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Sarilumab Set To Clear EU Hurdle In RA But Actemra Specter Remains

While Sanofi/Regeneron's sarilumab is set to be the first of the newer IL-6 products to be cleared for rheumatoid arthritis treatment in Europe and the US, its commercial success is under doubt with physicians trying anti-TNF treatments first, followed by Roche's established IL-6 drug Actemra.

SUKAINA VIRJI sukaina.virji@informa.com

With the European Medicines Agency's CHMP giving *Kevzara* (sarilumab) a positive opinion, Sanofi/Regeneron Pharmaceuticals Inc.'s IL-6 receptor antagonist is set for EC approval in the coming months. But making it a commercial success will prove to be a challenge.

"Its lack of differentiation from *Actemra* (tocilizumab; Roche) will prevent it from capturing significant market share," predicted Datamonitor Healthcare analyst Christina Vasiliou. "Overall, its clinical performance to date has been comparable to that of Actemra, and key opinion leaders note that they would consider using it in the same treatment setting where they currently use Actemra – primarily in non-responders to anti-TNF biologics, and as a first-line biologic in rare cases of high disease activity or comorbidities."

This lack of differentiation, namely the absence of a head-to head study between Kevzara and Actemra, will scupper the newcomer's chances unless Sanofi and Regeneron are competitive on price, believes Vasiliou.

And the potential for the market to become even more challenging for originators in the IL-6 space will increase over the next five years as Actemra's patents expire.

BIOSIMILAR PRESSURE

Datamonitor Healthcare believes tocilizumab biosimilars could enter the market in 2022.

According to Informa's Biomedtracker, three companies have a biosimilar tocilizumab in preclinical testing: Epirus, Mycenax and Oncobiologics.

"The arrival of biosimilar tocilizumab will put pressure on both Actemra as well as on new IL-6 inhibitors such as sarilumab as the biosimilar will likely get preferred access," added Vasiliou.

Jefferies analysts have forecast global sarilumab revenues of €581m in 2021.

Along with sarilumab, US and EU regulators are evaluating GlaxoSmithKline PLC/ Janssen Inc.'s IL-6 product sirukumab, which is just months behind sarilumab in both Europe and the US. Sarilumab's lead time took a hit when the FDA issued a complete response letter for the sarilumab BLA last October, citing manufacturing concerns following a routine site inspection of a 'fill-and-finish' plant in France. The sarilumab BLA at the time had an action date of Oct. 30.

Sanofi reported during a March 28 investor call that the two companies recently had re-filed the sarilumab BLA. They are hoping for a two-month review of the resubmission for sarilumab, which gained its first approval Feb. 1 in Canada.

The other late-stage biologic in development for rheumatoid arthritis, Eli Lilly & Co./Incyte Corp.'s oral selective JAK1/2 inhibitor baricitinib, had its prospects dashed by an FDA complete response letter earlier this month.

Published online 24 April 2017

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Few clouds on high-priced, ultra-orphan drug horizon (p18)

from the editor

eleanor.malone@informa.com

Last week first-quarter earnings reports began in earnest. The picture was far from bleak. Against the odds, Lilly actually managed to grow its revenues from diabetes products. Sales of AbbVie's Humira continued to motor upwards, and its blood cancer drug Imbruvica looked very strong. Even BMS's beleaguered Opdivo beat predictions to grow at 60%. Among European firms, Sanofi was an anomaly in missing targets: GSK's respiratory blockbuster Advair beat expectations, Novartis's pharma sales were solid and Roche's Q1 sales overtook analyst forecasts.

As companies and investors accustom themselves to new levels of global uncertainty, pharma still looks like a relatively safe haven. US pharma stocks have been on a mostly upward trajectory since Trump's notorious tweet about pharma companies "getting away with murder" in their drug pricing and his subsequent meeting with industry executives at the end of January. The S&P Pharmaceuticals Select Industry Index is up around 10% since the beginning of 2017, compared with a rise of about 7.5% for the S&P 500. Meanwhile, the S&P Biotechnology Select Industry Index is up nearly 20%.

Trump's threats on pricing and doubts over his support for scientific research notwithstanding, the prospects of business-friendly tax reform on the one hand and optimism over the industry's ability to develop valuable new therapies on the other look to be driving ongoing enthusiasm about the sector. Most biopharma executives believe the US will continue to reward innovation. Meanwhile, underlying growth in established pharma businesses can only be a good thing.

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LEADERSHIP
Phil Jarvis, Mike Ward

SUBSCRIPTIONS
Daniel Frere

ADVERTISING
Christopher Keeling

DESIGN SUPERVISOR
Gayle Rembold Furbert

DESIGN
Paul Wilkinson

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

CUSTOMER SERVICES
Tel: +44 (0)20 7017 5540
or (US) Toll Free: 1 800 997 3892
Email: clientservices@pharmamedtechbi.com

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scrip.pharmamedtechbi.com

TO ADVERTISE, CONTACT
christopher.keeling@informa.com

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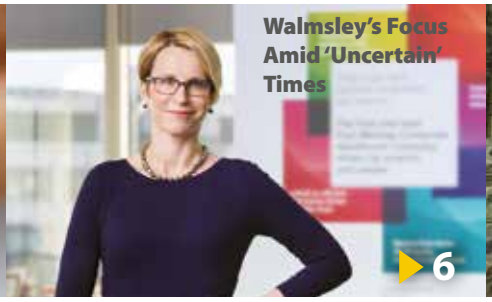

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Having closed a €160m venture fund focusing exclusively on microbiome-related fields – including pharmaceuticals, nutrition, biomarkers and diagnostics – Seventure Partners president and CEO Isabelle de Cremoux reveals how she expects to add another 10 companies this year to the nine she already has in her portfolio.

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Lilly Shows Diabetes Dominance, But Will It Last?

MANDY JACKSON mandy.jackson@informausa.com

Lilly's first quarter benefited from rising sales for most of its diabetes products, which has become one of the most difficult therapeutic areas to do business in due to competitive and reimbursement pressures.

Eli Lilly & Co. pulled off something at least one of its competitors couldn't in the first quarter: its diabetes portfolio contributed significantly to the company's 7% year-over-year revenue increase to $5.2bn.

Lilly's first quarter results reported on April 25 showed that having a diverse portfolio in a competitive sector that's facing intense pricing pressure pays off. The company's growing diabetes dominance doesn't guarantee a win every quarter, however, since new products continue to reach the market, new data may boost competing drugs and payers remain sensitive to cost.

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"Looking over the first quarter results for Lilly and listening to the corresponding call, we could not help but think that their results present a microcosm of what's going on in the overall diabetes drug sector," diabetic investor publisher David Kliff wrote in an April 25 report. "We have been noting when it comes to diabetes drugs two facts are clear: this market has commoditized and payers remain in control over pricing. This is not so much a story of innovation, rather growing volume/share, which drives manufacturing efficiencies, which in turn improves margins."

Payers have been increasingly tough on pharmaceutical pricing, especially in large categories with multiple competing drugs – like diabetes – and Lilly has felt that pressure. Insulins have seen increasing price pressures from payers and patients, with Lilly and other manufacturers now facing lawsuits and government investigations related to the medicines' costs.

Even so, the rapid-acting human insulin analog Humalog – Lilly's top-selling pharma product – was one of the firm's big gainers in the first quarter with $708.4m in sales, representing a 17% increase globally. The early 2017 gain reflected a bounce back from 2016 when the value of rebates and discounts the company provided to payers across all of its products increased 30% from the prior year.

Humalog's first quarter sales growth of 24% in the US was attributed to some increased demand, but mostly to a recovery from the concessions granted to payers in last year's first quarter. Ex-US sales increased 6% with higher demand and prices offset by unfavorable foreign currency exchange rates.

However, sales of the intermediate-acting human insulin Humulin fell 12% in the first quarter to $314.5m despite reduced rebates and discounts in the US compared to last year, because domestic demand for the product also decreased. Ex-US demand increased, but price declines were compounded by foreign exchange rates.

Lilly's diabetes portfolio – which totaled $1.4bn in sales in the first quarter, or 32.3% of the company's $4.5bn in pharma revenue – also benefitted from three new drugs. The glucagon-like peptide 1 (GLP-1) receptor agonist *Trulicity* (dulaglutide) brought in $372.9m, which was a 160% increase from the first quarter of last year. The growth was driven by rising demand for GLP-1 agonists in the US, the drug's greater share of GLP-1 sales and gains in ex-US markets, including Europe and Japan.

Revenue from Basaglar, Lilly's insulin glargine follow-on, jumped 321% to $46m, including $22m from US sales. Basaglar and the sodium-glucose co-transporter 2 (SGLT2) inhibitor *Jardiance* (empagliflozin) are marketed in partnership with Boehringer Ingelheim GMBH.

JARDIANCE MISSES CONSENSUS

Lilly recorded Jardiance revenue of $74m in the first quarter, which was a 94% year-over-year increase, but fell below analyst consensus of $102m; estimates had been high due to expectations over the product's expanded label recognizing a cardiovascular outcomes benefit observed in the EMPA-REG trial. The Jardiance revenue total includes Lilly's share of sales from the combination products *Glyxambi* (empagliflozin/linagliptin) and *Synjardy* (empagliflozin/metformin). Like Trulicity and the GLP-1 class, Lilly said Jardiance benefitted from both increased SGLT2 inhibitor use and greater demand for the drug in the US.

Despite the near doubling of Jardiance sales, Credit Suisse analyst Vamil Divan noted in an April 25 report that "uptake remains below our expectations."

Bernstein analyst Tim Anderson pointed out in his same-day report that Lilly and Boehringer do not have significant pricing power even though they have the competitive benefit of positive cardiovascular results in EMPA-REG, because there are other SGLT2 inhibitors on the market. Prescribers and payers may view the companies' cardiovascular data and AstraZeneca PLC's recently reported real world evidence study as validating all drugs in the SGLT2 class.

Lilly executives insisted during the company's April 25 earnings call that they were happy with Jardiance's market share gains to date. "We are pleased that our new-to-therapy share with both endocrinologists and primary care physicians has increased substantially since the FDA approval of the CV indication and the update to the [American Diabetes Association's (ADA's)] diabetes treatment guidelines," chief financial officer Derica Rice said.

