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Shadows Cast Over JAK Class Following Xeljanz Mortality Signal

EMILY HAYES emily.hayes@informa.com

The cardiovascular risks seen with a higher-than-approved dose of **Pfizer Inc.**'s Janus kinase (JAK) inhibitor *Xeljanz* in a long-term rheumatoid arthritis study required by the US FDA have cast a shadow over the drug's other indications and for the class overall.

Xeljanz (tofacitinib) has been approved by the FDA since 2012 at the dose of 5 mg twice daily for moderate-to-severe rheumatoid arthritis (RA) after inadequate response or intolerance to methotrexate. *(Also see "Oral Dosing May Not Be Enough To Win Speedy Adoption Of Pfizer's RA Pill Xeljanz" - Pink Sheet, 12 Nov, 2012.)*

An extended release formulation of tofacitinib – *Xeljanz XR* – was approved in 2016. *(Also see "PIPELINE WATCH – 10 Approvals, Two Breakthroughs And A Refusal To File Letter" - Scrip, 1 Mar, 2016.)* The drug's initial clearance came with a lot of safety baggage. A boxed warning notes risk for serious infections and labeling advised regular monitoring of lipid levels, because the drug is associated with an increase in cholesterol and therefore has a potential risk of cardiovascular (CV) safety events, notably pulmonary embolism (PE). *(Also see "Panel Backs Pfizer's Tofacitinib For RA, With Narrower Indication" - Pink Sheet, 9 May, 2012.)*

The FDA did not approve a higher 10 mg twice-daily dose and required the company to do a new clinical study post-approval to evaluate cardiovascular safety for both doses against an active comparator, as opposed to relying on post-marketing event reporting.

On Feb. 19, Pfizer reported some results from this trial – A3921133 — and the news was alarming. Unlike prior studies, this trial enrolled patients who were age 50 and up and had at least one cardiovascular risk factor, the company noted. The study tested Xeljanz on top of background methotrexate and included an arm with patients on a tumor necrosis factor inhibitor (TNFi). Results were monitored by an external Rheumatology Drug Safety Monitoring Board (DSMB)

"Based on the most recent analysis of the ongoing A3921133 study, the DSMB observed that patients treated with tofacitinib 10 mg twice daily had a statistically and clinically important difference in the occurrence of pulmonary embolism, compared with patients in this study who were treated with a TNFi. The DSMB also noted an increase in overall mortality in the 10 mg twice daily treatment group compared to the tofacitinib 5 mg twice daily and TNFi treatment arms," Pfizer said.

This safety signal has not been picked up in adverse event reporting systems, according to the company. The A3921133 trial is continuing and is still blinded, but the design has been modified so that participants will no longer be getting the higher dose.

"The DSMB stated it firmly believes that the risk-benefit profile of tofacitinib 5 mg twice daily in comparison to the TNFi group remains appropriately balanced in this study. We will work with the FDA and other regulatory agencies to review the full results upon comple-

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from the editor

eleanor.malone@informa.com

About six years ago, the first gene therapy was approved in Europe. Five years later it was withdrawn, and it was never filed in the US.

Glybera, for an ultra-rare hereditary disease that causes attacks of severe pancreatitis, was pulled from the market by its maker uniQure amid uncertainty over its effectiveness and resistance to its price tag of around €1m. Since its launch price caused uproar in 2015, much progress has been made in the field of gene therapy, even as Glybera itself crept off the stage in a puff of ignominy. But whereas in other industries the expansion of technology leads to costs coming down, the aspect of Glybera that once seemed so outrageous – its price – now seems less, not more, shocking.

Spark Therapeutics launched its gene therapy to treat a rare form of blindness at $850,000 last year. BioMarin's CEO reckons that should it win approval, the company's hemophilia A gene therapy could still represent good value at $2-3m – even though the disease is much more common than lipoprotein lipase deficiency, which Glybera treated (see p8). And Novartis has suggested that $4-5m would be a cost-effective price for its yet to be approved spinal muscular atrophy gene therapy Zolgensma.

While cost-effectiveness bodies – notably ICER in recent days – continue to challenge such prices, the focus of the wider debate has shifted from outraged resistance to more nuanced consideration of the parameters for measuring value and mechanisms for sharing risk and spreading payment.

And with more gene therapy makers triangulating around price, tolerance to the costs looks set to increase.

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LEADERSHIP
Phil Jarvis, Mike Ward, Karen Coleman

SUBSCRIPTIONS
Dan Simmons, Shinbo Hidenaga

ADVERTISING
Christopher Keeling

DESIGN SUPERVISOR
Gayle Rembold Furbert

DESIGN
Paul Wilkinson

EDITORIAL OFFICE
Christchurch Court
10-15 Newgate Street
London, EC1A 7AZ

CUSTOMER SERVICES
US Toll-Free: +1 888 670 8900
US Toll: +1 908 547 2200
UK & Europe: +44 (20) 337 73737
Australia: +61 2 8705 6907
Japan: +81 3 6273 4260
Email: clientservices@pharma.informa.com

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christopher.keeling@informa.com

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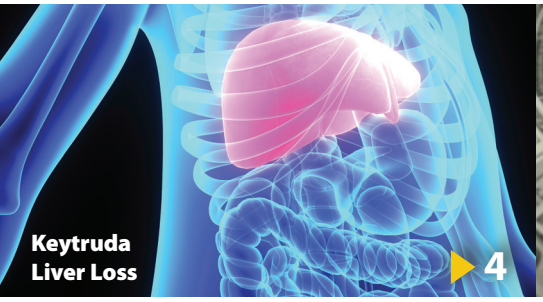

exclusive online content

Novo Nordisk CSO: Hemophilia Treatment 'Segmenting' Much Like In Diabetes

STEN STOVALL sten.stovall@informa.com

With earlier than expected FDA approval now in – and European passage expected soon for **Novo Nordisk AS**'s long-acting Factor VIII replacement therapy *Esperoct* (turoctocog alfa pegol), the Danish company has brought its R&D programs based on clotting factor deficiencies to a "successful result", says chief science officer Mads Krogsgaard Thomsen.

But Novo Nordisk will not be able to launch the product in the US before 2020, due to third-party intellectual property agreements. In the meantime, its efforts in treating the condition will turn next to studying its humanized mAb concizumab, Thomsen told *Scrip*.

Formerly known as N8-GP, Esperoct is an extended half-life Factor VIII for treatment of people with hemophilia A. The molecule is a glyco-PEGylated Factor VIII in which the B-domain, a region within the factor, is deleted. It has now been approved in the US for adults and children with hemophilia A as a routine prophylaxis to reduce the frequency of bleeding episodes, on-demand treatment and control of bleeding episodes and perioperative management of bleeding.

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tion of this study. Furthermore, the DSMB stated that other, ongoing studies of tofacitinib in RA, juvenile idiopathic arthritis, psoriatic arthritis, and ankylosing spondylitis should continue unchanged," the company added.

WHAT IT MAY MEAN FOR OTHER INDICATIONS

In addition to rheumatoid arthritis, Xeljanz is approved in the US for active psoriatic arthritis and moderate-to-severe ulcerative colitis (UC). In psoriatic arthritis, the drug is approved at the dose of 5 mg twice daily and the extended-release 11 mg formulation is also cleared. Dosing for ulcerative colitis is 10 mg twice-daily for an initial treatment period, followed by 5 mg or 10 mg twice daily. *(Also see "Pfizer's Xeljanz Approval In UC Includes Postmarket Study On Long-Term Effects" - Pink Sheet, 3 Jun, 2018.)*

Pfizer reported sales of $553m for the drug in the fourth quarter, up 35% from the same period in 2017, and $1.8bn for 2018, up by 32%. *(Also see "Pfizer: Time To Face The Lyrica Pain" - Scrip, 29 Jan, 2019.)* In its year-end earnings report, Pfizer highlighted the drug's performance prominently and noted that sales were "primarily driven by continued uptake in the rheumatoid arthritis indication and, to a lesser extent, from the launches of the psoriatic arthritis and ulcerative colitis."

Morgan Stanley's David Risinger said in a Feb. 19 note that the FDA "could add [a] more severe PE safety warning to the UC indication." He noted the current labeling "mentions four cases of PE observed in an UC long-term extension study."

POTENTIAL FALLOUT FOR OTHER JAK INHIBITORS

In a Feb. 20 note, SVB Leerink analyst Geoffrey Porges said that the change in enrollment in the A3921133 study "reinforces the potential liabilities of the JAK class ahead of the many catalysts for the class" this year.

"This outcome supports our cautious stance on the JAK inhibitor class, which to date has achieved narrow regulatory approvals with significant labeling limitations, and have correspondingly reported relatively disappointing sales to date," Porges said.

Eli Lilly & Co./Incyte Corp.'s *Olumiant* (baricitinib) is also approved for rheumatoid arthritis and has had its share of safety concerns. *(Also see "Lilly Prices Olumiant For JAK Battle, But Misses Approval For Higher Dose" - Scrip, 2 Jun, 2018.)* Due to the risk for thrombosis and other issues, FDA approved the drug in mid-2018 at a lower 2 mg daily dose, denying clearance of a higher 4 mg dose. *(Also see "Lilly's Baricitinib Wins US FDA Panel Thumbs Up For One Of Two Doses" - Pink Sheet, 23 Apr, 2018.)* The agency also cleared it only for patients after the failure of a TNF inhibitor, narrower labeling than Xeljanz has in this indication.

AbbVie Inc.'s JAK inhibitor upadacitinib is now under FDA review for rheumatoid arthritis, with an April user fee date. Two doses – 15 mg and 30 mg, both once daily – were tested but AbbVie only filed the lower dose, which appears to be associated with lower risk for thrombosis. *(Also see "AbbVie Soothes Safety Fears With More Upadacitinib RA Data" - Scrip, 7 Jun, 2018.)*

"AbbVie's decision to submit only the low dose of upadacitinib to the FDA appears appropriate," Porges noted, though he added that higher doses are being tested in other indications.

Morgan Stanley's Risinger said that he is confident of upadacitinib's approval, but can't predict how the agency will address the potential pulmonary embolism risk for JAK inhibitors in labeling.

"Importantly, the FDA is basing JAK labeling decisions on the long-term extension and open-label studies, which have collected tens of thousands of patient years of experience with results unknown to investors, at least until the public advisory committee for upadacitinib, which is expected in later Q2 or Q3," Porges added.

Gilead Sciences Inc.'s JAK inhibitor filgotinib is in Phase III, with data expected from two Phase III studies – FINCH 1 and FINCH 3 – this quarter. *(Also see "Rheumatoid Arthritis Data Position Filgotinib Ahead Of Competition, But It's Playing Catch-Up " - Scrip, 12 Sep, 2018.)*

Porges said Pfizer's news is "troubling" for upadacitinib and Gilead's filgotinib, and that now more than ever their potential rests on whether they can get differentiated labeling from the FDA.

The latest safety disclosure from Pfizer also decreases the likelihood that the JAK inhibitors will find a role in atopic dermatitis as planned, Porges said.

