 2017 with semaglutide's SUSTAIN 7 in the second half with data versus [**Eli Lilly & Co.**'s] *Trulicity* (dulaglutide), and Phase II in obesity and a positive Tresiba label update from SWITCH in the US in the third quarter."

But the analysts see the late part of 2017 as being more challenging.

"While we will get further label and approvals … as we head into contracting for 2018, we are more confident the pressure will increase."

When giving its quarterly update, Novo Nordisk said its operating profit rose 10% when reported in Danish kroner, and advanced by 6% measured in local currencies, to DKK 13.5bn.

Sales within biopharmaceuticals fell 24% to DKK 4.7bn, or by 25% in local currencies, mainly due to rebate adjustments in the first quarter of 2016, and a recent introduction of a generic version of *Vagifem* (estradiol vaginal inserts), both in the US.

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Ferring Looks For Early Microbiome Wins, But Willing To Do Heavy Lifting

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There may be some early wins when applying new thinking about the microbiome to novel approaches to therapy, but it's going to take time to link insights into the microbial flora with disease and to come up with new medicines, says Per Falk, executive vice-president and chief scientific officer at **Ferring International Center SA**, a mid-sized pharma that has the microbiome very much on its R&D agenda.

Falk, a 30-year veteran of research into this nascent therapeutic approach, believes the level of complexity involved in the microbiome interacting with its human host is likely to work against having many quick wins.

"There is a group of players who dive in and test their ideas, based on what they know and read, and you will see interesting trials and interesting reports, but you will also see setbacks," he told *Scrip* in a recent interview. "The likelihood of success is fairly small, because you know certain things but you don't know other influences. Indeed, we struggle to manage target discovery and pathway mapping with our current understanding of the human genome, but the microbiome is two orders of magnitude more complex," Falk noted.

On the other hand, there are researchers who are taking a more measured, platform-driven approach to understanding the microbiome. "They are the ones who move forward with better founded ideas and a higher likelihood of success," according to Falk. "If you want to build a therapeutic platform on understanding, you need to be methodical and meticulous."

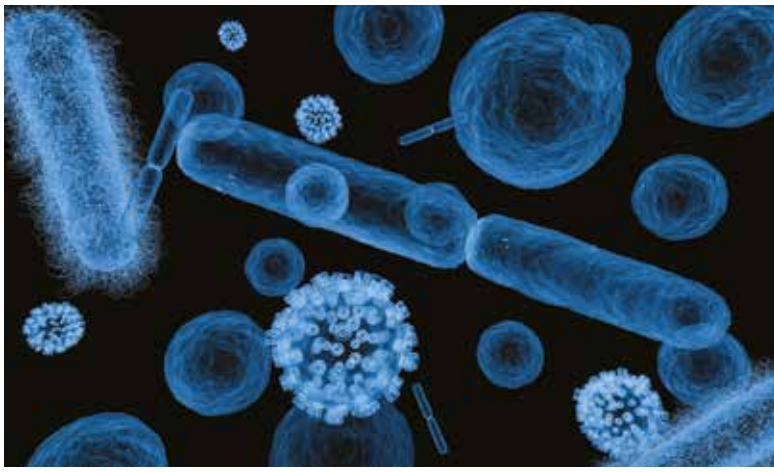
CAUTIOUS LONG-TERM PLANS

Ferring is looking at both short- and long-term approaches to microbiome research, underlying the recent conclusion from a "Scrip Asks" survey that the buzz around the potential of microbiome research to yield new therapeutics was growing. *(Also see "Scrip Asks… Is The Microbiome Hype Or Happening?" - Scrip, 12 Apr, 2017.)*

"We have taken a few bets by partnering with interesting biotechs with interesting ideas that are relatively easy to test early, but our long-term plans are more cautious," Falk said. In this regard, the St Prex, Switzerland-headquartered Ferring is active at working with academic partners to define a normal microbiome. "A lot of companies won't do this; it's likely to take too long for them, and they want to come in when a therapeutic is on the horizon," Falk noted. *(Also see "Ferring Adds Karolinska's Microbiome Expertise To Research Efforts" - Scrip, 28 Jan, 2016.)*

The mapping of the microbiome in healthy people and those with disease will explain a lot about the variability of the microbiome, its role in patients with aggressive or refractory disease, and in early and late disease, it is hoped. "Maybe by looking at the microbiome we might find a new way of understanding conditions like Crohn's disease, where the underlining molecular defect has not been identified, and where understanding their microbiomes might lead to developing tailored therapies for different disease variants."