President-Lilly diabetes Enrique Conterno noted that sales growth for the SGLT2 class was flat before the cardiovascular benefit claim was added to the Jardiance label, but now growth for the class is 30%. While there's rising demand generally for SGLT2 inhibitors in the US coupled with competitive pricing amongst drugs in the same class, Conterno said the value Jardiance's CV benefit adds for patients has been reflected in pricing in other markets.

"In the case of Germany, we have a new price – a higher price – for Jardiance based on the indication. And in the case of Japan, we did not get [a] price cut. We got a minor – a positive – price adjustment," he said.

Johnson & Johnson seems to be having a somewhat different experience with its competing SGLT2 inhibitor, however, since the company said its first quarter *Invokana* (canagliflozin) sales declined 17% from the prior year based on pricing pressures. Invokana's first quarter revenue still came in at more than three times Lilly's share of Jardiance sales. J&J will report its own cardiovascular outcomes data for its drug later this year.

Conterno noted that if Lilly's competitors in the SGLT2 class see negative or neutral results in cardiovascular outcomes trials reported later this year, "that probably would be the worst outcome for us. We clearly believe our data is highly compelling, but clearly we could benefit from the tailwind of having another SGLT2 basically have this similar data. If their data is positive, but not as positive as ours, that probably is the best case scenario for us."

Diabetic Investor's Kliff noted that Lilly is in the best competitive position of its peers in the diabetes field, because of the diversity of its portfolio, although he noted that "there are some threats on the horizon, but none that will immediately impact the company."

NON-DIABETES GROWTH?

With Trulicity adding the greatest amount to Lilly's sales growth and Jardiance's future looking positive, though competitive, where else will the company's future sales gains come from? Cancer and inflammatory diseases are among the Lilly's growth areas, but the company's development record is 1-for-2 in recent weeks among candidates in those two areas.

No additional guidance was given on what the US FDA will require to approve baricitinib for rheumatoid arthritis. The JAK1/2 inhibitor was approved as Olumiant in the EU, but received a complete response letter in the US seeking additional safety and dosing data. Lilly will give an update on whether a new clinical trial is needed after it meets with the FDA during the next few months.

The company also did not add any new insights regarding its second set of positive Phase III results in breast cancer for the CDK4/6 inhibitor abemaciclib. It is on track to submit two applications for FDA approval in the second and third quarters of this year based on the two different Phase III studies. Lilly's forecast for future growth acknowledges that the research and development pipeline will tally some wins and some losses, management noted during the first quarter earnings call.

"Even taking into account the impact of baricitinib, we still believe we could stay above that 5% minimum goal that we established in terms of average growth between 2015 and 2020," Rice said.

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Glenmark Readying Xolair Biosimilar Challenge

Glenmark has received US FDA clearance of an IND to start clinical studies with a proposed biosimilar version of Xolair. The Indian company appears confident of addressing any price-related challenges although the targeted launch is still some years away.

ANJU GHANGURDE anju.ghangurde@informa.com

The US FDA has approved Glenmark Pharmaceuticals Ltd.'s Investigational New Drug (IND) application to initiate a first-in-human study of GBR 310, the firm's proposed biosimilar version of Roche/Novartis AG's Xolair (omalizumab); the study will assess the biosimilar's pharmacokinetics in comparison to Xolair in healthy adult volunteers between 18 and 65 years of age.

GBR 310 is a recombinant DNA-derived humanized immunoglobulin G1 kappa monoclonal antibody and its current proposed indication is for the treatment of allergic asthma and chronic idiopathic urticaria.

Glenmark told Scrip that it believes it is the first firm to receive FDA approval to initiate studies for a biosimilar version of Xolair and is targeting a 2022 launch of the product in the US. It also expects to look at other markets like the EU and Japan since it has a "global program" for the product, though the first target will be the US.

Dr. Kurt Stoeckli, president and chief scientific officer at Glenmark, noted that in the seven years since the US approval process for biosimilar medicines was signed into law, there have been few candidates successfully developed.

"GBR 310 has the potential to be among the first biosimilar candidates to be submitted for approval for a respiratory or allergic disease," Stoeckli, who moved to Glenmark last year from Sanofi, said in a statement. Asked whether it is ahead of Sorrento Therapeutics Inc. in advancing its biosimilar Xolair, Glenmark told Scrip: "Based on our understanding, we believe that we would be among the first set of players to launch [a] biosimilar of Xolair."

Last year, Sorrento announced that its partner, Mabtech Ltd, had successfully completed a combined Phase II/III clinical study in China for STI-004, its biosimilar version, which met its primary endpoint in the placebo-controlled clinical trial.

In 2015, Sorrento licensed four biosimilar/biobetter antibodies, including STI-004, from Mabtech. In a May 2016 announcement, it said that it was making progress with the development of these products in Sorrento's territories that include North America, the EU, and Japan, while Mabtech will seek market approval for STI-004 in China.

Analysts have also previously claimed that Mylan NV and Momenta Pharmaceuticals Inc.'s collaboration to develop, manufacture and commercialize six of Momenta's biosimilar candidates could potentially include a Xolair version, going by Momenta's patent filings, but *Scrip* could not immediately verify these claims.

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GSK's Walmsley Focused On Upcoming Launches Amid 'Uncertain' Times

New CEO confirmed GSK's commitment to maintaining its three business unit structure – "as long as all three businesses continue to perform competitively" – as she chaired her first quarterly results presentation at the helm of the big pharma.

SUKAINA VIRJI sukaina.virji@informa.com

GlaxoSmithKline PLC's new CEO Emma Walmsley sees "both logic and benefit in being a three business healthcare company, not least because of some of the uncertainty and volatility that we [still] see in the high-return … pharma business," she said during the firm's first quarter earnings call April 26.

GSK's three units are pharmaceuticals, vaccines and consumer health. The company "believes in the synergies" between the business units, she added, "both from an operating point of view and a lifecycle management point of view."

Management would monitor the situation to ensure it continued to make sense, "hopefully not every quarter, but on a reasonably regular basis," she joked. "And we're always listening to shareholders on that."

Meanwhile, her priority is a focus on execution, and preparing "fantastically competitive launches for the few near-term launches that we do have." She's referring here to GSK's *Shingrix* shingles vaccine, which will compete with Merck & Co. Inc.'s *Zostavax*, and a once-daily closed triple combination therapy for COPD.

Successful commercialization with these products is particularly important for GSK given that its next wave of new product launches is not due until the early 2020s.

And "the really big priority" is creating the value for the company "in terms of the strength of our pipeline." Around 25 drug candidates are set to deliver crucial data of the next few years, and Walmsley and her team need to make sure they pick the winners. GSK intends to provide more color here at the end of the second quarter.

Emma Walmsley

Q1 FINANCIALS SOLID

GSK delivered a solid set of Q1 numbers. "Sales and core earnings [were] both slightly ahead of expectations," said Berenberg analyst Alistair Campbell. "Sales of £7,384m beat by 2%, as did core EPS of 25p." GSK's pharmaceuticals division reported sales of £4,189m. The major product lines were generally in line with expectations, although the respiratory franchise performed "largely due to a 3% beat from *Advair* which made up for the *Anoro* (15% miss) and *Relvar/Breo* (8% miss) underperformances," noted Campbell.

GSK's new asthma treatment *Nucala* is now being taken by more than 10,000 patients in the US and has grown the severe asthma market by 33%, according to GSK. However, its triple therapy for COPD, expected to be approved later this year, "will take some time to build in today's markets," admitted CFO Simon Dingemans, no doubt learning from GSK's experience with slow starters Anoro and Breo Elipta.

The vaccines business was notably strong, with sales of £1,152m, beating expectations by 11%. The division's 16% CER growth was attributed to a strong performance from the meningitis portfolio and improvements in the supply chain. "It also reflects an element of phasing relating to the timing of international tenders, including GAVI's *Synflorix* sales as well as CDC purchases and stockpile movements that boosted particularly *Pediarix's* growth in the US," said Dingemans. "While vaccine sales are often lumpy, the momentum in the business continues to give us confidence in the mid to high single digit outlook for the business over the medium term."

Consumer health sales of £2,043m reflected a steady 2% CER growth.

GSK maintained its 2017 guidance, which is contingent on the timing of generic Advair entrants to the US market. In the event of no generic Advair making it on to the US market, core EPS is expected to grow by 5%-7% CER. A mid-year introduction could see core EPS flat to a slight decline at CER.

Commenting on Teva Pharmaceutical Industries Ltd.'s recent introduction of an Advair-like product, Walmsley said: "Just a reminder that it's not substitutable for Advair without a prescription. It's a very different product with a different mechanism. We are much for focused on when a generic Advair might come through." According to Walmsley, "the really important thing is, we're ready. This is something the business is prepared for and we're very focused on building out our Ellipta portfolio."

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Amgen Hit By Enbrel 'Peculiarities,' Repatha Resistance

Amgen reported a surprising double-digit decline for Enbrel during the first quarter and sales for the cholesterol-lowering biologic Repatha showed that the PCSK9 inhibitor is not going to make up for the company's declining revenue any time soon – at least not while payers continue to block its use.

MANDY JACKSON mandy.jackson@informa.com

Amgen Inc.'s PCSK9 inhibitor *Repatha* (evolocumab) remains a long way off from driving the kind of revenue growth that the company needs to make up for declining sales of its legacy blockbuster products, including an unexpected 15% drop for *Enbrel* (etanercept) in the first quarter.

At $49m, Repatha's first quarter sales were three times higher than the $16m in revenue that the PCSK9 inhibitor generated during the same period in 2016, but this year's January-to-March total fell far below analyst expectations of $72m as payers continued to block prescriptions for many patients.

Sales of the LDL cholesterol-lowering biologic amounted to just 24% of Enbrel's $204m year-over-year decline to $1.18m in first quarter sales – and the TNF inhibitor was not the only blockbuster in Amgen's portfolio that experienced a double-digit dip during the first three months of 2017.

Amgen has not, however, given up on its high hopes for Repatha's potential to contribute meaningfully to the company's future revenue and earnings growth based on positive cardiovascular outcomes data reported for the product in March. That optimism holds even as payers continue to exercise utilization management practices that limit patient access to the drug.