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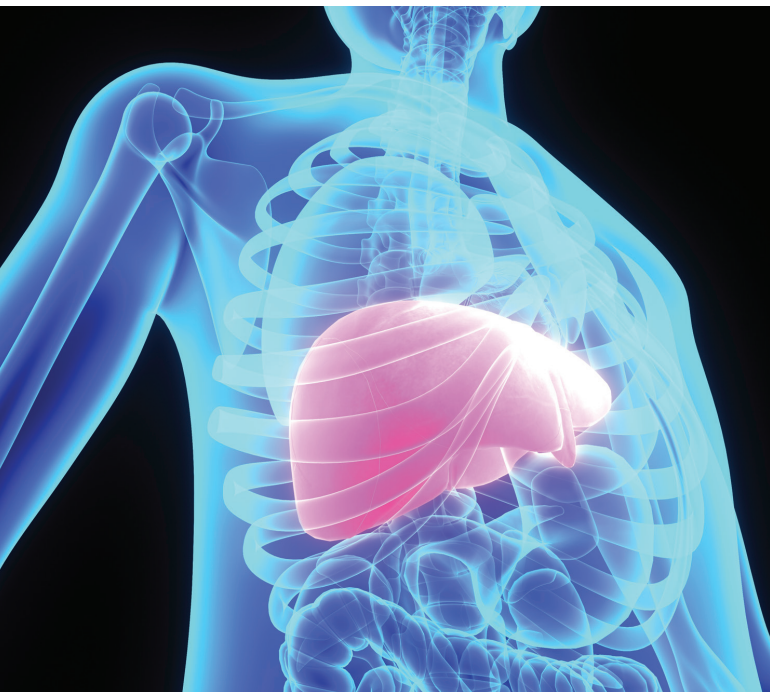
Merck's Keytruda Loss In Liver Cancer Could Be Gain For Rivals

EMILY HAYES emily.hayes@informa.com

The failure of **Merck & Co. Inc.**'s PD-1 inhibitor *Keytruda* in the KEYNOTE-240 confirmatory study in second-line hepatocellular cancer (HCC) stands in stark contrast to the drug's many successes and is likely to give competitors the upper hand in this tumor type. Keytruda (pembrolizumab) is an enormously successful drug, bringing in $2.2bn in the fourth quarter of last year alone. *(Also see "Keytruda/Inlyta Data Stoke Competition In Kidney Cancer " - Scrip, 12 Feb, 2019.)*

Its most recent clinical triumph came in the release of KEYNOTE-426 results at the American Society of Clinical Oncology Genitourinary Symposium on Feb. 16 in San Francisco, a study that some say establishes the combination with Pfizer's tyrosine kinase inhibitor *Inlyta* (axitinib) as the new standard of care in renal cell carcinoma. *(Also see "Merck's Keytruda Lead Widens Over Competing Checkpoint Inhibitors" - Scrip, 1 Feb, 2019.)*



Merck said that it had shared the results with the US FDA and declined to speculate on the agency's future actions on labeling for Keytruda in liver cancer.

In the trial, the combination demonstrated a 47% reduction in risk of death compared with the comparator – **Pfizer Inc.**'s *Sutent* (sunitinib).

On Feb. 19, however, came negative as well as positive additional news for the drug.

Merck announced after the market close that Keytruda in combination with best supportive care did not meet the co-primary endpoints of overall survival (OS) and progression-free survival (PFS) against a placebo/best supportive care comparator in the KEYNOTE-240 study, in 413 liver cancer patients previously treated with systemic therapy, though there were positive trends on this measure.

Also on Feb. 19, Merck announced that Keytruda picked up another US FDA approval for adjuvant treatment of melanoma with involvement of the lymph nodes, a development more in line with the PD-1 inhibitor's stellar performance.

This filing was supported by the KEYNOTE-054 study of 1,019 patients with high-risk Stage III melanoma, in which Keytruda demonstrated a significant reduction in disease recurrence or death compared with placebo. *(Also see "Keytruda Clears Low Hurdle In Stage III Melanoma" - Scrip, 9 Jan, 2018.)*

Bristol-Myers Squibb Co.'s competing PD-1 inhibitor *Opdivo* (nivolumab) was cleared in the adjuvant melanoma setting in December 2017. *(Also see "Pipeline Watch: Phase III Starts For BL-8040, Trigriluzole, MIN-101" - Scrip, 22 Dec, 2017.)*

PRIMARY ENDPOINTS MISSED

In the just-released KEYNOTE-240 liver cancer trial, Keytruda reduced the risk of death by 22%, with a p-value of 0.0238 and cut the risk of progression by 22% (p=0.0209). However, per the pre-specified statistical analyses for the study, these results were not statistically significant. The secondary endpoint of overall response rate (ORR) also was not considered to be significant, because the drug was not superior on the survival endpoints.

"It is intriguing from a statistical perspective that p-values of 0.0238 and 0.0209 were considered not significant. While we do not know the formal statistical plan, we speculate it could be based on a one-sided analysis that splits the alpha between the two endpoints (assuming an alpha of 0.02 for overall survival and 0.005 for PFS), resulting in near misses," William Blair analyst Andy Hsieh said in a Feb. 19 note.

Safety was consistent with previously reported studies.

Merck said that it had shared the results with the US FDA and declined to speculate on the agency's future actions on labeling for Keytruda in liver cancer.

ACCELERATED APPROVAL HANGS IN BALANCE

Keytruda received US accelerated approval on Nov. 9 for use in HCC patients previously treated with **Bayer AG**'s *Nexavar* (sorafenib). *(Also see "Keeping Track Of Approvals: Cancer, Cancer, And A Two-Week Cancer Review" - Pink Sheet, 18 Nov, 2018.)* The filing was supported by the Phase II KEYNOTE-224 study of 104 patients, in which Keytruda demonstrated an overall response rate of 17%.

The FDA has withdrawn accelerated approval 10 times, including the breast cancer indication for **Roche**'s vascular endothelial growth factor (VEGF) inhibitor *Avastin* (bevacizumab), due to failure to confirm results or to complete confirmatory studies.

Eli Lilly & Co.'s *Lartruvo* (olaratumab) failed in combination with doxorubicin in the Phase III ANNOUNCE study in advanced/metastatic soft tissue sarcoma in January, and the company said it will no longer market the drug, which originally received accelerated approval. *(Also see "Lartruvo Phase III Fail Rocks Lilly Oncology Plans" - Scrip, 21 Jan, 2019.)*

In the case of Keytruda's failure in liver cancer, Merck noted that while the study was not positive on the co-primary endpoints, "the results for overall survival, progression-free survival and objective response rate are generally consistent with findings from the Phase II study, KEYNOTE-224, which led to the accelerated approval of Keytruda for the treatment of patients with hepatocellular carcinoma who have been previously treated with sorafenib."

The Phase III KEYNOTE-394 study of Keytruda with best supportive care versus placebo and best supportive care in Asian patients with advanced HCC who previously were treated with systemic therapy is still ongoing.

ANALYST SEES EXELIXIS AS WELL POSITIONED

Keytruda's "rare mishap opens the door" for tyrosine kinase inhibitors (TKIs) in liver cancer and highlights the importance of TKIs in combination with immuno-oncology agents, William Blair's Hsieh said.

Exelixis Inc.'s TKI *Cabometyx* (cabozantinib) was approved for use as a monotherapy in second-line treatment after Bayer's

Nexavar in January. *(Also see "Keeping Track: FDA's Review Actions Carry On During Shutdown" - Pink Sheet, 20 Jan, 2019.)*

Liver cancer has been an active area for development and regulatory approvals in recent years. BMS's Opdivo and Bayer's *Stivarga* (regorafenib) have been approved for use as monotherapies after Nexavar since 2017.

The FDA also cleared **Eisai Co. Ltd.**'s *Lenvima* (lenvatinib), which is partnered with Merck & Co, for first-line unresectable HCC last August. *(Also see "First In 10 Years, But Lenvima's First-Line Liver Label Could Be Challenged Soon" - Scrip, 17 Aug, 2018.)*

While acknowledging the caveats of cross-trial comparisons, Hsieh also noted that the hazard ratio of 0.78 in the KEYNOTE-240 results is "numerically inferior" to hazard ratios reported in trials of VEGF-targeting agents in the HCC space – Cabometyx (0.76), Stivarga (0.63) and Lilly's *Cyramza* (ramucirumab) (0.71), the last of which is not yet approved for the indication.

"We admit it is difficult to predict regulatory actions taken by the FDA following a near miss; however, we believe checkpoint inhibitor use in HCC could be limited in the short term, at least until the Phase III CheckMate-459 trial results are announced (frontline HCC trial featuring Opdivo versus Nexavar)," Hsieh said.

"Similar to renal cell carcinoma, we believe the future treatment paradigm will likely incorporate the combination of VEGF inhibitors and immune checkpoint inhibitors," he added.

The analyst noted that Exelixis recently started a Phase III study of Cabometyx with Roche's PD-L1 inhibitor *Tecentriq* (atezolizumab) in first-line HCC.

"Therefore, we are encouraged by the various studies that could further establish Cabometyx as the tyrosine kinase inhibitor of choice in the combination study across various solid tumor settings."

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Intercept Retakes The Lead In NASH

JOSEPH HAAS joseph.haas@informa.com

A week after **Gilead Sciences Inc.** struck out with the first Phase III data readout in non-alcoholic steatohepatitis, **Intercept Pharmaceuticals Inc.** reclaimed its spot as the company most likely to reach the market first in NASH by achieving a fibrosis-reduction endpoint in its Phase III REGENERATE study.

The New York-based firm saw its stock price soar quickly, then moderate throughout the day Feb. 19, closing up 6% at $117.57 per share.

Intercept CEO Mark Pruzanski said in a same-day investor call that the company plans to file obeticholic acid (OCA) for approval in NASH in the both the US and EU during the second half of 2019; the drug already is approved under brand name *Ocaliva* for primary biliary cholangitis. *(Also see "'Clean Label' For Intercept's Ocaliva In PBC Bodes Well For NASH Claim" - Pink Sheet, 6 Jun, 2016.)*

Although OCA is the first drug to post successful Phase III data in NASH, the REGENERATE data were not an across-the-board win, as the drug met statistical significance for fibrosis reduction only in the larger of two doses tested and missed a co-primary endpoint for NASH resolution.

A farnesoid X receptor (FXR) agonist, OCA had been seen as the drug most likely to obtain the first regulatory approval for NASH, a multi-factorial liver disease characterized by buildup of liver fat resulting in inflammation and fibrosis and sometimes leading to cirrhosis, liver cancer and the need for liver transplantation.

Intercept became the presumed NASH leader on the basis of strong fibrosis-reduction data in the Phase II FLINT study, and has jockeyed with competitors, notably **Genfit SA**, Gilead and **Allergan PLC**, in recent years in the race to bring the first NASH therapy to market. *(Also see "Genfit May Be Gaining An Edge In NASH Race" -, 26 Oct, 2017.)*

Deep-pocketed Gilead was favored by some to overtake the field based on its resources and its previous success in hepatitis C, but its multi-drug, multi-mechanism approach to NASH has met with repeated setbacks, most recently the report that the Phase III STELLAR-4 study of its ASK-1 inhibitor selonsertib failed to hit a fibrosis reduction endpoint at 48 weeks. *(Also see "In NASH, Gilead Swung For The Fences And Struck Out Again" - Scrip, 12 Feb, 2019.)*

In top-line data from a planned interim analysis at 18 months of treatment, OCA dosed at 25 mg daily met REGENERATE's primary efficacy endpoint of at least one stage in fibrosis improvement from baseline as 23.1% of patients (n=308) met this standard at 18 months (p=0.002). A 312-patient group receiving 10 mg of study drug daily showed that 17.6% met this endpoint (p=0.446), but this was not statistically significant compared to the 11.9% of placebo patients meeting the endpoint.

The drug also missed significance on the second co-primary endpoint, NASH resolution with no worsening of fibrosis: 11.7% in the 25 mg arm met this measure (p=0.1268), compared to 11.2% in the 10 mg arm (p=0.1814) and 8% in the placebo arm.

MEETING EITHER ENDPOINT QUALIFIES AS SUCCESS

Pruzanski noted on the investor call that the REGENERATE protocols specified that meeting either of the co-primary endpoints would qualify as success. Intercept initially undertook the study with a protocol requiring that both endpoints be met, but adjusted in 2017 to success on either endpoint being sufficient. *(Also see "Intercept's Revised NASH Trial Improves Prospects" - Pink Sheet, 13 Feb, 2017.)* At the time, Pruzanski said the FDA agreed that "either endpoint, frankly, is clinically meaningful and reasonably likely to predict clinical benefit."