Ferring is also taking an agnostic approach to the type of therapeutic it will evaluate. "Bacteriophage have an interesting future; they have been used in the past as therapeutics, before the antibiotic era, and have great potential, particularly if combined with a probiotic approach," Falk said. "If you take a therapy like phage that reduce levels of specific bacteria, and combine it with colonizing bacteria, one might be able to accelerate a transition from dysbiosis to a normal microbiome."



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In March, 2017, Ferring licensed European marketing rights to **CDI Investments**' *VSL#3*, a probiotic food supplement containing eight different strains of live lactic acid bacteria, and in January 2017 it partnered with Baltimore, Maryland-based US firm **Intralytix Inc.** to collaborate on the development of bacteriophage-based treatments. In 2016, Ferring linked up with Gothenburg, Sweden-based firm **MetaboGen AG** to develop a microbiome-based treatment for intrahepatic cholestasis of pregnancy, and with the Karolinska Institute in Sweden to set up the Centre for Translational Microbiome research.

The microbiome field will likely see the first therapeutic breakthroughs in the gastrointestinal infection area, for example in patients with *Clostridium difficile* infections where both the addition of healthy bacteria and the use of bacteriophage as a "surgical strike" at problem bacteria hold promise, Falk said.

But the next area to benefit is likely to be dermatology, he continued. "There are some interesting studies underway involving the use of bacteriophage to treat *Staphylococcus aureus* infections associated with burns, for instance that are being undertaken by Intralytix Inc." Moreover, in women's health, the treatment of genitourinary infections might benefit from greater understanding of changes in the microbiome, he added.

Finally, in more complex disorders such as psychiatry, "there is no doubt there is a link with circulating microbiome-derived metabolites, that account for most of the circulating chemicals in the blood, but the interaction is hugely complex," he commented.

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Regeneron Hypes New Eczema Drug Dupixent In 1Q

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Regeneron Pharmaceuticals Inc. boasted about its recently approved atopic dermatitis therapy *Dupixent* (dupilumab) during its first quarter earnings call, but despite a successful US launch and the promise of several label extensions into indications such as pediatric atopic dermatitis, nasal polyps and eosinophilic esophagitis, the drug won't surpass *Eylea* (aflibercept) as Regeneron's core growth driver for several years.

Dupixent, an IL4R antibody developed in partnership with **Sanofi**, was approved by the US FDA in March for the treatment of adults with moderate-to-severe atopic dermatitis (eczema). Regeneron and Sanofi said about 2,500 prescriptions have been written for Dupixent since the drug's launch in late April, prompting analysts to raise their sales estimates for 2017.

Analysts at Canaccord Genuity are predicting US Dupixent sales of $118m in 2017; while Jefferies is forecasting $144m in 2017 total sales for the new therapy (up from a prior figure of $36m).

Despite Dupixent's strong start, the drug is not expected to overthrow Eylea as Regeneron's key revenue growth driver for several more years. However, sales of the treatment for age-related macular degeneration increased just 9% year-over-year to $854m, falling below first quarter consensus of $907m due to inventory reductions and higher price discounts, Jefferies analyst Biren Amin noted in a May 4 report.

Eylea is partnered with **Bayer AG**, but Regeneron books 100% of US revenues for the drug, which is approved for several ophthalmology indications. Meanwhile, only around 59% of Dupixent revenues are received by Regeneron.

If Dupixent is successfully approved in pediatric atopic dermatitis by around 2020, revenues for Regeneron's drug should accelerate substantially, analysts at Cannacord noted. In parallel, worldwide sales of Eylea are expected to steadily decline over the next decade as the drug loses patent protection.

Regeneron views Dupixent as a key product in its portfolio with several opportunities for expansion and within its May 4 earnings report the company reported positive results for Dupixent in a Phase II trial for inflammation of the esophagus associated with chronic allergies and immune conditions. It will present the full results of that trial at an upcoming medical conference.

CHALLENGING REGULATORY PATHWAYS

Regeneron president and chief scientific officer George D. Yancopoulos also highlighted Dupixent's potential as an allergy therapy on the back on the company's research into the drug as a treatment for eosinophilic esophagitis.

"It is believed that eosinophilic esophagitis can be a manifestation of food allergies, further supporting the rationale of exploring the efficacy of dupilumab in patients suffering from severe specific food allergies," he said during the company's earnings call. In the second half of 2017, Regeneron intends to initiate a Phase II study of dupilumab in food allergies.