"We expect Repatha to be an important product in the fight against cardiovascular disease and increasingly expect physicians, patients and other stakeholders to recognize that rejecting an innovative drug for high-risk patients, which demonstrated beyond 12 months a 35% reduction in the risk of heart attack, a 24% reduction in the rate of stroke and a 28% reduction in the rate of revascularizations is simply inappropriate," chair and CEO Robert Bradway said during Amgen's earnings conference call after the market closed on April 26.

REPATHA RISES

The company's stock price fell 3.1% in after-hours trading to $159.50 per share as investors responded to the missed expectations for Repatha, Enbrel and other key products.

First quarter 2017 *Neulasta*, *Aranesp* and *Sensipar* sales beat first quarter 2016 sales totals and met or exceeded consensus estimates. Enbrel, *Epogen* and *Neupogen* fell below first quarter 2016 and consensus figures. *Prolia*, *Kyprolis*, *Xgeva*, *Nplate*, *Vectibix*, Repatha and *Blincyto* beat first quarter 2016 sales, but missed first quarter 2017 analyst expectations. Only three products didn't disappoint on both metrics.

Amgen's $5.5bn in total revenue fell 1% from the first quarter of last year and was below analyst consensus of $5.6bn, but the company still managed to beat expectations in terms of earnings per share (EPS), which came in at $3.15 on a non-GAAP basis – a 9% year-over-year increase – versus consensus estimates of $2.99. Reduced operating expenses drove the earnings gain despite a revenue decline.

EXCUSES AND RESISTANCE

Amgen executive vice president of global commercial operations Anthony Hooper said during the company's conference call that investors and analysts shouldn't draw any conclusions about Enbrel's prospects for the rest of the year "based on some quarter one peculiarities."

The 15% decline in the first quarter seemed to be greater than the company previously anticipated in October when it warned investors about the potential for slower sales growth, but Amgen thinks Enbrel revenue will recover somewhat as the year goes on; Hooper noted that each month has brought greater sales totals.

Both Amgen and the prescription-tracking firm IMS Health saw "softness" in Enbrel's first quarter performance, particularly in rheumatology and dermatology, and they blamed the sales decline on various factors, including fewer shipping days during the first quarter, higher deductibles and out-out-pocket co-pay costs for consumers, and greater use of 90-day prescriptions.

While the reimbursement landscape is especially tough for Repatha, Hooper noted that the product enjoys greater market share across multiple segments of the PCSK9 inhibitor market, which also includes the Sanofi and Regeneron Pharmaceuticals Inc. biologic Praluent (alirocumab). Amgen won a patent lawsuit against the Praluent makers, but the decision has been appealed.

Amgen is the only company with a PCSK9 inhibitor on the market that has reported positive cardiovascular outcomes data, so it is trying to increase its market share by negotiating with payers to allow treatment of appropriate patients, including statin-intolerant individuals and people whose LDL cholesterol is not well-tolerated on statins.

The FOURIER clinical trial results were presented in March at the annual American College of Cardiology (ACC) scientific conference and the slow process of changing payers' minds based on the data is ongoing.

William Blair analyst John Sonnier said in an April 26 report that he still has a positive regarding the long-term clinical profile of Repatha, but he said "the drug remains a commercial 'show me' story in the near term."

The commercial near term may stretch into a long term, however, since Hooper indicated that the process of convincing payers to loosen their restrictions on PCSK9 inhibitors is a slow one, despite positive physician and medical group evaluations of the drugs' cardiovascular benefits.

"Since the ACC, we've been engaging with payers in the US and across the world on Repatha's clinical data and economic value. We are in active discussions with all of the large US [pharmaceutical benefit managers (PBMs)] and payers, and they recognize the importance of Repatha's outcomes data to patients," Hooper said. "We are focused on reducing barriers and improving processes to make it easier for a physician to prescribe REPATHA."

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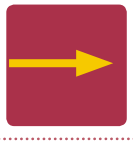

View Amgen's First Quarter 2017 Sales Versus 2016 And Consensus Estimates here: **http://bit.ly/2qxnE9J**

Hep B Cure May Lie In Reducing Surface Antigen

JOSEPH HAAS joseph.haas@informa.com

Among the topics at the European liver meeting was whether reducing HBV surface antigen might be part of a combination approach to curing chronic hepatitis B. One of the leaders in this approach, Arbutus, is working toward its own internal combo therapy for the virus.

With the success seen with the direct-acting antiviral drugs in hepatitis C, drug makers have shifted their sights toward potentially curative regimens for hepatitis B. At the recently concluded European Association for the Study of the Liver Meeting, one approach appearing to gain traction centered on reducing HBV surface antigen (HBsAg), perhaps even to undetectable levels.

The current standard of care for hepatitis B infection involves chronic therapy with one of several nucleotide analogues initially approved to treat HIV, but the experience in HCV shows that bespoke treatments can achieve near-perfect success rates.

Current drugs "are great at achieving viral suppression, but if a therapy can stimulate HBsAg loss and allow patients to stop treatment, then HBV would become the next HCV," Datamonitor Healthcare analyst Michael Haydock told *Scrip* following the conference held April 20-23 in Amsterdam.

Vancouver-based Arbutus Biopharma Corp., formerly the Ebola-focused Tekmira Pharmaceuticals Corp., is one of the companies investigating potential therapy to reduce HBsAg levels in patients with chronic HBV infection; it presented promising Phase IIa data at the conference. The biotech's longer-term goal is to develop a combination therapeutic regimen that might bring the same advances to HBV patients that have been benefiting HCV patients, Arbutus CEO Mark Murray said in an interview.

DMHC's Haydock said it is early days to determine which company, if any, has a step ahead in the next-generation HBV competition, but there is a lot of optimism around the concept of reducing HBsAg, given that recent HBV treatment guidelines point to this approach as an ideal efficacy measure.

"I think for pretty much every compound in early-phase development, it is too early to say if they will produce meaningful [progress] in HBsAg loss, but there were some that showed clear reductions in HBsAg levels as a starting point," the analyst said. "I think the consensus is that it will take a combination of approaches – including pegylated interferon, nucleotide analogs and new modes of action – together to be able to achieve HBV DNA suppression as well as HBsAg loss."

COMPANIES AT PLAY

Johnson & Johnson may have an early advantage in this race, Haydock added, because of its deep pockets and its ability to test multiple mechanisms of action internally, including capsid inhibition and inhibition of apoptosis proteins. One of the noteworthy datasets at EASL was a study testing Gilead Sciences Inc.'s proprietary HBV candidate with a checkpoint inhibitor (Bristol-Myers Squibb Co.'s Opdivo) as a potential combination regimen, he said, but this didn't show much potential for reducing HBsAg levels.

"But it shows the type of innovative thinking going on," Haydock noted.

The other companies working on HBsAg-reducing drugs include Replicor Inc., which has REP 2139-Mg in Phase II, and ContraVir Pharmaceuticals Inc. with its CRV431 in preclinical testing.

Meanwhile, RNAi-focused Arrowhead Pharmaceuticals Inc. presented data at EASL on ARC-520, which demonstrated proof-of-concept that surface antigen levels could be reduced with drug therapy – but the program was shelved last November due to safety concerns, Haydock noted. RNA-focused efforts have been a major focus for HBV research.

Arbutus may be farthest along with the HBsAg approach, with Phase II data showing reductions of surface antigen levels both in patients negative and position for HBV e-antigen. In 2016, it presented data from two trial cohorts testing ARB-1467, a lipid nanoparticle-delivered, small interfering-RNA therapeutic, along with nucleotide analogue therapy in patients negative for e-antigen. At EASL, the biotech showed that ARB-1467 also can reduce surface antigen in patients positive for e-antigen.

REDUCTION DEMONSTRATED

The latest data show the drug achieved a mean 0.7 log reduction in HBsAg levels from baseline in e-antigen positive patients using a monthly 0.4 mg/kg dose for three months. The earlier datasets demonstrated a mean 0.8 log reduction in e-antigen-negative patients on that dose and a mean 0.6 log reduction with a 0.2 mg/kg/month dose for three months.

Murray said ARB-1467 delivers three distinct RNAi triggers that target four different sites of the HBV genome, leading to degradation of viral transcripts and reductions of viral proteins. For now, the easiest of these markers to measure clinically is reduction in HBsAg, which is secreted in the patient's blood, the exec explained.

Murray said producing close to 1 log reductions in surface antigen with just three courses of treatment from a baseline of 3 logs is a significant therapeutic effect. "What we're interested in doing [next] is exploring more frequent dosing and extended dosing duration to see if we can get patients to very low, potentially undetectable levels of surface antigen, which would be a very important accomplishment in the field," he said.

Meanwhile, the data presented by Gilead testing its compound with *Opdivo* (nivolumab) – which showed seroconversion in one patient – at least shows the potential for advancing HBV therapy by combining an agent that reduces HBsAg with one that stimulates an immune response against the virus, the exec asserted.

Arbutus' longer-term goal is to test ARB-1467 in combination with an immunomodulator, possibly pegylated interferon. It also is testing a capsid inhibitor, ARB-423, in Phase I and hopes to move that drug into HBV-infected patients later this year. Together, an HBsAg-reducing agent, a capsid inhibitor and an immunomodulator may provide the paradigm for combination therapy to yield a functional cure in HBV, Murray noted.

"There are a number of companies reporting on [capsid inhibition], so it represents a very validated HBV target that a number of people are going after," Murray said. "The activity that you see when you inhibit capsid formation is predictable and understood – you reduce viral DNA repli-

cation. We expect our agent when it gets into patients will do the same. So from our perspective, it's confirmatory that capsid inhibition is a good place to be."

Currently, Arbutus is running a fourth cohort of the Phase IIa study, now testing a 0.4 mg/kg dose of ARB-1467 five times over three months – bi-weekly doses from day 1 to day 61 of treatment. It hopes to show that this larger regimen is safe – '1467 has been well tolerated in clinical testing to date – and determine whether more frequent dosing might produce a greater effect in reducing surface antigen, Murray explained.