"Being able to demonstrate that [nearly] twice as many patients receiving 25 mg of OCA improved fibrosis without worsening of NASH as compared to placebo in this larger study is enormously important, given how strong a predictor fibrosis alone is of adverse outcomes," Pruzanski said Feb. 19. "Based on this and other OCA-mediated effects, we continue to strongly believe in OCA's potential to become a backbone therapy in patients with fibrosis due to NASH if approved."

Several analysts hailed the trial results, with Jefferies' Michael Yee writing Feb. 19 that "this is essentially a near best case scenario." He reiterated Pruzanski's commentary on the call that clinicians increasingly have come to regard fibrosis reduction as more important to clinical outcomes than NASH resolution. REGENERATE is slated to continue for several years to provide follow-up data detailing OCA's long-term health outcomes and safety performance in roughly 2,000 patients.

"The company importantly hit fibrosis and that is the widespread expert physician consensus on what is important and the only surrogate efficacy endpoint that would support an eventual and probable clinical outcomes benefit, which would be important for payers as fibrosis is much more important and relevant to experts than NASH resolution," Yee said.

Liana Moussatos of WedBush called the data "impressive" and reiterated her "outperform" rating for Intercept's stock in a Feb. 19 note. "We project potential achievement of blockbuster ($1bn) revenue in 2022 for OCA for NASH after a potential US launch in October 2020," she said. "In our view, OCA's overall clinical profile and likely first-to-market advantage makes it the preferred front-line treatment option for NASH."

Intercept CEO Mark Pruzanski said in a same-day investor call that the company plans to file obeticholic acid (OCA) for approval in NASH in the both the US and EU during the second half of 2019.

Less enthused, however, was Joseph Schwartz of SVB Leerink, who deemed the REGENERATE data "not a home run." He questioned the overall magnitude of clinical benefit seen in the study, as well as safety/tolerability issues that could "raise questions about the drug's commercial prospects."

As was true in earlier studies, OCA showed a propensity to cause pruritus in patients, including cases of itching severe enough to end treatment; it also increased patients' LDL cholesterol levels. Pruzanski said in both cases, the findings were as expected and noted that patients' LDL levels increased early in treatment and then fell to levels close to baseline readings over the course of treatment.

More worrisome from a commercial standpoint likely is the pruritus issue. In the trial, 19% of placebo patients, 28% receiving the 10 mg dose of OCA and 51%

of patients receiving 25 mg reported pruritus. Intercept said the large majority of these cases were mild-to-moderate, but while severe pruritus occurred in roughly 1% of the control arm and 10 mg study drug arms, for patients receiving the larger dose of OCA, the severe pruritus rate was 5%. Discontinuation rates were below 1% in the placebo and 10 mg groups, but 9% in the 25 mg arm. This is cause for concern since the higher dose appears to be the approvable one based on efficacy findings.

Pruzanski noted that the trial protocol mandated that treatment be stopped if the trial investigator assessed the patient as experiencing severe pruritus. "It isn't possible to know if some number of such patients would otherwise have stayed on treatment," he said. For the purpose of the study, patients who did not complete treatment were recorded as non-responders.

One possibility for mitigating this concern would be to discuss with regulators the possibility of an approval with labeling recommending dose titration from 10 mg to 25 mg. Pruzanski noted that this practice already is used with some success in PBC patients receiving OCA.

"As anticipated, the 10 mg OCA dose demonstrated tolerability similar to placebo," the exec pointed out. "While we didn't evaluate the potential benefit of dose titration, we know from our extensive experience in the PBC setting that this approach helps to improve tolerability in that indication. And given that the 10 mg dose does appear to be active in NASH patients, we'll consider discussing with FDA and other regulatory authorities the potential for dose titration in this population."

Given OCA's lack of efficacy in NASH resolution, Pruzanski conceded that the longer-term therapeutic approach in NASH is likely to include combination therapy. "This is a huge, heterogenous and complex disease process," he told the call. "And you know one shoe will not fit all – there's no one magic bullet. So, we will continue to innovate and explore other mechanisms."

Morningstar analyst Karen Andersen wrote Feb. 19 that REGENERATE likely positions OCA to be first to market with "solid market share expectations in the medium term." But, she added, "we believe side effects leave room for competing drugs to take share in the long term."

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BioMarin CEO Suggests Hemophilia Gene Therapy Pricing In $2m-$3m Range

JOSEPH HAAS joseph.haas@informa.com

The appropriate pricing of potentially curative gene therapies remains a contested question, but **BioMarin Pharmaceutical Inc.** seems ready to push a high boundary. Execs indicated during the firm's earnings call Feb. 21 that it is looking to price the Phase III hemophilia A candidate valoctocogene roxaparvovec (BMN 270 or val-rox) at $2m-$3m, which would still represent savings compared to frequent infusions of Factor VIII therapies.

The first gene therapy approved in the US, **Spark Therapeutics Inc.**'s *Luxturna* (voretigene neparvovec-rzyl) treatment for a rare inherited form of blindness, was expected to come with a $1m price tag, but the company launched with a price of $850,000. **Novartis AG** is laying the groundwork for its spinal muscular atrophy candidate *Zolgensma* (AVXS-101), with pricing expected to be as high as $2m-$5m, and is exploring alternative payment options such as an annuity model.

BioMarin executives said during the fourth quarter/full-year 2018 earnings call that the company plans to file val-rox for US FDA approval during the second half of 2019 and that it still is determining whether to pursue accelerated approval.

BioMarin has fully enrolled the Phase III GENEr8-1 study, which allows patients to select between two dosing regimens. It also expects to present three-year data with the higher dose and two-year data with the lower dose of val-rox from an ongoing Phase II trial in July at the International Society of Thrombosis and Hemostasis conference.

The FDA indicated in May that if companies developing long-lasting hemophilia gene therapies can demonstrate coagulation factor production in patients, accelerated approval might be feasible, with efficacy to be confirmed post-approval. The agency issued a guidance later in 2018 stating that demonstration of a Factor VIII level near normal measured with a validated assay could be sufficient for accelerated approval.

Novo Nordisk AS obtained FDA approval earlier this month for its extended half-life Factor VIII *Esperoct* (turoctocog alfa pegol), which is expected to offer longer-lasting therapy than current clotting factor products.

However, gene therapies such as BioMarin's and a hemophilia B candidate partnered between Spark and **Pfizer Inc.**, fidanacogene elaparvovec (SPK-9001), offer a next wave of even longer-lasting treatment. These could be dosed several years apart or even one

time, as opposed to frequently dosed clotting factor infusions, which can cost hundreds of thousands or millions of dollars annually for a single patient.

Spark is also developing a possible hemophilia A competitor to val-rox called SPK-8011, which is fully owned and early in Phase III investigation.

During BioMarin's earnings call, CEO Jean-Jacques Bienaime noted that the biotech probably could increase manufacturing capacity from the current ability to serve 4,000 patients and up to 5,000 patients with a "minimum investment" in its existing facility. Adding that BioMarin is also planning for a second production site, he said "I'm looking forward to the day when … we're running out of capacity at 5,000 patients per year at about $2m or $3m per patient."

Later, Bienaime tried to back away from those specific numbers, but argued that a very high price would be warranted if BioMarin can produce data showing four-to-five years of benefit from a single administration of val-rox, compared to current Factor VIII products dosed multiple times a week. "For adult patients, [this can cost] between $700,000 and $800,000 a year, so you multiply this by four or five, and that's the background of the kind of economics we're dealing with," he explained.

With a new drug approved last year and several late-stage candidates, BioMarin is predicting aggressive revenue growth. It brought in $1.49bn in 2018, up 14% year-over-year, although the $353m reported for the fourth quarter was down 1% due to some stocking issues with *Aldurazyme* (laronidase), its enzyme replacement therapy for mucopolysaccharidosis 1 (MPS1).

PALYNZIQ, PHASE III CANDIDATES DRIVE GROWTH PROSPECTS

For 2019, BioMarin is guiding to total revenues of between $1.68bn and $1.75bn, including solid growth for its phenylketonuria (PKU) therapy *Palynziq* (pegvaliase-pqpz), approved by the FDA in May. *(Also see "BioMarin Gets Second PKU Approval, Anticipates Slow Ramp-Up For Palynziq" - Scrip, 25 May, 2018.)* Palynziq brought in $12.2m in US sales in 2018, including $8.1m in the fourth quarter. BioMarin's guidance is for sales of $70m-$100m in 2019.

Chief Commercial Officer Jeffrey Ajer noted during the earnings call that Palynziq had 335 reimbursed US patients as of Feb. 15, including some who switched over from BioMarin's established PKU drug *Kuvan* (sapropterin).

"Of those, 123 transitioned from our clinical studies and 212 are formerly naive to Palynziq," Ajer said. "We're very pleased with the opportunity that Palynziq provides to expand our reach into a broader patient population. We are seeing high levels of interest and enthusiasm from adult patients that had formally been on or trialed Kuvan, but were not at the time of Palynziq referral, as well as patients naive to both Kuvan and Palynziq."

With two PKU therapies, BioMarin's initial view of the market is that the two products will be complementary, with patients whose disease is not controlled on Kuvan switching over to Palynziq. Kuvan posted sales of nearly $434m in 2018, up 6% from 2017.

Credit Suisse analyst Martin Auster predicted that Palynziq's uptake will climb steadily, as BioMarin has another 131 patients waiting to start therapy once reimbursement goes through. "Of the new [Palynziq] starts, 35% had previously been on Kuvan, which should help BioMarin's PKU franchise defend against generic erosion," he wrote. Kuvan faces patent expiration in the US in 2020.

Morningstar analyst Karen Andersen said she expects a slower pace of growth for BioMarin in 2019 than the previous year, but growth of 20% or greater starting in 2020, driven both by val-rox and the firm's Phase III achondroplasia candidate vosoritide. She predicts $2bn in potential peak sales for val-rox and $1bn in peak sales for vosoritide.

Morningstar assessed the M&A prospects for the largest publicly traded biopharmaceutical companies in a recent analysis and determined that acquiring BioMarin would make business sense for basically any large pharma due to its focus on gene therapies and rare diseases. *(Also see "BioMarin Is Carrying The Biggest Target On Its Back, Morningstar Says" - Scrip, 18 Feb, 2019.)* Sanofi might make the most rational fit for BioMarin, Morningstar analyst Damien Conover told *Scrip*.

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Cell Therapies Forge Ahead In Japan with Reimbursement, Approval Decisions

IAN HAYDOCK ian.haydock@informa.com

As expected following its approval in December, Japan has granted national insurance coverage to a pioneering, but somewhat controversial, cell therapy for the treatment of spinal cord injuries.

Meanwhile, **Novartis AG**'s *Kymriah* now looks set to become the first CAR-T therapy to be launched in the country following a positive approval recommendation in both its main indications.

The spinal cord injury therapy *Stemirac*, developed initially by university researchers and to be commercialized by major Japanese medical equipment company **Nipro Corp.**, will be included in the national health insurance (NHI) tariff on Feb. 26, the last hurdle before commercial launch under the scheme.

The product, which is based on the intravenous re-injection of expanded numbers of patients' own mesenchymal stem cells isolated from bone marrow, has been granted a reimbursed price of JPY14.96m ($135,400) per single, weight-dependent "dose" ranging from 50-200 million cells.

But in deciding the price, the Central Social Insurance Medical Council (Chuikyo), an advisory panel to the ministry of health, labour and welfare, predicted a peak of only 249 patients annually will be treated with the therapy, and maximum annual reimburse-

ment level sales of a modest JPY3.7bn (around $33.4m), despite the relatively high price per dose.

Stemirac received an expedited but conditional approval under Japan's "sakigake" scheme for breakthrough therapies, and will be subject to a comprehensive, all-patient postmarketing surveillance scheme to ensure its safety and efficacy in a real-world setting.

STEMIRAC PROMPTS CONCERNS

Despite these safeguards, the approval and planned launch have come under attack from some experts in the field, centering largely on concerns about the design of the small trial on which the regulatory clearance was based. This included just 13 patients and was a non-double-blinded design, while the detailed results have still not been published or opened up to peer review.