Yancopoulos added that the positive data for dupilumab across four allergic or atopic conditions investigated to date – atopic dermatitis, asthma, nasal polyps and eosinophilic esophagitis – is consistent with the company's hypothesis that these allergic conditions reflect the same fundamental disease process triggered by over activity of the IL-4/IL-13 access. "Since dupilumab inhibits the key driver of this pathway in all these settings, we believe that it can represent a mechanism-based approach to treat the root cause of these allergic conditions rather than each individual indication on a separate basis," he said.

As a result, Yancopoulos is keen to discuss with regulators a new pathway for assessing its drug based on a mechanism-based approach to treatment.

The result of those discussions could impact Regeneron's clinical trial program for Dupixent in the future, though a change in regulatory procedure is a far-off expectation for the company. "We are very interested in discussing this type of mechanism-based approach for treating allergic or atopic disease with the regulatory authorities while we continue to pursue more conventional approval strategies," Yancopoulos said.

Dupixent will also be in two pediatric trials this year: for moderate-to-severe eczema in 12- to 17-year-olds and in uncontrolled persistent asthma in 6- to 11-year-olds.

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With Parion Deal Done, Shire CEO Looks To Next Bright Ophthalmic Innovation

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Future collaborations to build **Shire PLC** 's ophthalmology activities could in theory resemble that signed this week with US-based biotech **Parion Sciences Inc.**, whereby the Dublin-based, London-listed group acquired worldwide rights to a Phase II dry eye disease drug dubbed P-321.

Or, they could be struck with academia partners – provided they are innovative and meet unmet medical needs, the CEO of Shire said in an interview.

"Innovation comes in many shapes and forms and Shire is focused on rare and highly specialized conditions and we have an open-door policy – it doesn't need to be invented by us; we cast the net wide and seek out collaborations, it doesn't matter whether it's a commercial or academic entity," Flemming Ornskov told *Scrip*.

EYEING FURTHER OPPORTUNITIES

He was speaking May 2 as Shire released better-than-expected first-quarter results - and the day after announcing an agreement that gives Shire exclusive worldwide rights to develop and commercialize P-321, an investigational epithelial sodium channel (ENaC) inhibitor designed to promote tear volume on the eye surface as a treatment for dry eye disease in adults.

Orkskov, a Dane and a physician by training, came to Shire four years ago with deep experience in ophthalmology and quickly made that therapy area a priority for the company, now the world's biggest maker of drugs for rare diseases. His insight drew on prior experience as a member of the *Lucentis* (ranibizumab) team at **Novartis AG**, where he headed the ophthalmic operation, and the *Eylea* (aflibercept) team at **Bayer AG** , and from his tenure at **Bausch & Lomb Inc.**

Today, Shire's ophthalmology pipeline includes candidate SHP640 for viral/bacterial conjunctivitis, which has now moved into Phase III trials and top line data for which is expected in the second quarter of 2018. It also has preclinical candidates for autosomal dominant retinitis pigmentosa (SHP630) and glaucoma (SHP639). Another compound, SHP607, was discontinued in 2016 for retinopathy of prematurity following Phase II trial results in that condition and is now being carried forward for other complications of prematurity.

"When I came to Shire … I told the board that if we wanted to expand and diversify Shire's portfolio in highly specialized conditions, then I thought the ophthalmic area was an excellent fit. I also told the board it's going to take us some time and I thought that the best way of building a portfolio would be to go for molecules that were differentiated, have indications that will build that portfolio, and so we set out and did that."

XIIDRA NOW HAS 22% US MARKET SHARE

Its first acquisition in ophthalmology was *Xiidra* (lifitegrast), which was launched in at the beginning of August 2016 for dry eye disease. Since then Shire has continued to drive expansion of the US dry eye disease market, with Xiidra increasing its market share to 22% as of March 2017.

"The fact that we've grown the market from flat to over 20% since the introduction of Xiidra showed that there's a significant opportunity there, and although Xiidra is an excellent product, we think there's further opportunity for additional mechanisms of action and products that would supplement Xiidra," he told *Scrip*.

Parion Sciences' product seem to fit that bill. "I think it's a perfect fit. P-321 would be a first-in-class novel mechanism of action for dry eye. The mechanism of action is also developed for other indications," Ornskov said. Parion also has an alliance with **Vertex Pharmaceuticals Inc.** for cystic fibrosis.

PARION COLLABORATION TERMS

Under its deal with Parion, Shire will make an initial $20m upfront license payment with an additional $20m payment based on the achievement of a near term development milestone. Parion will be entitled to receive additional potential milestone payments, with a total potential deal value of up to $535m. Parion has the option to co-fund through additional stages of development in exchange for enhanced tiered double-digit royalties. Parion also has the option to co-fund commercialization activities and participate in the financial outcome from those activities.