In that cohort, patients who achieve a preset level of HBsAg reduction will be enrolled in a 10-month extension, he said, with a goal of seeing if '1467 ultimately can produce undetectable levels of HBsAg. If successful, that would provide a stepping stone to testing '1467 with nucleotide analogue therapy and an immunomodulator.

"The idea there would be a feasibility proof-of-concept way to see once you've used '1467 to reduce surface antigen to low levels, whether subsequent immune stimulation will trip patients over into this so-called seroconversion zone, where they raise antibodies to surface antigen and then they get into a zero surface antigen level for an extended period of time," Murray explained. "It's feeling like we're getting very close to being able to test some important parameters there."

Simultaneously, Arbutus is working on next-generation candidates that might improve upon the efficacy of ARB-1467, an intravenous infusion, and ARB-423, including potential small-molecule drugs that produce similar effects. This is another way in which HBV drug development might someday mirror the advances in HCV, as therapeutic benefits for patients are increased through succeeding generations of drugs, Murray said.

ARBUTUS' THEORY PROMISING

In an April 23 note on Arbutus' data, Leerink Partners' analyst Michael Schmidt said the biotech's data so far are encouraging but in a preliminary stage. For one thing, the therapeutic benefit of reducing surface antigen has to be demonstrated more clearly, he noted.

"Although correlation between the extent of HBsAg reduction and clinical benefit is not well understood, permanent HBsAg suppression to undetectable levels is hypothesized to be an important step toward potentially achieving a functional cure in HBV," Schmidt wrote.

Tekmira suspended its work in Ebola virus in mid-2015 and said it would alter its focus to hepatitis B. Toward that end, it merged with another HBV-focused firm, OnCore Biopharma Inc., that same year, with the new entity adopting the Arbutus name. Tekmira had raised nearly $143m in a follow-on public offering in March of 2015.

Schmidt said Arbutus is expected to pick candidates to move forward with for HBV combo therapy in 2018 and that at current capitalization it should have runway for roughly another 18 months.

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Fresenius Covers Bases With Akorn/Merck Deals

SUKAINA VIRJI sukaina.virji@informa.com

Fresenius is shoring up its near-term US growth prospects by acquiring generics firm Akorn, as well boosting its future outlook by entering the biosimilars space via a deal with Merck KgaA.

German healthcare company Fresenius SE & Co. KGAA has accelerated the pace of its M&A activity since promoting its CFO Stephan Sturm to the CEO role in July last year.

Following its acquisition of Spanish private hospital group Quironsalud for $6.1bn in 2016, Merck has confirmed it is buying US generics firm Akorn Inc. for $34 per share – around $4.3bn - plus around $450m of Akorn net debt.

Simultaneously, Fresenius announced it is entering the biosimilars space with the acquisition of Merck KGAA's biosimilars business for up to $670m. Of this, €170m will be paid up front; the remaining €500m is linked to development milestones. Merck announced during its annual results presentation in March this year that the unit was up for sale.

"The [Akorn] transaction should enable Fresenius to significantly reinforce its Kabi division (19% of sales) at a time when management was more cautious on US growth prospects," noted Bryan, Garnier & Co analyst Hugo Solvet in an April 25 research note. Fresenius has been benefiting from a drug shortage situation "which boosted its margins and would have normalized at some point," he added.

Akorn has forecast 2017 revenues of around $1bn and adjusted EBITDA of $363m to $401m. Solvet estimated Akorn will add an extra 85 ANDAs to Fresenius's 52. He also noted that Akorn has increased its focus on alternate dosage forms "which complements Fresenius's strategy of bringing to the market generic products with value-added such as the Simplist range which feature ease of use."

Fresenius expects the bulk of around $140m in integration costs to hit in 2018, with mid-term cost and growth synergies of around $100m per year, which will have a positive impact from 2019.

BIOSIMILAR BOOST

Fresenius expects the first sales from a Merck-derived biosimilar program by the end of 2019, and believes it could ramp up the business to a "high triple-digit million sales from 2023 onwards based on the current product development schedule." It has agreed to pay single-digit percentage royalties to Merck based on sales. "The acquisition creates a platform for further growth," added Fresenius's CEO Mats Henriksson. Fresenius is committed to investing up to €1.4bn until 2022 in its new biosimilars business.

The assets being acquired include two biosimilars in development, one of which is an adalimumab *(Humira)* program in Phase III.

Jefferies analyst Chris Cooper has "mixed thoughts" on the biosimilar deal. "Having stated for years that biosimilars were not of direct interest, Fresenius changed its tone over the last 12 months," he wrote in an April 25 research note. "We believe this deal provides greater comfort over the long-term sustainability of [Fresenius] Kabi's growth and margin profile."

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AbbVie's Gonzalez Calls Break-Up Proposal Rational, But Premature

CEO says the idea of forming one company around Humira and its earnings and another around the R&D pipeline holds merit but he wants to wait to see the outcome of US tax reform, which could address some of AbbVie's issues.

JOSEPH HAAS joseph.haas@informa.com

Every AbbVie Inc. earnings call since its inception in 2013 has included a significant focus on the maturing autoimmune mega-blockbuster Humira (adalimumab), far and away its top-seller, and what the firm would do next. During its first quarter earnings call April 27, Chairman and CEO Richard Gonzalez both acknowledged and swatted away a suggestion that the company split into two – one for the commercial Humira business and another for its R&D pipeline.

Itself a spinout of Abbott Laboratories Inc., AbbVie was built around the pharma business – with *Humira* and a few other commercial products to offset the costs of developing a significant pipeline – while Abbott focused on the medtech and consumer businesses. Among its big pharma brethren, AbbVie has seen Pfizer Inc., in particular, juggle the possibility of a split-up or divestment of certain businesses.

During the call, Jami Rubin of Goldman Sachs asked Gonzalez to ponder whether separating out Humira, which presents a double-edged sword of huge revenues but near-term biosimilar competition, might allow a possibly undervalued pipeline to be viewed on its own merits. During the first quarter, Humira accounted for 63% of AbbVie's net revenues with global sales exceeding $4.1bn, down about 4% from nearly $4.3bn the prior quarter, but still a 15.1% increase year-over-year, including a 22.8% increase in the US.

Gonzalez said emerging tax reform policies from the Trump administration could mean that AbbVie would enjoy better access to its significant offshore cash, which would put it on a more competitive footing with peer companies, especially those based outside the US. "It would certainly give us a lot more encouragement to invest in the US and create US jobs," he said. "So, I find the discussion encouraging, and I think it would be extremely beneficial for companies, certainly in our industry and across other industries."

He called Rubin's proposal "well done" and said he agrees with her thesis "wholeheartedly."

"We have a business that generates tremendous cash flow, and we anticipate that that cash flow is sustainable over the long term," Gonzalez replied. "That cash flow certainly, as it is generated, far outweighs what we would envision … is required for us to reinvest back in the business. We're certainly going to reinvest back in the business as we have historically. But I'd say as we project forward, we would be building cash offshore."

He also asserted that AbbVie is undervalued by the market, both for the contribution of Humira and for the potential of its pipeline. AbbVie expects data readouts from a dozen pivotal studies this year, including JAK inhibitor ABT-494, risankizumab in psoriasis and ABT-414 in brain cancer. Phase III data for '494 in rheumatoid arthritis are anticipated in the next few months, Gonzalez added, and AbbVie also is advancing label-expansion efforts for *Venclexta* (venetoclax) for broader use in relapsed/refractory chronic lymphocytic leukemia.

In an April 27 note, BMO Capital Markets analyst Alex Arfaei said that despite his growing confidence in AbbVie's strategy to hold down commercial losses to Humira biosimilar competition, he does not think the pipeline offers sufficient potential to offset the eventual losses that will be sustained.

"While we have become more comfortable with AbbVie's IP defenses for Humira, we expect rapid erosion during the biosimilar years," the analyst wrote. "Moreover, we believe that AbbVie can't offset declining Humira sales during the biosimilar years. Therefore, AbbVie will likely trade at a discount to its growth."

Taking an opposing view, however, is Damien Conover of Morningstar, who said AbbVie boasts a "strong late-stage pipeline that should enable stable cash flows over the long term." In his April 27 note, Conover named Venclexta, ABT-494 and risankizumab all as future blockbuster sellers.

Adalimumab Biosimilars

There is already one adalimumab biosimilar to clear FDA, Amgen Inc.'s *Amjevita*, and Boehringer Ingelheim GMBH's BI 695501 is under review. Amjetiva was approved last September and was granted a positive opinion by the EU's Committee for Medicinal Products for Human Use (CHMP). The product has not been launched yet in either market due to ongoing patent litigation. A recent victory by Samsung Bioepis and Fujifilm Kyowa Kirin Biologics in the UK could pave the way for launch. Biomedtracker lists 20 sponsors currently working to develop biosimilar versions of adalimumab.

MAJOR M&A NOT NEEDED

If tax reform beneficial to AbbVie was enacted in 2017 or 2018, one of AbbVie's areas of focus beyond R&D spend would be accessing its ex-US cash to return more of Humira's proceeds to investors, whether by a special dividend or some other method, Gonzalez said.

Rubin followed up by asking if AbbVie would need to undertake further M&A activity to make its pipeline viable as the foundation for a spinout or if bolt-on acquisitions to bolster current pipeline areas would be necessary. Gonzalez indicated no major M&A is upcoming for AbbVie but added that its business development strategy always looks for ways to enhance existing franchises.

"For the most part, I'd say we have the major platforms that we need, so we don't envision the need for large platforms," the exec explained. "We did that work with both Pharmacyclics Inc. and with Stemcentrx Inc., and think we're well positioned for

that. There's certainly additional assets that we'd look for, but I'd say they look more like … individual kinds of products or smaller groups of products, would be a higher priority for us going forward."

Later on in the call, asked specifically about non-alcoholic steatohepatitis (NASH), an area of expanded deal-making activity in recent years, Gonzalez said it is on AbbVie's priority list for possible business development.

"What we do from a business development or licensing-and-acquisition standpoint is we have a strategic roadmap within each franchise of what we're looking for," he explained. "I can tell you NASH is on that roadmap. We haven't … found anything yet that has met the criteria that we're looking for that gives us enough confidence for us to pursue an asset. We've looked at a number of different things, and we'll continue to look. We have some internal efforts at an early discovery level, looking at some different mechanisms as well, but those are fairly early on."