Commenting on the trial and the likelihood of pricing in a recent article in *Nature*, US expert Arnold Kriegstein, a stem cell researcher at the University of California, San Francisco, was quoted as saying: "I do not think it is morally justified to charge patients for an unproven therapy that has risks."

Despite the criticism, both the trial coordinators and Japan's regulators appear satisfied about the safety and efficacy of Stemirac, given the medical need in the roughly 5,000 cases of serious spinal cord injury annually in the country, and the safety net provided by the conditional approval process.

Given the lack of comparator products, the price was calculated through a cost-based assessment, a process designed to reflect the actual cost of production, which tends to be higher for cell-based therapies given their nature.

NHI SCHEME IS ACCEPTING

Despite the broad financing challenges facing its national health provision schemes amid a rapidly aging population, Japan's NHI program has so far been generous in awarding relatively high prices for cell and regenerative therapies. This is in line with a supportive policy and regulatory environment for the sector, where the government sees the country as potentially developing a world-leading position.

The first such products to be approved included another mesenchymal stem cell product, **JCR Pharmaceuticals Co. Ltd.**'s *Temcell* (licensed from **Mesoblast Ltd.**), which was given an NHI price of JPY868,680 in 2015, resulting in a total course cost of JPY20.8m, above that of Stemirac.

Under the NHI scheme - where patient drug co-payments are usually 30% - financial assistance is available for high-priced products above a certain total cost level to assessed patients, dependent on personal income, which effectively limits out-of-pocket payments.

But the system still bears the ultimate overall costs, something which seems to be coming to the fore again with the approvals of several cell and regenerative therapies.

PRICES PROMPTING SCRUTINY?

Japan has also just granted approval for the first clinical trial globally with an induced pluripotent stem cell-based therapy for spinal cord injury, signalling that more such products are on the way; nine cell/regenerative therapies have already been granted formal sakigake status. *(Also see "Another World-First As Japan OKs Spinal Injury Cell Therapy Trial" - Scrip, 19 Feb, 2019.)*

Given the ongoing developments in the field and the public outcry there was a few years ago around the high price to patients and the system of **Ono Pharmaceutical Co. Ltd./Bristol-Myers Squibb Co.**'s immuno-oncology drug *Opdivo* (nivolumab), there have been some recent early signs that the ministry may take a closer look at the "appropriate" pricing of regenerative medicines.

What shape these discussions may take is still not clear, however.

Opdivo's reimbursement price was initially cut in half in 2016, followed by further reductions, as the government sought to reduce costs stemming from increased use in its larger, secondary indication of non-small lung cancer, which followed on from malignant melanoma, a much smaller patient population.

KYMRIAH RECOMMENDATION

Meanwhile, Kymriah (tisagenlecleucel) received a positive recommendation from a ministry panel, for the twin indications of B-cell acute refractory/relapsed lymphoblastic leukemia in patients up to 25 years of age, and diffuse large B-cell lymphoma resistant to two or more earlier systemic therapies.

The CD19-directed, autologous T-cell immunotherapy, which is administered just once, was filed for approval in Japan in April 2018. It was cleared for both the same indications in the EU last August, and was the first CAR-T therapy to be approved in the US, in August 2017 for the leukemia use and then in May 2018 in the lymphoma setting.

Assuming smooth negotiations and formal final approval from the health ministry, the product could receive a reimbursement price in Japan in May, clearing the way for its commercial launch around the same time. But the likely high price, despite the need for only a single dose, could add further fuel to the fire around pricing discussions for cell and regenerative therapies.

Amid plans for the wider adoption of a formal cost-effectiveness analysis scheme, the research-based pharma industry has been calling for consideration of the wider overall economic benefits of new therapies, an approach that may become more pronounced with this new generation of products. *(Also see "Japan Firms Up Cost-Effectiveness Plans As Industry Concerns Linger" - Pink Sheet, 13 Feb, 2019.)*

Novartis is also awaiting the approval in Japan of its novel gene therapy AVXS-101, for spinal muscular atrophy.

ROMOSOZUMAB, OTHERS PRICED

Other products approved in January were also granted reimbursement prices by Chuikyo, effective Jan. 26. These include **Amgen Astellas BioPharma KK**'s anti-sclerostin antibody *Evenity* (romosozumab) for ostetoporosis, which was approved for the first time worldwide (see side bar) and will be reimbursed at JPY24,720 per 105mg/1.17mL vial.

The council is predicting peak sales of JPY32.9bn for the drug, while among other expected large sellers, **Daiichi Sankyo Co. Ltd.**'s *Tarlige* (mirogabalin mesylate) for peripheral neuropathic pain, is seen peaking at JPY25.9bn.

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From the editors of PharmAsia News.

Another World-First As Japan OKs Spinal Injury Cell Therapy Trial

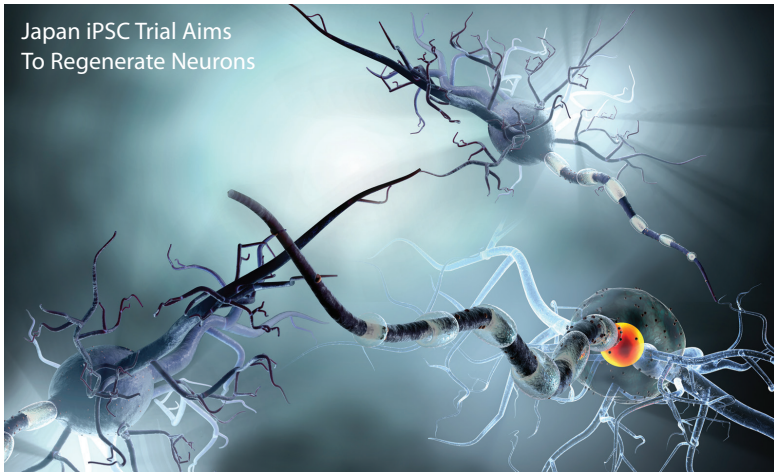
IAN HAYDOCK ian.haydock@informa.com

Despite controversy over a recent pioneering marketing approval of a cell-based therapy for spinal cord injury, Japan has taken another world-leading step in this arena as it looks to build a global leadership position.

An advisory panel to the country's ministry of health, labour and welfare has allowed for the first time globally a clinical study with another form of cell therapy in the same indication, giving the nod on Jan. 18 to a small trial using induced pluripotent stem cells (iPSCs).

The planned four-patient study, in adults with spinal cord injuries that have affected movement and neurological function, will be led by researchers at Keio University in Tokyo under Professor Hideyuki Okano, who said it will start within this year, possibly in the summer.

The iPSCs, sourced from an existing bank at Kyoto University's Center for iPS Cell Research and Application, will be directed to differentiate into neuronal cells, which will then be injected within two to four weeks of the original injury. The maximum "dose" will be two million cells, although this may be raised to 10 million as the study progresses and depending on initial response, and the researchers said they hope for initial findings within a year or so of the trial start. Earlier primate studies have already showed some positive impact on restoring motor function, the researchers said.


Japan iPSC Trial Aims To Regenerate Neurons

The participants will also receive standard immunosuppressant therapy to dampen potential rejection and other medication during the trial.

STEAMING AHEAD

The regulatory clearance marks the fifth time a clinical study with iPSCs (mostly university-led programs) has been allowed in Japan, where the government sees the country as a leader in the field following the 2012 Nobel Prize win by iPSC pioneer Shinya Yamanaka of Kyoto University.

The cells, which can be derived from skin and other organs, have the ability to be directed through genetic manipulation to transform into almost any cell type of cell, aiding functional organ regeneration.

A clear and highly supportive policy and regulatory framework for cell and regenerative therapies has been enacted, including revised and new dedicated regulations that came into force in late 2014, and the "sakigake" system of expedited reviews for pioneering therapies.

This has already led to the other iPSC study approvals, which have included small-scale clinical research on iPSC-derived retinal cells for age-related macular degeneration, neuronal regeneration in Parkinson's disease, and planned studies for corneal and cardiac tissue regeneration.

More controversially, this environment in late December resulted in the first marketing approval globally for a stem cell-based therapy in spinal cord injury, Nipro's Stemirac. The conditional clearance by the health ministry came after an expedited review. In that case, the therapy involved the cultivation and intravenous re-injection of mesenchymal stem cells derived from patients' own bone marrow, within several months of the initial injury.

But the allowance of broader commercial use - potentially under reimbursement by Japan's national health insurance system - generated scrutiny and some criticism from cell therapy experts around the world. The main concern was that it was granted on the basis of a 13-patient, non-double-blinded trial, no detailed results from which have yet been peer reviewed or published.

Researchers maintained in summary results that there was improved motor function in some cases, while risks, safety and efficacy in wider use will be closely followed up in a post-approval all-patient monitoring program under the conditional approval.

Nevertheless, one US researcher described the decision as "an unfortunate step away" from cumulative experience in valid clinical practice. *(Also see "Surprising SanBio/Sumitomo Stroke Stumble Slams Stocks " - Scrip, 31 Jan, 2019.)*

Whatever the risks, researchers and regulators in Japan apparently see these worth taking given the clear medical need in a highly debilitating and usually untreatable condition. Serious spinal cord injuries are estimated to affect around 5,000 people annually, and around 100,000 in total, in the country.

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Tanezumab Dances Through Back Pain Studies With "Acceptable" Safety Answers

JO SHORTHOUSE joanne.shorthouse@informa.com

Topline data released Feb. 19 from the TANGO trial of **Eli Lilly & Co.** and **Pfizer Inc.**'s partnered nerve growth factor (NGF) inhibitor tanezumab in patients with moderate-to-severe chronic lower back pain (CLBP) have shown a mixed bag of dosing efficacy, with answers for some long-questioned safety concerns.

The drug candidate hit its primary endpoint at 10 mg, the highest dose, demonstrating a statistically significant improvement in pain at 16 weeks compared with placebo. However, the 5 mg arm of the trial demonstrated a numerical improvement in pain, but critically did not reach statistical significance compared with placebo at the week 16 analysis.

Analysts from Credit Suisse were not put off by the lower-dose data, however, stating that "while only the higher dose of 10 mg hit the efficacy primary endpoint, we think the lower dose of 5 mg will still likely make it to market as well," because of positive results from two Phase III osteoarthritis (OA) pain studies which evaluated 16 and 24 weeks of treatment with tanezumab. *(Also see "Pfizer/Lilly's Tanezumab Reduces Osteoarthritis Pain, But Is It Safe?" - Scrip, 18 Jul, 2018.)*

Safety has been called into question in previous studies of anti-NGF agents, which are now attempting to claw back credibility after the FDA 2010 clinical hold on the entire class.

Questions dating back nine years have dogged tanezumab's long-term safety when the FDA shut down a 2010 trial of the drug after some patients experienced a worsening of their osteoarthritis that led to joint replacement. *(Also see "Pfizer forced to discontinue more trials for novel pain drug tanezumab" - Scrip, 20 Jul, 2010.)*

Eli Lilly and Pfizer have attempted to answer some safety matters with this study. Preliminary safety data show that tanezumab was generally well tolerated during the 56-week treatment period, and the study also included a 24-week safety follow-up period, making it an 80-week observation.

Rapidly progressive osteoarthritis (RPOA) was observed among 1.4% of patients receiving tanezumab and 0.1% of patients in the other treatment groups, and was mostly the less serious type 1 (joint narrowing). These ratios were "acceptable given the lack of other options for these patients and in the context of the US opioid epidemic and the need for non-opioid

TANGO Study Design

TANGO was a randomized, double-blind, placebo- and active-controlled, multicenter, parallel-group Phase III trial in subjects with moderate-to-severe CLBP.

The study evaluated the efficacy and safety of subcutaneous administration of tanezumab compared to placebo for a total of 16 weeks, and oral tramadol prolonged release (PR) for a total of 56 weeks.