Shire was speaking to *Scrip* while updating markets on the group's first-quarter results, which contained a better-than-expected 14% jump in earnings, helped by cost savings and higher drug sales. Still, the company kept its guidance for the full year unchanged despite that strong quarterly performance.

Ornskov said the integration of **Baxalta Inc.**, which aims to achieve at least $700m in cost savings by the third year, was ahead of schedule.

"We're still in the first full year after the close of the deal and we're clearly on track to produce the $300m we promised for the first year and on track for the $700m for the third full year. At this stage, we have no plans of upping that guidance - but we will continue to look for synergies where they are," he said.

2017 PRIORITIES

The CEO said investors are taking a relaxed view about Shire's debt level acquired through its recent M&A spree. "Debt paydown continued during the quarter and Shire remains on-track to achieve its year end debt target. We've said we aim to get it down to a level of between two to three times net debt to EBITDA by end of this year, and that's what we'll strive to do."

"Our priorities for the rest of 2017 remain unchanged: launching new products while driving commercial excellence, generating operational efficiencies, and advancing our pipeline of novel therapies. Also, we continue to prioritize paying down debt, and we are on track to achieve our full-year financial guidance."

He ruled out any further big M&A activity while the company focuses on those priorities.

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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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Selected clinical trial developments for the week 28 April – 4 May 2017

LEAD COMPANY/PARTNER	COMPOUND	INDICATION	COMMENTS
Phase III Suspended			
AEterna Zentaris Inc.	*Zoptrex* (zoptarelin doxorubicin)	uterine cancer	ZoptEC; missed primary endpoint of increased survival.
Novartis AG	*Reasanz* (serelaxin)	acute heart failure	RELAX-AHF-2; missed primary endpoints.
Phase III Results Published			
Roche	*MabThera* (rixuximab)	indolent non-Hodgkin's lymphoma	SABRINA; *The Lancet Haematology* online May 2.
Updated Phase III Results			
Merck KGAA	cladiribine tablets	multiple sclerosis	CLARITY; greater treatment effect in higher risk patients.
Foamix Pharmaceuticals Ltd.	FMX101 (minocycline) foam	acne	Mixed results, another Phase III trial planned.
Phase III Interim/Top-line Results			
H. Lundbeck AS/Otsuka Holdings Co. Ltd.	*Rexulti* (brexpiprazole)	agitation in Alzheimer's disease	Mixed efficacy results .
AMAG Pharmaceuticals Inc.	*Feraheme* (ferumoxytol)	iron-deficiency anemia	FIRM; Non-inferior to *Injectafer*, backs label expansion.
Camurus AB/Braeburn Pharmaceuticals Inc.	CAM2038 (weekly and monthly depot buprenorphine)	opioid use disorder	Positive long-term safety study.
Kala Pharmaceuticals Inc.	KPI-121 (loteprednol) in mucus penetrating particles	ocular inflammation and pain after cataract surgery	Effective and well tolerated.
Phase III Initiated			
AbbVie Inc.	*Rova-T* (rovalpituzumab tesirine)	small cell lung cancer	Compared with topotecan.
AstraZeneca PLC	*Imfinzi* (durvalumab) plus tremelimumab)	bladder cancer	STRONG; a safety study.
Daiichi Sankyo Co. Ltd.	*Savaysa* (edoxaban)	stroke prevention in atrial fibrillation	ENVISAGE; versus standard of care.
Ampio Pharmaceuticals Inc.	*Ampion* (human serum albumin fraction)	osteoarthritis, knee	A 12-week study.
Phase III Announced			
Janssen-Cilag International/ Genmab AS	*Darzalex* (daratumumab)	multiple myeloma, relapsed and refractory	APOLLO; plus pomalidomide and dexamethasone.
Soligenix Inc.	dusquetide (SGX942)	oral mucositis	IDR-OM-02; in head and neck cancer patients.
Phase II Suspended			
Roche	lebrikizumab	chronic obstructive pulmonary disease	VALETA; missed primary endpoint.

Source: Biomedtracker

Tymlos, Evenity Pricing: Should Generic Zoledronic Be Reference Point?

CATHY KELLY catherine.kelly@informa.com

The Institute for Clinical and Economic Review (ICER) concludes in a new draft report that data are insufficient to distinguish the effectiveness of three anabolic agents for osteoporosis – Radius Health Inc.'s recently-approved *Tymlos* (abaloparatide), Amgen Inc.'s pending Evenity(romosozumab) and Eli Lilly & Co.'s established *Forteo* (teriparatide) – from the older, generic bisphosphonate zoledronic acid.