In oncology, another growth field for AbbVie, Gonzalez highlighted the ongoing successful launch of Venclexta, while suggesting that recent Phase III failures with velaparib in squamous non-small cell lung cancer and triple-negative breast cancer would not prove a major setback for AbbVie's ambitions in cancer. Nonetheless, the company will not continue with development of the PARP inhibitor in those two indications.

"This program carried a higher degree of risk because we were testing a new hypothesis, that hypothesis being whether PARP inhibition enhances chemotherapy-induced DNA damage," Gonzalez pointed out. "While the outcome was not what we hoped for, we have not considered velipa-rib one of our near-term growth drivers."

Hematology stalwart *Imbruvica* (ibrutinib) brought in $551m in the first quarter, up 45% year-over-year, and showed strong continued uptake in the first-line CLL setting, the CEO said. "The most recent market share data indicate that we now hold the leading position in new patient starts in the front-line segment, with more than 21% of patients starting Imbruvica as front-line CLL therapy," Gonzalez said. "And given Imbruvica's duration of therapy, more than 30% of total treated frontline patients now use Imbruvica."

It was another tough quarter for AbbVie's HCV combination therapy, *Viekira Pak* (ombitasvir/paritaprevir/ritonavir tablets with dasabuvir), which netted global sales of $263m, down 22% from a year earlier, including domestic revenues of just $38m, a 70% decline. But AbbVie holds out hope for its next-generation combo regimen of glecaprevir and pibrentasvir, being evaluated for approval currently in the US, EU and Japan.

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ASLAN Firms Up IPO Plans As Lead Asset Progresses

IAN HAYDOCK ian.haydock@informa.com

Amid recent progress for its lead molecule, ASLAN has firmed up plans for the timing of its initial public offering, which is now expected to take place in Taiwan mid May with the newly listed shares set to begin trading in early June.

The Singapore-based, oncology-focused venture Aslan Pharmaceuticals Pte. Ltd., which is developing a pipeline of assets for Asia-prevalent tumor types, will float on the Taipei Exchange (TPEx) after holding an auction for the planned IPO in the middle of May.

KGI Securities is the lead underwriter for the offering, under which ASLAN expects to have paid in capital of TWD1,157m ($36.5m) and to start trading in early June.

CEO Dr. Carl Firth told *Scrip* at a conference in Tokyo earlier this year that the company viewed Taiwan as an attractive location for the float given its well-developed biotech sector, an active pharma/biotech sector, and strong investor interest in this. The IPO "will enable us to implement our development strategy going forward," he added in a new statement. ASLAN's basic business model is to acquire assets for cancer types common in Asia, develop these to proof of concept making use of the expertise and clinical capabilities available in the region, and then to consider licensing and partnership agreements with partners to aid commercialization.

There has been recent progress for ASLAN's pipeline with the acceptance by the China FDA of an application to begin a Phase II trial with its lead molecule varlitinib (ASLAN001), as a second-line therapy for biliary tract cancer. The Chinese study is now due to start recruiting in the fourth quarter.

A US IND has also just been approved for a global pivotal study with the drug - a reversible small molecule pan-HER (HER2/HER4/EGFR) inhibitor - in the same indication, for which there are currently no approved therapies.

The two-arm TreeTopp program will enroll around 120 patients who have failed first-line therapy across around 60 sites worldwide including in the US, Japan, Europe, South Korea and China, led by the MD Anderson Cancer Center's Dr. Milind Javie.

The primary endpoint is response rate and ASLAN says the study will enable accelerated approval in the US, where varlitinib already has orphan status for cholangiocarcinoma and gastric cancer. Orphan status for the second-line biliary indication has also been granted in South Korea.

ASLAN notes that studies indicate the HER mechanism may be important in biliary tract cancer, for which Biomedtracker shows that other drugs in Phase III development include Agios Pharmaceuticals Inc.'s IDH1 inhibitor AG-120, Delcath Systems Inc.'s melphalan kit, and AstraZeneca PLC's VEGF inhibitor recentin.

Originally licensed in globally by ASLAN from Array BioPharma Inc. for all indications, varlitinib has also completed Phase II studies in gastric and metastatic breast cancer.

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Roche Delivers Strong Quarter On Ocrevus Launch, Pipeline Promise

STEN STOVALL sten.stovall@informa.com

Roche's strong first quarter and promising array of innovative medicines left investors wondering why it didn't also lift its financial guidance for the year.

Roche left its financial guidance unchanged – at least for the time being – despite announcing better-than-expected quarterly sales and voicing confidence its pipeline and newly launched drugs will generate revenue and profit growth even as older therapies see their sales eroded by cheaper copies.

The company reported total group sales in the first three months of 2017 rose 4% to CHF12.94bn ($13.02bn) when measured at constant exchange rates. Pharmaceutical revenue came in at CHF10.2bn, up 3% when measured at constant exchange rates, and ahead of consensus forecasts.

Key franchises mostly performed well, with the so-called HER2 division that includes *Herceptin* (trastuzumab), *Perjeta* (pertuzumab) and *Kadcyla* (ado-trastuzumab emtansine) up 6% from the same year-ago period. Ophthalmology drug *Lucentis* (ranibizumab) had a particularly strong quarter, with sales up 9% at CHF392m.

Still, Roche stuck to its 2017 target of a low- to mid-single-digit sales growth rate, with similar core earnings per share growth.

"We had solid sales growth of 4% and major positive readouts this past quarter regarding our portfolio, but still it's very early in the year, so we concluded to stick to the guidance for the time being," Roche CEO Severin Schwan told analysts. "Depending on how things progress in the year we could possibly upgrade our guidance, but it is a bit too early at this stage."

Immuno-oncology remains a core focus as it continues to build its pipeline. But Schwann noted in interviews with journalists that there are other areas that it also plans to increase activity in, such as multiple sclerosis, hemophilia and ophthalmology. "We have a strong foothold in oncology and we are expanding into other therapeutic areas," he said.

GOOD START

A highlight of the first quarter was the US approval of *Ocrevus* (ocrelizumab) for the treatment of relapsing and primary progressive forms of multiple sclerosis, the first approved treatment for both forms of the disease. Around 90% of all MS patients are covered by the US label, according to the company.

> 'Depending on how things progress in the year we could possibly upgrade our guidance, but it is a bit too early at this stage'

Roche priced the drug at a level that won't hinder access – a strategy that seems to be borne out by the early launch reports. Initial sales have been strong, helped by a good safety profile. "We are off to a very good start with this in the US," Schwan said. "We launched at the end of March and there has been very good initial demand and it is one of the major opportunities for us for the future."

Pharma head Daniel O'Day noted that Ocrevus has been priced around $65,000 per year, "which we think is roughly in parity to the net prices of, if you like, the other MS drugs on the marketplace. What's probably most encouraging is that based upon this clinical data, based upon the benefit to patients, based upon our access programs, the adoption of Ocrevus in healthcare plans is progressing very, very well."

In Europe, Roche expects approval later this year. "We're continuing to proceed with the normal discussions with the regulatory authorities in Europe for the approval of Ocrevus. So, continued progress there as well," O'Day told the call.

He said further efficacy data were disclosed at the American Academy of Neurology (AAN) meeting in Boston that support early treatment with Ocrevus in relapsing MS, due to rapid onset of disease control after eight weeks. O'Day said the OPERA I and II trials suggested that "patients who switched from *Rebif* (interferon beta-1a) to Ocrevus experienced the reduction rate in annual relapse rate, T1 lesions and new and enlarging T2 lesions that was consistent essentially with the outcomes of the patients who received Ocrevus right away. So, after switching, they basically get the same effect as if they started originally with Ocrevus in a very short time period."

He said the trials showed strong sustained benefit of Ocrevus in relapsing MS patients after three years, with no new safety findings. "So, there was a lot of enthusiasm and excitement about Ocrevus at AAN – and it's up to a very, very good start," O'Day said.

FULL SAIL AHEAD

Roche is moving ahead with late-stage development for both of its anti-beta amyloid antibodies, crenezumab and gantenerumab, for Alzheimer's disease despite earlier failures for both drugs.

"You may say, why," O'Day acknowledged. "First and foremost … crenezumab and gantenerumab are distinct from each other. They both affect beta amyloid. However, they're effective in different ways. So, the binding studies generally show that crenezumab predominantly blocks the oligomers in the brain while gantenerumab primarily removes the plaque from the brain."

Although uncertainty remains about whether all or only some of these beta amyloid forms are predominantly responsible for the symptoms of Alzheimer's, O'Day said: "there's substantial evidence that both oligomers and plaques are toxic."

"Of course, it continues to be a program that carries high risk with it. But based upon the medical need, based upon the fact that this is a relatively conserved part of our overall R&D spend, we made a decision to move forward with both," he explained.

Roche has designed the late stage studies of crenezumab and gantenerumab to include gating mechanisms "that will allow us at interim reads to inform our decision-making and, if and as necessarily, take appropriate steps at that time," he added.

ANALYSTS APPLAUD

Overall, Roche's latest quarterly update was well-received by analysts, with many predicting better news to come. The general view seems to be that Roche is in a strong position to continue innovating in new therapy areas while also expanding its breast cancer franchise beyond Herceptin regardless of biosimilars, which the company now expects later this year in Europe, and in 2019 in the US.

"Roche management's tone was very bullish overall, especially on various compounds in its pipeline and upcoming data sets. We continue to think Roche is a good set-up in 2017," Bernstein analyst Tim Anderson said in a same-day note.

On the topic of biosimilar threats, Anderson added: "While this concern seems like it will never go away, in reality not much is going to be learned new on this topic in 2017; it won't be until 2018 and beyond that it starts to become easier to know how to model erosion [of sales due to bio-copies of Roche drugs]."

In the meantime, Anderson noted that Roche has one of "the most meaningful and active Phase III pipelines in 2017" in big pharma, "and it is most often pipeline traction that makes drug stocks work."

US TAX REFORM

Earlier in the day Schwan was asked on Bloomberg Television about what Roche thought about potential changes in the US tax landscape initiated by the Trump Administration.