A total of 1,832 patients were randomized to one of four treatment groups in a 2:2:2:3 ratio.

alternatives to treat chronic pain," despite the 10 mg dose according to Credit Suisse analysts.

Patients were not eligible to participate in the study if they had OA in the knee, hip or shoulder.

"Overall, the unmet need is very high in these patients, and the significant pain relief with the 10mg dose coupled with low incidence of RPOA with 56 weeks of tanezumab is encouraging," said BMO Capital Markets analyst Alex Afraei, who estimates that tanezumab could make peak sales of $1.8bn in the chronic low back pain indication.

"These were very difficult to treat patients that had inadequate response to three classes of pain drugs. These patients often cycle through different opioids for pain relief," he said.

While there were no observations of osteonecrosis, as has been seen in other tanezumab trials, subchondral insufficiency fracture and total joint replacement were observed in 0.4% and 0.7% of tanezumab-treated patients, respectively, and were not observed in the other treatment groups.

The companies expect that one additional Phase III study in OA pain, and one additional Phase III study in CLBP will read out in the first half of this year.

It is thought that 33 million Americans have CLBP, with about eight million of those complaining of moderate-to-severe symptoms.

PIPELINE

While tazenumab is the furthest along NGF-inhibitor in the pipeline for pain, it is not being developed in isolation.

In direct competition is **Regeneron Pharmaceuticals Inc.**'s fasinumab, developed with partner **Teva Pharmaceutical Industries Ltd.** for CLBP and OA. Studies for this therapy have been put on clinical hold in the CLBP setting by the FDA following a case of adjudicated arthropathy in a patient receiving high dose fasinumab who had advanced osteoarthritis at study entry. However, the NGF-inhibitor is still in Phase III trials for OA. Topline data from this study showed that all endpoints were met, but safety was still a concern. *(Also see "Regeneron And Teva's Fasinumab Crosses One Threshold; More Remain" - Scrip, 16 Aug, 2018.)*

Further down the development road for pain is **AstraZeneca PLC**'s Phase I product MEDI7352 for osteoarthritis pain. The study is expected to readout in June 2019.

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BioMarin Is Buyout Target, Morningstar Says

JOSEPH HAAS joseph.haas@informa.com

More merger and acquisition activity, including deals among large-cap biopharma companies, seems sensible and likely, according to a new analysis from Morningstar, which thinks **Pfizer Inc.** still is on the lookout for a potentially transformative deal despite recent comments to the contrary. **Merck & Co. Inc.** and **Johnson & Johnson** also are logical fits for a big deal, the report says, while **BioMarin Pharmaceutical Inc.** makes sense as a buyout target for just about all of the 19 largest publicly traded biopharmas.

In its new *Healthcare Observer* report, the financial firm concluded further industry consolidation appears likely because cash-rich companies need innovative new products and pipeline candidates, while a challenging reimbursement environment makes cutting-edge R&D work more financially risk for less-wealthy companies.

"Scale helps with both of these, as riskier research and development bets can be spread out with larger budgets," the report states. "Also, a large portfolio should help in negotiations with increasingly consolidated private payers in the United States. In addition to scale, we think there are strategic and cost-cutting benefits to [potential] Pfizer/**Bristol-Myers Squibb Co.** and Merck/**Eli Lilly & Co.** combinations. Bristol would give Pfizer full control of *Eliquis* (and likely cost-saving opportunities) as well as a much stronger immuno-oncology franchise, and Pfizer could support a deal post-**Celgene Corp.** Lilly would give Merck strong diversification away from *Keytruda*, and there is a fit between their oncology and diabetes portfolios."

In the aftermath of January's proposed Bristol/Celgene merger, opinions have varied on whether that deal – the third-largest in industry history if it goes through – augurs additional mega-merger activity in the biopharma space. *(Also see "Bristol/Celgene Made Perfect Sense, But Doesn't Promise Big M&A Year, EY Says" - Scrip, 8 Jan, 2019.)* Previously, industry observers, including Morningstar, had speculated that 2018 would yield major biopharma mergers, due in part to the benefits of US tax reform, but that surge didn't materialize beyond the **Takeda Pharmaceutical Co. Ltd./Shire PLC** merger. *(Also see "Why The M&A Boom Many Expected In 2018 Didn't Happen" - Scrip, 14 Dec, 2018.)*

Morningstar assessed the M&A fit among the 19 largest companies by market cap, identifying nine as potential acquirers and nine as potential take-outs (with some overlap – **AbbVie Inc.**, **Amgen Inc.** and **Gilead Sciences Inc.** appear on both lists). (*See chart overleaf.*) Of 78 potential combinations among these companies, the report classifies 32 possible acquisitions as "rational combinations."

BIOMARIN OFFERS DIVERSIFICATION, GROWTH, NO PATENT EXPIRY RISK

All of the nine potential acquirers are seen as good fits for a buyout of BioMarin, whose rare disease and gene therapy portfolios would likely prove beneficial to any. The report also predicts that

BioMarin will produce 19.3% top-line annual revenue growth from 2017 to 2022, higher than the consensus estimate of 15.6% over that time span.

Helpfully, BioMarin will face no revenue erosion due to patent expirations during that period, a characteristic shared among its peer companies only by **Biogen Inc.**, **Novo Nordisk AS** and **Regeneron Pharmaceuticals Inc.** Also, Morningstar predicts that BioMarin will derive 35% of its sales from current pipeline assets in 2022, greater than any of the other 18 biopharmas in the list. *(Also see "BioMarin Gets Second PKU Approval, Anticipates Slow Ramp-Up For Palynziq" - Scrip, 25 May, 2018.)* Only Biogen and Celgene also are expected to derive 20% or more of sales in 2022 from current R&D candidates.

So, while BioMarin's therapeutic focus and modality expertise both address a sweet spot for most of its large-cap competitors, Damien Conover, Morningstar's director, pharmaceuticals, thinks **Sanofi** holds the best rationale to purchase the Novato, Calif.-based firm. "Sanofi is also very focused on rare diseases and I think BioMarin could fold very nicely into Sanofi's strategy, sales force and pipeline execution," the analyst told *Scrip*. "If I had to pick out one company that'd be very likely to buy out BioMarin, I'd say Sanofi is at the top of the list, but I think a lot of the [large-cap companies] would like to buy BioMarin."

SEVERAL BIG TARGETS COULD FIT WITH PFIZER

For Pfizer, Morningstar sees solid acquisition targets in Amgen, due to its immunology, cardiology and oncology assets; Biogen, with its strength in neurology; Bristol, which would offer full control of Eliquis (apixaban) and synergy in oncology; and Regeneron, which would bolster both oncology and immunology. *(Also see "Pfizer On Reorganizing, M&A And Investing In Internal R&D " - Scrip, 1 Aug, 2018.)*

Conover does not give much credence to new CEO Albert Bourla's insistence that the New York pharma plans to grow organically, rather than through major deal-making. *(Also see "Pfizer: Time To Face The Lyrica Pain" - Scrip, 29 Jan, 2019.)*

"One thing I've always found throughout the years is leadership of pharmaceutical firms will say regarding major M&A,

Assessing Likely Biopharma M&A Fits

Key Acquirers \ Key Targets	AbbVie	Amgen	AstraZeneca	Biogen	BioMarin	Bristol	Gilead	Eli Lilly	Regeneron
AbbVie		too large, product overlap (TNF)	too large, product overlap (BTK, PARP)	ABBV's early-stage neuro pipeline fit	**rare disease and gene therapy platforms are broadly attractive**	too large post- CELG	too large, product overlap (HCV, JAK)	too large, product overlap (JAK)	oncology fit (adds PD1, bispecifics)
Amgen	too large, product overlap (TNF)		immunology partnered in oncology complementary	**AMGN/NVS immunology partnered in neuro, have interest**		too large post- CELG	immunology & CAR-T fit (but AMGN has BiTE focus)	too large, diabetes a poor fit for AMGN	product overlap (PCSK9, bispecifics)
Gilead	too large, product overlap (HCV, JAK)	too large	too large	tuck-in neurology arm		too large post- CELG		too large	oncology fit (adds PD1, bispecifics)
Johnson & Johnson	Imbruvica Partners, but product overlap	poor fit ex-immunology, product overlap (TNF)	oncology fit, but product overlap (BTK)	**tuck-in neurology arm**		**oncology/ immunology fit**	**HIV/oncology/ immunology fit**	product overlap (IL23, SGLT2)	oncology fit (adds PD1, bispecifics)
Merck	**oncology fit, boosts immunology**	AMGN oncology pipeline adds to Keytruda	poor fit, already have PD-1/L1	**tuck-in neurology arm**		PD-1 product overlap	CAR-T interest, but HIV overlap	oncology, diabetes fit	MRK has PD1, but could add combo drugs
Novartis	oncology and immunology fit	neurology partners, boosts oncology pipeline	oncology fit	product overlap in MS, SMA		too large post CELG, CAR-T overlap	product overlap (CAR-T)	product overlap in immunology (IL17, CGRP)	product overlap in ophthalmology
Pfizer	good oncology fit, but JAK overlap	good immunology, cardiology, oncology fit	PARP/PD-L1 overlap, prior failed bid	tuck-in neurology arm		post-CELG (Eliquis and oncology synergy)	adds NASH, product but JAK/HIV overlap	product overlap (JAK, CDK 4/6)	REGN adds to oncology, immunology
Roche	blood cancer product overlap	Roche already strong in bispecifics	PARP/blood cancer/asthma fit, but PD-L1 overlap	product overlap (neuro pipelines)		PD-1/L1 product overlap	unclear HIV/ HCV interest, pricey entry to CAR-T	oncology fit, but unclear diabetes interest	product overlap (ophthal, oncology, immunology)
Sanofi	too large	too large	too large	tuck-in neurology arm		too large post-CELG	too large	too large	established partner, adds Eylea

Rational combination **Less likely combination** **Very unlikely combination**

'we're going to continue to look for what makes the most sense,'" Conover said. "Generally speaking, they talk about these bolt-on acquisitions. That being said, there also has been massive consolidation over the last decade and a half, so I do think Pfizer is evaluating what is in the best interests of shareholders, which is in line with what they're talking about, but I think that also includes larger acquisitions. Over a long period of time, the next five years, I'd be pretty surprised if they didn't make a major acquisition."

The Morningstar report posits that Pfizer buying Bristol and Merck acquiring Lilly are two major deals that seem likeliest if a wave of industry consolidation occurs. It projects that each deal might occur around 2020, with a 30% premium to the acquired company's stock price. Pfizer might realize greater than $4bn in annual cost synergies by acquiring Bristol, the report says, while Merck could realize more than $3bn in annual synergies from absorbing Lilly.

Beyond cost-cutting, Bristol would offer significant immuno-oncology strength to Pfizer, while Lilly would balance out Merck's risk by reducing its reliance on *Keytruda* (pembrolizumab) to drive growth, Morningstar asserts.

The price tag to acquire Bristol might be a record-breaker M&A deal for biopharma, so the nascent Celgene merger probably increased the pharma's valuation above where most peers could afford to play. *(Also see "Bristol/Celgene A Record-Setting Merger, If It Happens" - Scrip, 3 Jan, 2019.)* Morningstar sees only Pfizer and J&J as the exceptions that could still afford such a deal. Bristol would add oncology and immunology strength for J&J, the report notes.

"There is some product overlap, but the main rationale for not acquiring Bristol now is it's just too large when you think about the debt and the equity component," Conover said. "I think it has priced out a few of the names that potentially would have been interested before the Celgene announcement. AbbVie, maybe Amgen, those two companies could have been a little bit more interested in Bristol prior to that announcement versus after."

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Bayer Bags Full Vitrakvi Rights As Lilly Signs Off Loxo Buy

KEVIN GROGAN kevin.grogan@informa.com

With **Eli Lilly & Co.** sealing the deal to acquire its partner **Loxo Oncology Inc.**, **Bayer AG** has moved swiftly to take full control of its tissue-agnostic drug *Vitrakvi* rather than share the rights to the closely watched cancer therapy with a fellow big pharma.