"There is insufficient evidence to distinguish the anabolic agents from each other and from zoledronic acid for vertebral fractures," the report says. "The differences in fracture reduction are small … so the therapies may be comparable. The evidence is even less certain for non-vertebral fragility fractures and, in particular, hip fractures."

The conclusion raises the question of whether, for payers, the more costly anabolic agents (assuming Evenity will be priced on par with Tymlos and Forteo) are worth the extra expense versus zoledronic acid. Radius was approved April 28; Evenity is not yet approved, but has a July 19 user fee date; and Forteo has been on the market since 2002.

The annual wholesale acquisition cost for Forteo is $32,734.08. Radius has priced Tymlos below Forteo, with an annual WAC of $19,500, in an effort to take share from the older product. *(Also see "Radius Prices Osteoporosis 'Blockbuster' Tymlos To Compete, Grow Market" - Scrip, 1 May, 2017.)* By comparison, zoledronic acid has a WAC price of about $197 annually, ICER estimates.

ICER explained it selected zoledronic acid as the comparator to the anabolic agents, because "several osteoporosis guidelines recommend it for individuals at high risk for fracture and because multiple stakeholders recommended it as the most appropriate comparator." Comparing the agents to zoledronic acid "allowed us to evaluate the relative incremental benefits and harms of these agents when used first line in patients at high risk for fragility fractures."

Amgen questioned the validity of the comparison. "We disagree with ICER's approach, methodology and assumptions," a spokesperson said in an email. "The findings are based on a comparison to bisphosphonates, front-line agents used for chronic therapy in patients with very different clinical characteristics than patients who need short-term bone builder therapy."

The company added, "We are concerned that ICER's review does not recognize the unmet need for a new class of osteoporosis therapies in patients at high near-term risk of fractures, fails to recognize the appropriate place in therapy and value of short-term bone-builders, and that its short-term budgetary focus will be used to create access barriers to innovative medicines like Evenity."

The cost effectiveness review focused on postmenopausal women who needed treatment to prevent osteoporotic fractures, with a focus on high-risk individuals, and patients who had not received prior treatment for osteoporosis. However, Tymlos was approved and Evenity is under consideration only for patients at high risk for a fracture, who've had a previous fracture or who can't tolerate other osteoporosis treatments – not as front-line agents for all postmenopausal women. ICER looked at data from the pivotal randomized trials of the drugs, focusing primarily on fracture outcomes (vertebral, hip, wrist, non-vertebral) and potential harms.

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APPOINTMENTS

Metrion Bioscience Limited., a specialist ion channel CRO and drug discovery company, has promoted ***Andrew Southan*** to chief operating officer and has appointed James Beaumont head of business development. Having initially trained as a chemist, Beaumont brings more than 20 years of sales, business development and marketing experience within the biotech and pharma industry to the company. Southan joined Metrion in 2016 and has over 25 years' experience within the life sciences, along with 14 years managing CRO services.

Fortuna Fix Inc. has announced the launch of its scientific advisory board with ***Professor Michael Fehlings***, ***Father Kevin FitzGerald***, ***Dallas Hack*** and ***Professor James Giordano***. Fortuna is a biotech aspiring to be the first to eliminate the need for embryonic fetal stems cells by using direct reprogramming of autologous cells for the treatment of neurodegenerative diseases. Fehlings is vice president of research for the department of surgery, co-director of the spine program and a professor of neurosurgery at the University of Toronto. FitzGerald is a professor at Georgetown University, advisor to the Vatican on bioethics and the Dr. David Lauler chair of catholic health care ethics in the center for clinical bioethics at Georgetown University. Hack recently retired from the US military where he was director of the US army combat casualty care research program and chair of the joint program committee for combat casualty care. He was also the senior medical advisor to the principal assistant for research and technology, US army medical research and materiel command from 2014 to 2015. Giordano is professor in the departments of neurology and biochemistry, and chief of the neuroethics studies program at the Pellegrino center for clinical bioethics of Georgetown University medical center, Washington, DC.

Fumie Griego has joined the International **Federation of Pharmaceutical Manufacturers and Associations (IFPMA)** as assistant director general. Before this, Griego was head of global oncology policy and strategy, global government affairs & policy at Merck KGAA and vice president for international health policy at pharmaceutical research and manufacturers of America (PhRMA).

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