"We certainly welcome if the US becomes more competitive on the tax side, but there are other factors in the US which are probably even more important to us than tax," the CEO replied.

Schwan expressed that Roche, which is domiciled in Switzerland, is attracted to the innovation culture and opportunities in the US. "Two of the most important innovation clusters are in the US and that is why we are there," he said. "That's the reason why we invest in the US. And I am very bullish on the US and think it will continue to reward this kind of innovation."

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Biogen's Spinraza Needs Long-Term Confirmatory Data, Says EMA

JOHN DAVIS john.davis@informa.com

The EMA may have quickly assessed the US biotech's antisense spinal muscular atrophy therapy for Europe, but the product's rapid clinical development means long-term data, and data on its effects in milder disease, or even cures, still need to be collected.

Although the clinical development of Biogen's antisense product *Spinraza* (nusinersen) for spinal muscular atrophy (SMA) in around five years is a remarkable achievement, it does mean the long-term effects of the product are relatively unknown.

In recommending approval of the drug on April 21 following review by the Committee on Medicinal Products for Human Use (CHMP), the European Medicines Agency notes that because patients treated with Spinraza have not yet been followed for a long period, it is not yet known whether the drug's effects will be maintained in the longer term, or indeed whether it will be a cure for some patients with SMA.

There is also only limited data on Spinraza's use in milder disease that is associated with a later age of onset and less severe outcomes, the EMA says. However, it can be assumed that Spinraza works the same way in milder and less severely-ill patients, and data will be collected post-approval to confirm that this is the case, the agency adds.

The EMA's comments are unlikely to affect the regulatory process of nusinersen that is fueled by the lack of therapies for SMA. The product has EU orphan drug status and is being reviewed under the EU's accelerated assessment program, reflecting the significant unmet need for an effective SMA treatment. SMA is usually diagnosed within the first year of life, and infants typically fail to sit up without help, exhibit little improvement in motor skills, and usually die within their first two years of life because of progressive muscle weakness.

The most common side effects seen in clinical trials with Spinraza were upper and lower respiratory tract infections, and constipation, the EMA noted. The drug is administered by intrathecal injection every four months, and final approval by the European Commission is expected in the next several months, adding to the Dec. 23, 2016, approval in the US.

Biogen exercised an option to license global rights to nusinersen from Ionis Pharmaceuticals Inc. in August 2016.

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In the US, there has been concern about the high price for the therapy, around $750,000 in the first year, and the slow initial uptake of the therapy. Biogen has said little about its reimbursement plans for Europe; as with all new drugs, the company will finalize the product's price with each EU country individually; the US biotech believes the drug has a "compelling efficacy profile" and has "the potential to make a meaningful impact for individuals with SMA in the EU, " it said in an April 21 statement.

The CHMP recommended approval of Spinraza for the treatment of 5q SMA, the most common form of the disease representing around 95% of all cases of SMA, based mainly on two studies, ENDEAR, in infantile-onset SMA, and CHERISH, in later-onset SMA.

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Read more about the studies CHERISH And NURTURE here: **http://bit.ly/2p1q1PT**

Bristol's Lynch Defends Lung Cancer Plans, Proclaims R&D Priorities

Opdivo first-quarter sales were still strong at $1.1bn, largely driven by lung cancer use and helping to drive overall performance, but potential approval of Merck's competing Keytruda with chemotherapy in first-line lung cancer is right around the corner.

EMILY HAYES emily.hayes@informa.com

Bristol-Myers Squibb Co.'s new chief scientific officer Thomas Lynch championed the company's lung cancer strategy and laid out immuno-oncology R&D priorities going forward, including a heavy emphasis on translational medicine, during Bristol's first quarter earnings call April 27.

The company reported sales of $4.9bn in the first quarter, which was above expectations and driven by better-than-expected performance of its PD-1 inhibitor *Opdivo* (nivolumab), its novel oral anticoagulant *Eliquis* (apixaban) and the CTLA-4 inhibitor *Yervoy* (ipilimumab), among other drugs (see table). Lynch and other Bristol executives spent a lot of time during the earnings call detailing the company's plans to maintain its immuno-oncology dominance as Merck & Co. Inc. and other competitors get closer to market with new PD-1/PD-L1 indications and combination regimens.

Opdivo's performance is noteworthy as the drug has been at risk of losing ground to Merck's competing PD-1 inhibitor Keytruda (pembrolizumab), which took the lead in first-line non-small cell lung cancer (NSCLC) in October 2016 with US FDA approval as a monotherapy in patients with high-expression of PD-L1 – an indication in which Opdivo failed as a monotherapy in the CheckMate 026 study. The FDA now is considering Merck's application for accelerated approval of a Keytruda/chemotherapy combination in first-line NSCLC with a user fee date of May 10.

Opdivo is approved for second-line NSCLC, melanoma, renal cell carcinoma and classical Hodgkin lymphoma. However, the company said during its earnings call that 55% to 65% of Opdivo sales in the US are in lung cancer and the PD-1 inhibitor's share of sales in that indication is even bigger outside of the US. But even with competition increasing in lung cancer, Bristol said that, contrary to prior expectations, Opdivo sales are set to increase in the US in 2017.

With strong first quarter performance for Opdivo and several other drugs, the company increased non-GAAP earnings per share (EPS) guidance to $2.85-$3.00 from $2.70-$2.90.

Bristol-Myers Squibb: First-quarter 2017 Sales Drivers

DRUG	FIRST-QUARTER SALES	% INCREASE FROM 1Q 2016
Opdivo	$1.12bn	60%
Eliquis	$1.11bn	50%
Yervoy	$330m	25%
Sprycel (dasatinib)	$463m	14%
Orencia (abatacept)	$535m	13%
Total	**$4.9bn**	**12%**

CHALLENGES AHEAD

Strong sales performance aside, many challenges remain. As BMO Capital Markets analyst Alex Arfaei said in an April 27 note, Opdivo appears to be hanging on to a more than 50% share of the second-line lung cancer market, but "the key question is, how long will this last?" The durability of Bristol's lung cancer dominance still is in doubt given the impressive launch of Roche's *Tecentriq* (atezolizumab), which was approved for second-line NSCLC in October 2016, and increased uptake of Keytruda in first-line NSCLC, following probable FDA approval of the Keytruda/chemo combination by May 10.

Yervoy beat analyst expectations by about 20% in the first quarter, which suggests better than expected uptake of the drug in adjuvant melanoma and for the combination with Opdivo in first-line melanoma, but "combo sales may be under pressure" following the release of results from the CheckMate 067 study, Arfaei commented.

Overall survival results from the CheckMate 067 study were presented at the American Association for Cancer Research meeting in early April. The Yervoy/Opdivo combination demonstrated a significant improvement in overall survival compared to Opdivo monotherapy, but some clinicians and analysts questioned whether the difference was big enough to make doublet use worthwhile, especially given the high rate of severe adverse events.

Chief commercial officer Murdo Gordon said that the 067 data have largely been viewed positively as confirmation of the combination's effectiveness. However, the exec added that for those who have used it and believe in the combination, the data confirm use, but those who have been skeptical, particularly about toxicities, remain concerned.

In addition to taking the lead in first-line NSCLC, Merck also is ahead in the co-development of PD-1 with IDO through an advanced partnership with Incyte Corp. to test the Keytruda/epacadostat combination in a Phase III melanoma study, though Bristol also recently announced it is stepping up development of Opdivo with epacadostat, with plans to start pivotal trials in NSCLC, head and neck cancer, and melanoma by the end of the year.

Bristol's recent actions surrounding IDO made some investors concerned that the company was losing confidence in the CTLA-4 inhibitor Yervoy and spreading its bets.

In particular, the latest developments raise more questions about prospects for the CheckMate 227 study of Opdivo/Yervoy in first-line lung cancer, following the company's recently announced decision not to file the combination for accelerated approval. Data from the multi-arm study are expected in the first half of 2018.

COMMITTED TO CTLA-4

Success in first-line lung cancer is crucial for Bristol's immuno-oncology strategy and it was up to new CSO Thomas Lynch to step up to the plate in vigorous defense of Bristol's lung cancer development plans in a range of areas during the first-quarter call, including CTLA4 inhibition.

Lynch moved from a role on the company's board of directors and assumed the position of CSO on March 16. He replaces Francis Cuss, who is retiring, but will be acting as an advisor for three months. Lynch is the former chairman and chief executive officer of Massachusetts General Physicians Organization and former director of the Yale Cancer Center.

The CheckMate 067 study validates CTLA-4 as an important partner for Opdivo and this is the only combination with a proven survival advantage, the exec noted. Bristol's deep commitment to CTLA-4 as a target is proven by the company's development of two other candidates with the same mechanism of action, one of which – BMS-986218 – just moved into a Phase I/II melanoma study in combination with Opdivo (NCT03110107).

"We believe it is important for Bristol-Myers Squibb to be looking at CTLA-4 as an important target," Lynch said.

However, Bristol realizes that there is no one size fits all for first-line lung cancer.

Lynch cited a New England Journal of Medicine paper on genomic diversity in lung cancer published by University College London's Jamal-Hanjani and other researchers with the Tracking Non–Small-Cell Lung Cancer Evolution through Therapy (TRACERx) project on April 26.

The TRACERx investigators examined 100 early-stage tumors with whole exome sequencing in a prospective cohort study.

"We observed widespread intra-tumor heterogeneity for both somatic copy-number alterations and mutations. Driver mutations in EGFR, MET, BRAF, and TP53 were almost always clonal. However, heterogeneous driver alterations that occurred later in evolution were found in more than 75% of the tumors and were common in PIK3CA and NF1 and in genes that are involved in chromatin modification and DNA damage response and repair," the *NEJM paper* reported.

NSCLC is really hard to treat due to the genomic diversity and there are multiple approaches to treatment, including IO/IO and IO/chemo combinations. Bristol is pursuing a broad, diverse, balanced approach in this indication, Lynch said.