The German major first teamed up with Loxo back in November 2017 and a year later the FDA approved Vitrakvi (larotrectinib) for the treatment of both adults and children with solid tumors that have a neurotrophic receptor tyrosine kinase (NTRK) gene fusion. Examples of tumor types with an NTRK fusion that have been shown to respond to Vitrakvi, a tropomyosin receptor kinase inhibitor, include soft tissue sarcoma, salivary gland cancer, infantile fibrosarcoma, thyroid cancer and lung cancer.

However the picture became a little complicated at the beginning of this year when Lilly agreed to splash out $8bn to buy Loxo. That deal closed on Feb. 15 and Bayer wasted no time in exercising an option linked to a change of control at Loxo, to obtain the exclusive licensing rights in the US for Vitrakvi and BAY 2731954 (formerly LOXO-195), a follow-on TRK inhibitor being evaluated in a Phase I/II trial in patients who have acquired resistance to larotrectinib.

> "We have two compounds in our precision oncology portfolio and we are committed to expanding this portfolio by bringing forward highly differentiated and promising additional projects."

When the new arrangement takes effect, co-promotion in the US will end and instead of a sharing of commercial costs and profits on a 50/50 basis for the US market, Bayer will now pay Lilly royalties. Under the terms of the original deal inked with Loxo, in addition to a $400m upfront, the biotech was eligible to earn up to $450m in approval and first commercial sales milestones, with another $200m in milestones tied to approval and first sales of LOXO-195 in selected markets. *(Also see "Loxo's Tissue-Agnostic Approach Brings $400m Upfront From Bayer" - Scrip, 14 Nov, 2017.)* Robert LaCaze, head of the oncology strategic business unit at Bayer, said in a statement that the collaboration with Loxo "was an important milestone" and exercising the option on Vitrakvi and BAY 2731954 would "strengthen our leadership in this field." He added, "We have two compounds in our precision oncology portfolio and we are committed to expanding this portfolio by bringing forward highly differentiated and promising additional projects."

Bayer had previously forecast peak sales of Vitrakvi at around €750m and analysts are hoping that it will be one of the therapies that will help the German major overcome the looming patent cliff it will soon face on the anticoagulant *Xarelto* (rivaroxaban) and eye drug *Eylea* (aflibercept). Vitrakvi is the first treatment to receive a tumor-agnostic indication at

the time of initial FDA approval, but finding the patients who will benefit will be a challenge, given there are expected to be only around 2,500 to 3,000 new cases per year in the US and testing for the mutation is not yet common. *(Also see "Q4 Preview: How Will Bayer Survive Patent Cliff?" - Scrip, 13 Feb, 2019.)*

As for Lilly, it is interesting to note that when it announced the Loxo purchase on Jan. 7, the US major highlighted Vitrakvi and LOXO-195 but stressed that another compound, LOXO-292, was "the most substantial single component of the deal." Speaking about the Bayer partnership in January, Anne White, president of Lilly Oncology, said the company would be discussing the plans with the Leverkusen-headquartered group, but stressed that Lilly had a history of working "very successfully" on co-promotion alliances. However, it seems fair to assume Bayer had made its intentions clear concerning Vitrakvi, hence the emphasis on LOXO-292, a first-in-class oral rearranged during transfection (RET) inhibitor, which was wholly owned by Loxo. *(Also see "Lilly/Loxo Deal Came Together Quickly " - Scrip, 17 Jan, 2019.)*

As Lilly confirmed the closing of the acquisition of Loxo on Feb. 15, the company again highlighted the importance of LOXO-292, which has been granted breakthrough therapy designation by the FDA for three indications – RET fusion positive non-small cell lung cancer, RET fusion positive thyroid cancer and RET mutant medullary thyroid cancer – with a potential launch in 2020.

Lilly believes the therapy will not just be first but also best in class because of impressive overall response rates to date in the three aforementioned indications, and because of its good safety profile. Data from clinical trials so far indicate a 68% overall response rate in lung cancer and between 59% and 78% in thyroid cancer.

The other key Loxo drug is LOXO-305, an oral Bruton's tyrosine kinase (BTK) inhibitor, which is in Phase I/II trials and is designed to address acquired resistance to currently available BTK inhibitors, the most notable example being **AbbVie Inc.**'s blood cancer blockbuster *Imbruvica* (ibrutinib).

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MPM Raises $400m To Build Early-Stage Biotechs

KEVIN GROGAN kevin.grogan@informa.com

MPM Capital, the US-based life-sciences venture capital firm, has set up its seventh fund and raised $400m to invest in early-stage biotechs.

The focus of the fund, called BioVentures 2018, will be to tap into "disruptive scientific developments across multiple therapeutic areas," the firm said including oncology, immunology and neuroscience "as well as emerging modalities of cell, gene and nucleic acid therapies." In an interview with *Scrip*, Ansbert Gadicke, MPM co-founder and managing director, noted that it was not a particularly difficult financing round, with both existing backers and "a group of high quality new investors" participating. It took "only a very small number of trips to do and it mostly happened by phone so it was a good experience to raise the funds."

As well as BV2018, MPM invests across two other vehicles – an oncology-only crossover fund and another cancer-focused investment initiative with the Dana-Farber Cancer Institute. Gadicke, co-founder and managing director, said that the opportunity to drive innovation in drug development "is more attainable than ever before [and] we believe this is particularly true in oncology." MPM has 29 portfolio investments in the latter therapeutic space and approximately $1bn of capital dedicated to developing novel cancer therapies.

Gadicke said that in terms of the research coming out of academia, oncology "is still the largest target from a scientific quality standpoint and is far ahead of neuroscience. Having said that, we really love to invest in neuroscience; we are following it closely and hopefully over the next few years, there will be more and more breakthrough science that will be worth investing in."

MPM invests in about five start-ups per year and commits funding for around four years and in the main, it get involved in businesses from the ground, Gadicke noted. "We are looking for technologies and projects out of academia that have the potential to offer a big difference over existing therapies in some really important indications; in addition, typically they need to have good intellectual property and good preclinical data. We don't really need anything else because we build companies from scratch. We typically populate them, to start with, with our own executive partners and do all the work that entrepreneurs would do."

A couple of examples of companies founded and led by MPM include **Harpoon Therapeutics Inc.** and **TCR2 Therapeutics Inc.**, both of which completed initial public offerings this month. South San Francisco-based Harpoon, which is developing a novel class of T-cell engagers called TriTACs, raised $76m while TCR2, headquartered in Cambridge, Massachusetts, speared $75m to help develop its next generation of novel T-cell receptor therapies.

Gadicke noted that the technologies at both Harpoon and TCR2 are based on the research of Patrick Baeuerle, an executive partner at investment firm MPM and "the pioneer of T-cell engagement." The latter helped bring the first bispecific antibody to the market, **Amgen Inc.**'s *Blincyto* (blinatumomab).

Other success stories for MPM are the immuno-oncology firm **Potenza Therapeutics Inc.**, which has just been acquired by **Astellas Pharma Inc.** for up to $405m. The Japanese firm also bought another MPM company, the mitochondrial drug developer **Mitobridge Inc.** at the beginning of 2018 for up to $450m. *(Also see "Astellas Exercises Option To Acquire Potenza, For Up To $405m" - Scrip, 14 Dec, 2018.)*

Gadicke told *Scrip* that while the arrival of innovative IO treatments in the last few years had improved options for around 20% of cancer patients, he was expecting to see an acceleration in the pace of therapies being developed that will help the other 80% of patients. As for neuroscience, it is "several years behind oncology as the understanding of the mechanisms of disease is far earlier and that wave will come later."

He added,"Over the last five years, we have probably seen 10 times more scientifically sound opportunities for product development than the five years prior and I believe that over the next five years we will again see an acceleration of opportunities."

As to where those opportunities will be found, Gadicke said that while academic innovation was similar on both sides of the Atlantic, "what is easier in the US is building companies and particularly if you look at a location like Boston, you can build a successful biotech company there and do everything by walking or taking the T," referring to the city's subway system. He added that in Massachusetts, "you have the top universities, the top hospitals, most of the large pharmaceutical companies are there with research centers, you have top venture funds and top public investors, you really have an ecosystem within walking distance."

He went on to say that setting up a company in that environment was much easier "and that's why we have built the majority of our companies in Boston and the San Francisco Bay Area. That doesn't mean that the science isn't as good in Europe," Gadicke stressed, pointing out that partner Baeuerle spends half of his time in Europe scouting for technologies.

The VC world is a competitive one but Gadicke believes that MPM's record to date puts the firm ahead of its rivals. Since its first fund in 1997, MPM has raised $3.9bn of capital and its portfolio can collectively boast 49 FDA-approved drugs, with over 100 IPOs and acquisitions having been realized.

"Some of the products that have come from the companies have become incredibly large and important products," he said, one of them being **Gilead Sciences Inc.**'s hepatitis C blockbuster *Sovaldi* (sofosbuvir); MPM built **Pharmasset Inc.** which Gilead bought in 2011 for $11bn. "We are not just looking for sexy technologies but we're really building companies that are successful in bringing important products to patients," and many more of them than MPM's competitors have been able to achieve, Gadicke concluded.

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Shire Solid But Hemophilia Challenges Looming?

IAN HAYDOCK ian.haydock@informa.com

In the last set of stand-alone annual figures ahead of the completion of its acquisition by **Takeda Pharmaceutical Co. Ltd.** in early January, **Shire PLC** logged 4% growth in global product sales to $4.6bn, driven mainly by new products and neuroscience, although there were some wobbles in the hemophilia franchise, which was affected by prices and competition.

On the plus side, major approvals during the year included *Takhzyro* (lanadelumab-flyo), a first-in-class antibody to prevent hereditary angioedema (HAE), in the US, Canada and Europe, and the US clearance of *Motegrity* (prucalopride), a serotonin-4 receptor agonist for adult chronic idiopathic constipation.

Takeda, which reported the Shire figures, noted Takhzyro was off to a strong start in the US, where sales were $11m in Q4, "with patients coming from both prophylaxis and acute therapies" and "meaningful commercial demand" resulting in large destocking.

But Shire's total sales in the HAE space fell by 5.4% to $1.35bn in the 12 months to Dec. 31, affected by lower demand for older therapy *Cinryze* (C1 esterase inhibitor), which was hit by destocking and competition; Q4 sales of the drug fell to $45.1m.

Shire's top product overall in the year remained *Vyvanse* (lisdexamfetamine dimesylate) for attention-deficit hyperactivity disorder, which saw 11% growth to $2.40bn, helped by net prices and higher demand, and offsetting rising competition for *Adderall XR* (amphetamine/dextroamphetamine).

HEMOPHILIA CHALLENGES?

Overall hemophilia sales for the year were flat at $2.99bn amid lower prices outside the US and destocking and forex effects, along with a fall in sales of older inhibitor therapies. Deutsche Bank analyst Joseph Cairns said in a Feb. 11 note issued ahead of the results that he sees a generally "tougher outlook" for Takeda/Shire's hemophilia business due to the stronger than expected growth of **Chugai Pharmaceutical Co. Ltd.**/**Roche**'s bispecific antibody *Hemlibra* (emicizumab-kxwh). "As our base case for hemophilia sales, for the period between 2017 and 2022, we now forecast a 40% decline for FVIII therapies (vs Shire guidance -30%), and a 56% decline in bypass therapies (vs Shire guidance -50%)," the analyst said.

Chugai said recently that it views Hemlibra as one of its core mid-term growth drivers globally, helping to offset expected generic challenges to some other key oncology products in Japan.

Shire's operating income from continuing operations was 32% higher at $3.2bn, helped by completion of the $2.4bn sale of oncology operations to **Servier SA** in August, while operating cash flow for the year hit $4.6bn (+8%), which had de-leveraged debt to 2.1x of non-GAAP EBITDA (earnings before interest, taxes, depreciation and amortization) by December.