The company has recognized IDO as an important next-generation target and acquired candidates in this space through the purchase of Flexus Biosciences Inc. for $800m up front in early 2015. The company believes it has a best-in-class asset through this deal (BMS-986205), but is partnering with Incyte on that company's epacadostat to be competitive from a timing perspective. Phase I/II data will be presented for the combination of epacadostat and Opdivo in a range of advanced tumors at the American Society of Clinical Oncology (ASCO) meeting in early June.

Bristol also will be presenting some early data for candidates aimed at the GITR and LAG3 immuno-oncology targets at the ASCO meeting.

Lynch noted that the company has 10 IO targets with 12 agents, with many possibilities for combinations.

Bristol wants to accelerate delivery of the next wave of immuno-oncology assets, understand the biology of resistance with a "laser-like focus" to overcoming it so that it will be possible to target tumors that have not historically responded to checkpoint inhibitors and continue to develop combination regimens, he said.

Looking ahead, Lynch said that the company is looking to build on its R&D resources in three areas. Bristol is aiming to enhance its translational medicine capability, with biomarker development that helps select the right drug for the right patient at the right time; it plans to invest in research of cancer biology; and it wants to invest in data analytics. Collaborations will help the company achieve its goals.

"Given the fast pace of scientific innovation happening today, collaboration across the entire health care ecosystem is becoming increasingly important," Lynch said.

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Kiadis Aims To Boost Stem Cell Transplant Market

SUKAINA VIRJI sukaina.virji@informa.com

ATIR101 has just been filed in Europe on the strength of data from single dose Phase II trial.

Kiadis Pharma Netherlands BV believes 30,000 patients in Europe and North America who need a hematopoietic stem cell transplantation (HSCT) could be helped with ATIR101, a cell-based product designed to enable HSCT from partially matched (haploidentical) family donors for blood cancer patients who do not have a standard of care stem cell donor available.

The firm has filed for regulatory approval of ATIR101 as an adjunctive treatment in HSCT for malignant disease using the company's single dose Phase II trial with ATIR101 as the pivotal study.

"The data generated thus far for ATIR101 has been very positive and we are optimistic that we will receive a positive outcome from the EMA during the second half of 2018, allowing us to make ATIR101 available to transplantation centers across the EU in 2019," said Arthur Lahr, who took over from Manfred Rudiger as Kiadis's CEO at the start of April. "Since the number of transplantation centers in the EU is limited, Kiadis could commercialize the product itself," he told *Scrip*. "It is a great achievement that Kiadis has reached this milestone on its own merit, which only a very few biotech companies accomplish, and it is testament to the strength of the unique data and of the Kiadis organization."

Positive data from the single dose Phase II trial were reported in December at the annual meeting of the American Society of Hematology (ASH). The data showed that ATIR101 significantly improved overall survival compared to a historical matched control. In addition, relapse and Graft-versus-Host-Disease (GVHD) rates were significantly lower than those reported for alternative approaches for HSCT. Specifically, ATIR101 did not elicit acute grade III-IV GVHD in any patient.

While Kiadis is hoping to secure EU approval on the strength of existing data, it won't pursue a US filing without completing a Phase III trial. Kiadis received regulatory approval from Canadian and Belgian authorities earlier this year to initiate a Phase III trial, and has also filed for permission to include US sites in the trial.

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Disrupt Or Be Disrupted

VIREN MEHTA

Biopharma managements remain understated in their public commentary on the implications of IT for their business prospects. To date, regulatory barriers and divided stakeholder interests have given the biopharma industry reasons for not addressing the IT frontier head-on, but tech pioneers can see major opportunities and will not be held back forever.

Many industries are being profoundly disrupted by IT. The survival of the publishing industry is in question as ad rates have plummeted in response to data and content transparency in the digital world. Digital technology has enabled pricing transparency that is fundamentally shifting spending patterns in travel, entertainment, transportation and many other industries.

The biopharma industry so far has not felt too much heat—thanks to the complexity of its business. But let it be noted that other industries looked complex in their own way—until, that is, some newcomers figured out ways to deploy the right tools to overcome the complexity. Often they succeeded in creating parallel channels to provide the necessary product or service, completely bypassing existing structures, while adapting regulatory barriers to their advantage. Uber and Airbnb are two of the better known examples.

DIGITALIZING THE PHARMA PIE

To appreciate the implications for biopharma, let us recall the way its economic pie comes together. Biopharma's share of US healthcare spending is approximately 15%. In round numbers, a tenth of this biopharma spending goes to the cost of producing the medicines, a fifth goes to R&D, and two fifths to selling, marketing, and operations, leaving an attractive profit that fetches the biopharma sector one of the highest stock market valuations. Production has already been greatly automated, and now IT promises to reshape much of the rest of the biopharma pie.

The benefits of IT in biopharma today are most evident in new product development, and especially clinical trials. From accelerated recruitment of patients into clinical studies, to wearables that simplify data gathering, to faster analytics and automated regulatory submissions, clinical development is beginning to benefit from new tools. These incremental improvements should make the D portion of the R&D spending more efficient, although the regulatory processes themselves are unlikely to improve quickly enough over the next decade to make a dramatic difference in how the value of new product development evolves.

The impact of IT on two other fronts, drug discovery and the way health consumers procure their healthcare, including drug therapies, promises to be more dramatic and quicker. IT tools are more effectively overcoming regulatory and other barriers along these two fronts, helping to combat healthcare and biopharma inefficiencies with the power of data.

Well over one-half of healthcare spending goes towards outpatient care, and a vast majority of biopharma's 15% share of healthcare spending is in the outpatient setting. The healthcare consumer today already has at her disposal an ever-expanding range of IT tools that break open the regulatory veil, educating her not only about the disease that needs to be treated, but more importantly, about the value of the various therapeutic alternatives. Equally importantly, US payer groups, including the US government bearing the majority of the US healthcare costs, are demanding transparency to assess the cost-benefit ratio of therapy options – and increasingly they are getting it. After all, they are the ones processing the health claims. This also is true of most centralized, single-payer healthcare systems of Europe and Asia. Payers around the world are sitting on data treasure troves. They are yet to fully deploy deep-data analytics, but they are beginning to do so.

The results will turn evidence-based medicine from a buzzword to a true analytic power accessible to all key stakeholders, patients, payers and prescribers alike, blowing apart the low-transparency business model of biopharma and forcing a value-focused transformation of every biopharma business practice. In the US, no longer will the next product automatically be paid for at a premium to the previous generation, and the days of regular price increases regardless of value addition are history. Above all, the industry strategy of increasing prices by extraordinary amounts on the eve of US patent expiry is increasingly untenable.

TELEMEDICINE

Mobile health tools are reducing the role of middlemen, enabling the patient to work via telemedicine with the most appropriate clinician, not just the physician. Many of these IT tools effectively adapt the regulations, enabling easier entry for new entrants, further intensifying the competitive landscape. These interlopers range from small mobile health start-ups to the Amazons, Apples, Googles, and Microsofts of the world who have already invested tens of billions dollars in deep-data intelligence, along with an aggressive push to integrate imaging and devices to greatly enhance the entire value chain, targeting healthcare system inefficiencies from diagnostics to treatment to monitoring.

IT integration is influencing new product innovation even more rapidly. Artificial intelligence is being fed an ever-increasing stream of life science data, leading to higher probability pathways, while pruning out potential dead-ends early. Here again, newcomers, from 21andme to Illumina to IBM, to mention just three, are not only selling their wealth of data to the biopharma companies, but, lacking the burden of big pharma bureaucracy, are deploying these insights into their own discovery platforms, ready to show that a new and truly valuable drug need not cost a billion dollars and take over a decade to reach the patient – nor would it necessarily entail the high selling and marketing costs of the traditional biopharma output.

One constant will remain: growth based on efficient innovation will be key to maintaining biopharma market valuations. But IT pioneers are challenging who qualify to be a part of this biopharma universe. It is time for the current biopharma managements to choose the path of the disruptor, or to be disrupted themselves.

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Viren Mehta founded and is managing member of Mehta Partners, LLC, a globally integrated boutique providing strategic insights to senior management teams in the biopharmaceutical sector for nearly 30 years.

Sanofi Scouting For Cancer Deals, Diabetes Drugs

Sanofi is seeking asset deals to bulk up its oncology pipeline in 2017 – specifically, the big pharma is on the lookout for oncology compounds with potential in prostate cancer or breast cancer, the company highlighted during its first-quarter earnings call.

LUCIE ELLIS lucie.ellis@informa.com

Sanofi's diabetes and cardiovascular products drastically missed their sales targets in the first quarter of the year – but the company has high hopes for its R&D pipeline this year and the spotlight is on oncology.

The French drug maker also highlighted during its April 28 earnings conference call that it is seeking asset acquisitions in the near-term, specifically oncology programs with potential in prostate and breast cancer.

Sanofi's 1Q 2017 In Brief

Group sales: €8.6bn, up from €7.8bn in 1Q 2016
EPS: €1.42
Global sales for diabetes products: €1.7bn, down by 6% from 1Q 2016
Global sales for rare disease products: €712m, up 8% from 1Q 2016
Global sales for MS drugs: €496m
Global sales for oncology products: €412m, up 13% from 1Q 2016

While Sanofi's current commercial portfolio is dominated by therapies for cardio-metabolic diseases and multiple sclerosis, as well as drugs for rare diseases, management highlighted the company's "multi-tiered" strategy in oncology during the call.

Sanofi said it would focus on continued development in oncology around its anti-CD38 molecule, isatuximab, which is currently in Phase III studies as a treatment for multiple myeloma and Phase II for acute lymphocytic leukemia (ALL).

Noting that CD38 is typically a target for myeloma therapies, Sanofi's president of global R&D, Elias Zerhouni, said that the target had potential in other cancers. "Science shows that CD38 has other potential indications, such as other hematology or [solid cancer] malignancies, and we're going to explore that," he explained.

Zerhouni added that Sanofi was also already assessing the use of its CD38-targeting, humanized monoclonal antibody in combination with other cancer immunotherapies, such as programmed cell death protein 1 (PD-1) inhibitors. "Science is showing that CD38 seems to be in itself a checkpoint inhibitor," Zerhouni said, adding that isatuximab was driving a "very important growth pillar" for Sanofi's overall R&D strategy.