Takeda has been putting emphasis on this indicator given its large borrowing as part of the Shire deal, and has stressed multiple times that it intends to reduce its own net debt associated with the transaction - currently around $48bn - to 2x adjusted EBITDA within three to five years.

Shire's net income slid by 45% to $2.3bn due to what Takeda said was the effect of higher US tax reform benefits in 2017, which led to $300m in additional tax payments in 2018.

In other developments, Shire's new US plasma manufacturing facility in Covington, Georgia received FDA approval to manufacture *Gammagard Liquid* (immune globulin infusion), and is expected to expand capacity by around 30% once fully operational, helping to sustain anticipated growth in this sector.

Helped by planned divestments by Takeda, Deutsche Bank predicted "by mid-year, strong cash generation of the combined business should be apparent, and investor comfort with the deleveraging plan should increase." The first joint results and guidance for the combined company will be released in mid-May at the time of Takeda's figures for the fiscal year ended March 31.

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IQVIA Could Be CRO Bellwether As Tech Offering Outperforms Expectations

JO SHORTHOUSE joanne.shorthouse@informa.com

Three years on from the Quintiles and IMS merger, which combined data with clinical research skills to create the largest tech-driven CRO in the industry, and **IQVIA** is now starting to stretch its legs in technology, impressing analysts with its latest results and potential future revenue streams.

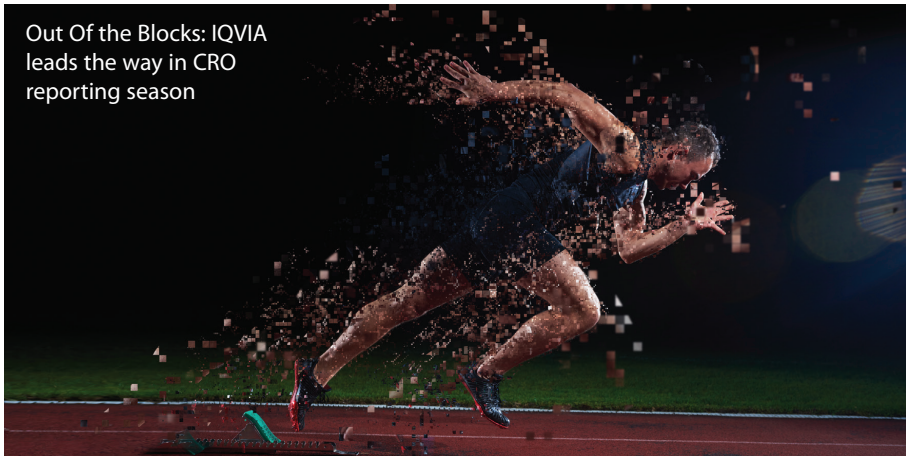
While the markets had focused on IQVIA's clinical research offering (which made $1.4bn in Q4), the value of its data and technology potential has been somewhat sidelined, but with its technology & analytics solutions (TAS) division generating $1.2bn in Q4, it cannot be underestimated.

IQVIA management suggested that TAS sales momentum would likely continue with 100 pending contract wins for its orchestrated customer engagement (OCE) platform, which connects sales, marketing, medical and other functions, and currently has around 30,000 users. The company is also rolling out an integrated suite of clinical technology applications this year, which could help extend the better growth into the next two years.

"In OCE, IQVIA has achieved something that has proven very difficult for software companies to do – acquire multiple pieces of software and stitch them together into a cohesive solution suite that customers will buy," said Jefferies' David Windley in a recent research note.

While a lot of IQVIA's growth in this division has come from smaller customers, it has won contracts from **Roche** and **Novo Nordisk AS**, with the Roche contract thought to be worth up to $100m.

SMART trials, which integrate data from IMS' database into clinical studies, now represent around one third of all trials ran by IQVIA, with management stating that there was an opportunity to double this number over time. Large pharma has been embracing this approach, and now represents an increasing proportion of SMART trial bookings, from less than 20% two years ago to around 60% in the quarter. John Kreger, equity analyst at William Blair called the financial results "impressive, with better-than-expected revenues in two out of three segments".



Out Of the Blocks: IQVIA leads the way in CRO reporting season

IQVIA Q4 Numbers

Q4 revenue: $2.7bn,
8.1% growth from Q4 2017

FY2018 revenue: $10.4bn,
6.8% growth from FY2017

Full year 2018 net new business growth: 28.9%

Full year 2019 revenue guidance: $10.9bn to $11.1bn

AN ENCOURAGING START

"The results and management commentary from IQVIA are certainly encouraging signs for broader demand trends," said Kreger in an interview with *Scrip*, stating that results from IQVIA are "a good indicator for later-stage demand."

The strong biotech funding environment is still having an impact on the CRO industry's workload, evidenced by IQVIA's booking acceleration throughout 2018 now giving it the highest CRO book-to-bill ratio last year.

"Capital in-flows for the biotechnology industry are becoming more important – perhaps most important," said Kreger. "Conversely, the amount of M&A among large pharma is arguably becoming a less important negative driver of the industry as the source of innovation continues to shift from larger pharma to smaller biotech."

Beyond the biotech boom, key pharma drivers on the CRO industry will continue in the same vein as the last decade; overall R&D spending growth, overall growth (or lack of growth) in the number of drug candidates being tested in clinical trials, and the portion of that work that is being outsourced.

In its annual CRO survey, William Blair asked pharmaceutical clients how the number of active clinical projects will change this year, 71% answered that they would be increased, which is the third highest percentage since 2011.

"Interestingly," said Kreger, "while there is a lot of commentary out of Washington DC about taking steps to lower drug prices, we have not yet seen this uncertainty impact R&D activity levels." In its CRO survey, William Blair found that responses from pharma generally indicated that their R&D spending plans would stay the same even in the case of a lower drug price environment.

The investment community will be looking with interest at results from the other main contract research organizations; **ICON PLC**, **Medpace Inc.**, **Syneos Health** and **PRA Health Sciences Inc.**

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AZ China Growth Pops Again But Clouds Loom

BRIAN YANG brian.yang@informa.com

A strategic bet on oncology and a focused strategy in emerging markets, especially China, have paid off for **AstraZeneca PLC**.

The UK-based company's fourth quarter showed growth in China was particularly strong, driven by new drugs to treat cancer. The overall growth of 22% for the quarter and 28% to $3.8bn for the 2018 full year at constant currency rates put it among the leaders among pharma multinationals in China.

The eye-popping growth was driven by the oncology business, up by 44% to $810m in the year, with *Tagrisso* (osimertinib) the top growth driver. The EGFR inhibitor was launched locally in 2017 for second-line non-small cell lung cancer after chemotherapy for patients with the TM790 gene mutation, and a Chinese regulatory decision on first-line use in NSCLC is expected in the 2019 first half, noted the company. *(Also see "Tagrisso Climbs Close To Top Of AstraZeneca Sales Tree" - Scrip, 14 Feb, 2019.)*

Another new cancer treatment, *Lynparza* (olaparib), had an "encouraging" launch in China for ovarian cancer, where it was the first PARP inhibitor to be launched. Overall emerging market sales for the drug were $51m in the year.

Oncology aside, the company's respiratory and cardiovascular business continued to grow well in China, its largest emerging market. *Symbicort* (budesonide and formoterol), which declined in the US by 22% due to price erosion, by contrast grew by 24% in China, reflecting AZ's large investment in respiratory treatment infrastructure including inhalation centers in the country. *Pulmicort* (budesonide) also grew by 17% to $795m in the year, becoming the company's second-largest selling product in China.

The UK firm hopes new drug launches will be able to make up some of the impact in China, where two new therapies gained the green light recently.

Cardiovascular and diabetes products were the third driver in this market, propelled by *Brilinta* (ticagrelor), up by 48%, and *Forxiga* (dapagliflozin), which rose 52%.

PRICING PRESSURE AND BIDDING WAR

Despite the strong showing, AZ expects growth to taper off in China, where a combination of price negotiations (and often reductions) in exchange for inclusion in reimbursement schemes, and a massive new centralized bidding process, will bring more pressure to bear on prices.

Tagrisso, for one, has already been included in China's National Reimbursement Drug List, but this was achieved only with price concessions. During the quarterly earnings call, corporate management acknowledged that inventory price adjustment had partly offset the strong momentum.

Also, among the company's large-selling cardiovasculars, *Crestor* (rosuvastatin) faces a headwind under China's new "4+7" centralized bidding mechanism for major cities, as the cholesterol-lowering drug was not selected in the winning round of bids.

The scheme aims to cut prices further by combining hospital procurement for commonly prescribed drugs in four mega-cities and seven regional hub cities, which account for the lion's share of total drug purchases by volume. The initiative is expected to put a further dent into popular medicines already under pressure from generic competition.

LUYE DEAL IMPACT

Meanwhile, AstraZeneca last year divested commercial rights to *Seroquel* (quetiapine) in the UK, China and other international markets to China's **Luye Pharma Group Ltd.** for $538m. *(Also see "Deal Watch: Genentech Gets Down In The Dirt With Lodo Therapeutics" - Scrip, 11 May, 2018.)*

The UK firm hopes new drug launches will be able to make up some of the impact in China, where two new therapies gained the green light recently. One is roxadustat, developed by **FibroGen Inc.** for anemia in dialysis patients, the first such approval in the world. *(Also see "First Approval For AZ's Roxadustat With China Green Light " - Scrip, 18 Dec, 2018.)* The other is *Linzess* (linaclotide) for irritable bowel syndrome.

PENDING APPROVALS

Pending approvals for the firm include *Imfinzi* (durvalumab) for unresectable Stage III NSCLC, although this will enter an already crowded arena. Four immuno-oncology agents are already approved in China and the AZ drug will become the fifth PD-1/PD-L1 inhibitor to be launched in the country.

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From the editors of PharmAsia News.

Sanofi Releases Annual Drug Price Report Ahead Of Senate Hearing

MANDY JACKSON mandy.jackson@informausa.com

Sanofi released its annual Pricing Principles Report on Feb. 21 showing that the average US list price increase across its 76-drug portfolio in 2018 was 4.6%, though net prices decreased 8% after $11.8bn in rebates given to payers.

Those numbers reinforce big pharma commentary during recent earnings calls that list price increases were offset by rebates promised to pharmacy benefit managers (PBMs) and other payers to guarantee inclusion on government and private health plans' drug formularies. It's probably no coincidence that Sanofi's report also comes just days before CEO Olivier Brandicourt will testify with six other biopharma company heads in front of the Senate Finance Committee on Feb. 26.

Sanofi raised the list prices on less than half of its drugs in 2018 – 35 out of its 76 commercial products. However, the company noted that 55% of its gross from drug sales was rebated to payers, including $4.5bn in mandatory rebates to government payers and $7.3bn for private payers.

All list price increases were in line with the pricing pledge Sanofi made in May 2017, which was based on three principles: there would be a clear rationale for all pricing decisions, price hikes would be no more than the projected growth rate for the US National Health Expenditure (NHE) published annually by the Centers for Medicare & Medicaid Services (CMS), and Sanofi would be transparent about its pricing practices, including when prices are raised more than projected NHE growth. *(Also see "Sanofi's Drug Pricing Pledge Ties Increases To National Health Expenditure" - Pink Sheet, 9 May, 2017.)*

The projected NHE increase in February 2018 was 5.3%, so Sanofi's 4.6% average list price increase in 2018 fell below that level. However, it's also the highest list price hike of the past three years, compared with 1.6% on average in 2017 when net prices fell 8.4%. The company's list prices increased 4% in 2016, though net prices fell 2.1% that year.

It's worth noting, however, that Sanofi's pledge to keep price increases below the NHE makes the hikes lower than the limits set by some of its peers that have pledged to keep increases below 10%. *(Also see "Who's Promised What: A Guide To Pharma Drug Pricing Pledges" - Scrip, 23 Jul, 2018.)*

In terms of its insulins, Sanofi provided a little more context to show the impact of rebates to payers on list price increases. While the average list price of its insulins rose 126% between 2012 and 2018, net prices fell 25%, which may or may not be illuminating to Senators attending next week's Finance Committee hearing who have constituents complaining about the rising out-of-pocket costs for their diabetes medicines.

SHARING THE BLAME FOR HIGH COSTS

While the industry has previously relied on a strategy of pinning much of the blame for high consumer drug costs on payers and other middlemen, Sanofi takes on some of the burden in its report – which could signal the approach Brandicourt will take at the Senate hearing. *(Also see "Big Pharma CEOs Get Ready To Testify: Preparing For A No-Win Situation" - Pink Sheet, 13 Feb, 2019.)*

"While many factors, including decisions affecting patient out-of-pocket spending and insurance coverage, are often controlled by other health care players, we recognize that there are actions we can take to help improve access for patients and affordability for the system as a whole," the report states. "For our part, we recognize that we must price our medicines transparently and according to their value, while contributing to broader solutions that improve patient outcomes and the sustainability of the US health care system."

Brandicourt, as the sole representative from the industry's three big insulin makers, is likely to take some of the toughest questions at that hearing given the growing outrage over insulin costs. That may be why Sanofi's drug pricing report gives insulin special attention.

The company explained the pricing rationale for three new products, including *Admelog* (insulin lispro), which launched in April at what Sanofi says is the lowest list price of any mealtime insulin – $90 per 3 mL pen and $233 per 10 mL vial. This product is part of the company's Insulin ValYOU Savings Program, which means that uninsured patients pay $99 per vial or $149 for a pack of five pens. Sanofi has sought access to this program for patients covered by government health plans. *(Also see "Lowering Insulin Costs: Sanofi Seeks HHS Support For Expanding Assistance To Medicare Patients" - Pink Sheet, 8 Jun, 2018.)*

The company's drug pricing report also notes that the higher capacity *Max SoloStar* version of *Toujeo* (insulin glargine), which was launched in June, was priced at $259.15 – the same price per unit as the original version of the drug.

In addition to its new insulin products, Sanofi said the price of the **Regeneron Pharmaceuticals Inc.**-partnered drug *Libtayo* (cemiplimab-rwlc) – $9,100 per three-week treatment cycle – reflects the PD-1 inhibitor's clinical value as the only approved treatment for metastatic or locally advanced cutaneous squamous cell carcinoma who are not candidates for surgery or radiation. *(Also see "Sanofi/Regeneron's IO Springboard Libtayo Cleared For Skin Cancer " - Scrip, 28 Sep, 2018.)*

The company also outlined investments it made in patient assistance programs in 2018 to offset out-of-pocket costs for its drugs. There were 334,818 patients who used Sanofi co-pay assistance cards last year for total savings of $342m. Under the ValYOU program for insulins launched in April, 9,618 diabetic patients saved $6.2m. Another $508m was saved by 93,148 patients who obtained free medicines under Sanofi's patient assistance programs.

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GSK's Terrell On 'Relentless' Digital Consumption Across The Spectrum

ANJU GHANGURDE anju.ghangurde@informa.com

Karenann Terrell expects digital technology to transform various aspects of business at **GlaxoSmithKline PLC**, including drug discovery and development and customer engagement. A range of interesting initiatives across markets are already underway at the UK-based multinational.

In a wide-ranging interview with *Scrip*, Terrell, who took charge as GSK's first chief digital and technology officer in September 2017, noted that in geographies where physician numbers are limited, reliance on and experimentation with digital platforms tends to be higher compared with markets where physicians are plentiful.

The executive, who spearheaded the push to transform Walmart's use of data, analytics and digital engagement in her stint as the US retail giant's chief information officer, also sees the Indian market as a great place for experimentation with digital channels and services to healthcare professionals for established products.

Terrell spoke to *Scrip* during a visit to India, where she was scheduled to address the BioAsia 2019 meeting in Hyderabad, among other events.

GSK Chief Digital And Technology Officer Karenann Terrell

Q: Traditionally, the pharmaceutical industry's digital maturity curve has lagged several other industries – retail, telecoms, insurance - and you've seen the other sides function. Are things now changing rapidly at the pharma end, in general, especially with non-traditional players wading into the healthcare space?

A: When you look at what is the real state of technical enablement and digital maturity at pharma, you need to look at it in two senses. First, a lot of the compliance and regulatory pieces of our business are set up intentionally to be slow moving. They are not meant to be consumer oriented and driven that way. In the area of manufacturing, drug development, in the way that we file and do clinical filings, they are intentionally – because they are so focused on patient safety – set up to move at a second pace. But there are parts of our model – how we internally present data analytics, information for decision-making within our business, the way that we look at our commercial model of selling and use technical people to do this – which are not nearly as regulated, which I think are moving fairly rapidly. The pharmaceutical model around retail is also heavily regulated and moves at a different pace and speed than the fast-moving e-commerce direct-to-consumer model. In the pharmaceutical business, you have to look at it in the fast-moving part of the business around the commercial model and modernization as opposed to the regulated piece. Still, the pharma business tends to be in the lower half of speed and pace in terms of change on the digital side of things versus the consumer businesses of media, technology, retail and consumer products. GSK has a consumer healthcare business and the pharmaceutical business, with vaccines directly between the two. At least in GSK, we are looking at the pace and the movement of the consumer-based business and how that applies from a learning orientation into the GSK business – that I know is Emma's [GSK's CEO Emma Walmsley] intention and mine having had pharma experience [Karenann was with Baxter International prior to Walmart] and then retail experience and then coming back to pharma. That's what makes GSK so exciting.

Q: GSK has an alliance with **Exscientia Ltd.** and also co-founded the private-public Accelerating Therapies for Opportunities in Medicine (ATOM) consortium based in the US, among other such linkages. What could all of this mean in terms of potential opportunities to transform R&D at GSK?

A: If you are going to do anything truly innovative when it comes to clinical trials, drug discovery or any part of the true innovation part of the strategy, you've got to be a member of/participating in a value-oriented way in a digital ecosystem. That's true in any business under disruption that's

CONTINUED ON PAGE 23

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

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

PIPELINE WATCH, 15–21 FEBRUARY 2019

Event Type	Lead Company	Drug Name	Indication	Comments	Change To LOA (%)	LOA (%)
Phase IIIb Published Results	Johnson & Johnson/Bayer	Xarelto (rivaroxaban)	Venous Thromboembolism	CASSINI; NEJM, Feb. 21, 2019	0	100
Phase III Published Results	Pfizer/Merck KGaA	Bavencio (avelumab) Plus Inlyta (axitinib)	Renal Cell Cancer	JAVELIN Renal 101; NEJM online Feb. 16, 2019	0	100
Phase III Published Results	Indivior plc	Sublocade (buprenorphine) Extended-Release	Substance Use Disorder	Low Dose/High Dose; The Lancet, Feb. 19, 2019	0	100
Phase III Published Results	Gilead Sciences, Inc.	Viread (tenofovir disoproxil fumarate)	Hepatitis B	Study 103; The Lancet Gastroenterology & Hepatology, Feb. 19, 2019	0	100
Phase III Published Results	Amgen, Inc.	Prolia (denosumab)	Bone Complications Of Breast Cancer	ABCSG-18; The Lancet Oncology, Feb. 19, 2019	0	100
Phase III Published Results	Achaogen Inc.	Zemdri (plazomicin)	Urinary Tract Infections, Complex	EPIC; NEJM, Feb. 21, 2019	0	100
Phase III Updated Results	AVEO Pharmaceuticals, Inc.	tivozanib	Renal Cell Cancer	TIVO-3; Improved PFS, Response Rate	0	30
Phase III Top-Line Results	Pfizer Inc./Lilly	tanezumab	Chronic Low Back Pain	TANGO; Met Primary Endpoint	3	55
Phase III Top-Line Results	Intercept Pharmaceuticals, Inc.	Ocaliva (obeticholic acid)	Non-Alcoholic Steatohepatitis (NASH)	REGENERATE; Positive Results	1	63
Phase III Top-Line Results	Merck & Co., Inc.	Keytruda (pembrolizumab)	Hepatocellular Cancer, Second-Line	KEYNOTE-240; Missed PFS, OS Endpoints	0	100
Phase III Top-Line Results	Seikagaku Corp/Ono	SI-613	Osteoarthritis Pain	Improved Knee Pain	0	24
Phase III Top-Line Results	Foresee Pharmaceuticals	FP-001 (leuprolide) 3-Month Depot	Prostate Cancer	Achieved Primary Endpoint	5	40

Source: Biomedtracker | Informa, 2019

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delivering really disruptive value and value proposition. Instead of looking at it from a vendor point of view, if you look at it through the orientation of strategic partner, you can see how their value propositions and ours [value proposition] can really deliver more than one plus one equals two. That is the only way that real disruption and high-end innovation will pursue…not for us to behave like a vendor-client but for us to think in terms of digital ecosystem and strategic partnering. That is directly the intention with our 23andMe [the consumer genetics and research company] relationship, that was directly the intended benefit in ATOM as we look at those to reach beyond vendor and client.

Q: Do you see digitally-backed improved patient outcomes/digital biomarkers playing a significant role in reimbursement decisions in the developed world, especially for new expensive personalized drugs or maybe in neurology/psychiatry where monitoring may tend to be a bit subjective.

A: There's no question that whether it be in developed markets like the US or in looking at single payer national health systems that value-based orientation is a drive from the payer and the health system to understand, especially in areas of innovation drugs, where the real differentiators are. And the use of real world evidence in that equation in order to look at what is happening from a biomarker basis, standard of care with the medicine is not just a trend, it actually is the direction that health systems are going.

Q: How important is it to balance the traditional face-to-face engagement with physicians/patient groups and high digital engagement strategies? Is there a very sharp shift in preferences towards digital engagement in most markets, including emerging markets that GSK operates in?

A: A doctor's expectation of digital experience is informed by his arrival at his office in an Uber [ride hailing service]. It starts with he as a digital being inside of that environment, and his expectations of how he will be served as a doctor are no different than how he is served as a consumer. The speed at which we can actually serve him and focus on him as a customer with digital platforms and capability could be a point of differentiation for pharmaceutical companies. It depends a lot on geographies – in geographies where doctors and specialists are scarce, there's probably a much greater reliance/expectation and experimentation going in with regard to digital platforms, versus an environment where doctors are plentiful. In the west, it's probably a lower level of experimentation. So in emerging markets, whether they be Central Europe, India and China... or continuing in that experimenting to see exactly how we can get that model right where there are not enough doctors to service the patients. That's where we are seeing the greatest set of examples.

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APPOINTMENTS

Executive	To Company	New Role	From Company	Previous Role	Effective Date
Peter B. Leone	Bicycle Therapeutics Ltd	Chief Business Officer	Arrowhead Pharmaceuticals	Vice President, Strategic Business Initiatives	20-Feb-19
Jodie Morrison	Cadent Therapeutics	Chief Executive Officer	Keryx Biopharmaceuticals Inc	Interim Chief Executive Officer	14-Feb-19
Phillip Williams	Emergex Vaccines Ltd	Chief Scientific Officer	Midatech Pharma	Principal Scientist	18-Feb-19
Rachelle Jacques	Enzyvant Sciences Ltd	Chief Executive Officer	Alexion	Senior Vice President, Global Franchise Head, Complement	21-Feb-19
Peter Tummino	Nimbus Therapeutics	Chief Scientific Officer	Johnson & Johnson Pharmaceuticals Group	Vice President, Global Head, Lead Discovery	14-Feb-19
Rick D. Scruggs	RedHill Biopharma Ltd	Chief Operating Officer, US	Salix Pharmaceuticals Inc	Executive Vice President, Business Development	20-Feb-19
Robert Morgan	Verastem Inc	Senior Vice President, Development Operations	Samus Therapeutics Inc	Chief Regulatory/Quality and Contracting Officer	20-Feb-19

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Source: Medtrack | Informa, 2019

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