Sanofi already has an ongoing collaboration with Regeneron Pharmaceuticals Inc. for the development of immuno-oncology combination therapies, and the two companies are jointly developing REGN2810, a PD-1 inhibitor that is currently in Phase II for advanced cutaneous squamous cell carcinoma. While analysts see little to distinguish Sanofi and Regeneron's PD-1 drug from the rest of the checkpoint field – which includes marketed anti-PD-1 products from Merck & Co. Inc. (Keytruda) and Bristol-Myers Squibb Co. (Opdivo), an approved PD-L1 compound from Roche (Tecentriq), and a slew of other PD-1 inhibitors in development – the next stage of cancer immunotherapy testing will focus on combination trials. As such, Sanofi and Regeneron will be hoping for success with their own in-house PD-1 product.

Under the initial agreement in 2015, Sanofi committed an investment of up to $2.17bn in the exclusive collaboration with Regeneron, including $640m in upfront payments and a potential sales milestone of $375m.

Now the big pharma is looking to up the ante for its immuno-oncology portfolio through M&A. "We are continuing to build on a complementary strategy to that of the Regeneron/Sanofi collaboration," Zerhouni said, adding that Sanofi would expand its offering in combination IO therapies, the "dominant approach in cancer control."

Analysts at Bernstein noted that "M&A remains something that could change the story in 2017 as Sanofi continues to hunt for targets."

DIABETES HEADWINDS WILL WORSEN

Meanwhile, Sanofi's 1Q call was dominated by discussion around the firm's sinking cardio-metabolic franchise in the US.

Despite group sales for the first quarter of 2017 coming in 3% ahead of consensus at €8.6bn, Sanofi is still being weighed down by its diabetes and cardiovascular portfolios due to increasing pricing pressures in the US – and this scenario is set to worsen throughout the year.

The firm's *Lantus* (insulin glargine) follow-on drug Toujeo – which was launched in 2015 in the US for the treatment of type 1 and type 2 diabetes – continues to underperform and in the first quarter of 2017 it saw sales of just €192m, missing analysts' estimates by 9%.

Analysts at Berenberg said in an April 28 note that overall Sanofi's 1Q 2017 glargine sales were down by 16% in the US, reflecting the impact of pharmacy benefit manager CVS Health's formulary exclusion. "Of note, Sanofi's US diabetes sales decline is expected to accelerate through the year as further formulary (United Health) exclusions take hold," analysts said.

Meanwhile, Sanofi's PCSK9 inhibitor *Praluent* (alirocumab), which is also partnered with Regeneron, missed sales expectations in the first quarter by 26%. The drug's poor performance, with 1Q sales of only €34m, is being blamed on payer utilization management restrictions in the US and limited market access in Europe. Praluent, an LDL cholesterol lowering drug, gained US regulatory approval in 2015 for the treatment of dyslipidemia.

The PCSK9 drug class has struggled in the last couple of years to gain market traction because of the availability of generic products on the cholesterol market, and in particular the common use of statins. Leading developers Amgen Inc. and Sanofi/ Regeneron are currently fighting to gain statin intolerant claims for their PCSK9 inhibitors *Repatha* (evolocumab), and Praluent, to expand the use of these drugs. However, the companies and regulators have struggled to agree on a definition for statin intolerance. The companies are having to carry out cardiovascular outcomes studies for these drugs and Amgen recently presented the first CVOT for the PCSK9 class at the American College of Cardiology annual meeting in March.

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Few Clouds On High-Priced, Ultra-Orphan Drug Horizon

With BioMarin's Brineura hitting the market with a $702,000 annual price tag, recent experience for other high-priced rare disease drugs supports the theory that payers will accept high costs for ultra-rare pediatric disease therapies.

MARY JO LAFFLER & EMILY HAYES

Pricing has never really been an issue for rare disease drugs, given the low exposure payers have to the therapies and the significant benefits usually offered. But with ultra-orphan price tags ticking higher and higher and drug pricing a simmering political controversy in the US, it is worth checking on the experience of recent launches as BioMarin Pharmaceutical Inc. introduces its Batten disease therapy *Brineura* (cerliponase alfa) at just over $700,000.

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Two antisense oligonucleotide therapies approved last year for different neurodegenerative conditions, Biogen/Ionis Pharmaceuticals Inc.'s *Spinraza* (nusinersen) for spinal muscular atrophy (SMA) and Sarepta Therapeutics Inc.'s *Exondys 51* (eteplirsen) for Duchenne muscular dystrophy (DMD), offer relevant case studies for the sort of reception BioMarin could face for Brineura.

Both drugs, like Brineura, were the first approval for rare, life-threatening diseases that affect children – a fact that could mean a lot to payers as companies seeks favorable reimbursement. But the Biogen/Ionis and Sarepta drugs both came to market with extremely high prices in the midst of a volatile debate over rising prescription drug prices; Spinraza costs $750,000 for the first year and $375,000 each year after that, and Exondys comes in at $300,000 annually.

And, in February, Marathon Pharmaceuticals LLC was set to debut its DMD therapy *Emflaza* (deflazacort) at a cost of $89,000, but abandoned the launch days later amid controversy over the price. PTC Therapeutics Inc. purchased the rights to Emflaza, which has been available generically overseas for decades, and has signaled it will revisit pricing.

That has left lingering concerns about whether high prices would put up any roadblocks to access for Spinraza and Exondys, which would likely also affect Brineura. The companies' first-quarter sales and earnings reports, however, show that the expensive therapeutics are performing well right out of the gate.

SPINRAZA'S SUCCESS

Biogen reported Spinraza is off to a strong start – a performance that was unexpected given that the company was signaling a gradual uptake while reimbursement was put into place.

"We are still in the early days of the launch and have much more to achieve. We will not be satisfied until all of the patients and families that seek this treatment are able to receive therapy," CEO Michel Vounatsos told the firm's April 24 earnings call. "This will take some time and tremendous effort from many, such as the dedicated medical teams that treat SMA, the passionate families, the remarkable advocates that rally for these patients, and our team of committed Biogen professionals, all of whom have been working seemingly non-stop to secure access and building up point of care."

Vounatsos hinted at a couple of factors that have proven to be critical in successful rare disease launches – working with patient advocacy groups and offering a suite of support services, including running interference with insurers. BioMarin has its own "RareConnections" support program and will work on disease awareness.

Biogen's CEO estimated that 75% of commercially insured lives in the US have a health plan with an established policy on Spinraza, and half of those have broad access. So far, the drug has been approved for individual use by 100 commercial plans, he said. As for Medicaid, 65 plans have covered use with 20 having a formal policy and half of the covered lives having broad access, he added.

> 'We are still in the early days and have much more to achieve. We will not be satisfied until all of the patients receive the therapy'

There had been concerns that use would initially be limited to patients with Type 1 SMA, the form that is most severe and affects infants, though the approval covers all types in adults and children. Most Spinraza patients have been Type 1, but there has been approval for Type 2 and 3, Vounatsos said. Even in plans without a policy or with a restricted Type 1 policy, "often patients are still able to get approval through an appeal process or medical necessity request," the CEO added. Biogen also has new data from the CHERISH trial it thinks will help expand use and access.

"In the US, it continues to be our goal that no patient will forego treatment because of financial limitation or an insurance denial. To date, roughly 25% of units dispensed have been provided through the free drug program," Vounatsos said. Outside of the US, Biogen has 353 Type 1 patients enrolled in an expanded access program "across 20 countries, of which 306 of those patients are in Europe." Spinraza was recommended for approval in the EU on April 21, though regulators called for long-term data to show sustained effect.

"With respect to Europe, we effectively have been putting pre-launch efforts in place on a country-by-country basis, prioritizing, obviously, those countries that we expect to get reimbursements earlier as opposed to later," CFO Paul Clancy added, including Germany, the Nordic countries and the UK. "And I think it's going to be a very similar dynamic with respect to trying to accommodate and get through infusion capacity."

The price tag hasn't been the only obstacle for Spinraza – the infrastructure for administering the drug is also a challenge. So management was clear that obstacles remain. "Insurance coverage has been and remains a bottleneck," Vounatsos declared. But "motivated families, patients, parents, advocacy groups, a professional team at Biogen, dedicated providers, the leadership of the hospital," have all been factors helping to progress the launch.

"It's a battle every day, and we are not yet where we want to be," the CEO stated.

SAREPTA WINNING

Sarepta reported in its April 27 call that the Exondys launch was going well. The drug was approved after a controversial review by FDA in September 2016, securing labeling with no restrictions for age or ambulatory status, despite concerns about the efficacy data supporting the filing.

Payers initially balked at the annual price of $300,000, with some denying coverage, but the company says they have been coming around.

Sarepta reported $16.3m in first-quarter sales of Exondys 51, up from $5.5m from its short time on the market in the fourth quarter. Pleased with the launch, the company raised its full year revenue guidance from $80m to exceeding $95m.

Alexander Cumbo, senior vice president of global commercial development, said that the company continues to have productive discussions with payers and has made significant progress securing reimbursement for patients.

The mix of commercial to Medicaid carrier coverage among current patients taking the drug is about 60%/40%. Medicaid coverage continues to grow – most states take six months to review a new drug and a lot of plans put a policy in place this quarter, Cumbo said. One of the biggest ones to come on board is California, with the help of key opinion leaders (KOLs).

"California put out a policy that's very favorable. It's broad access. And they reached out to a lot of the KOLs to help design this policy. A lot of the KOLs throughout the country understand what California did and they're pushing their states to do the same. And a lot of the state plans are actually looking toward California, of how they came up with this policy. So I think it's a very positive trend to come. Obviously, we have a lot of work to do. We do have a lot more visibility heading into Q2 than we did in Q1," Cumbo said.

Much like getting patient advocacy groups involved, something Sarepta benefited from throughout the regulatory process, leveraging KOLs and mobilizing the practitioner community can be a significant factor in gaining coverage. Roger Longman, CEO of reimbursement consultancy Real Endpoints, suggested physician requests might help improve market access for PCSK9 inhibitors – cholesterol-lowering drugs that have been criticized for costing roughly $14,000 per year for a much wider population.

Despite concern about payers limiting use to only the most severe patients, the experience with Exondys and Spinraza is not bearing that out. Much like Biogen reported that Spinraza is being cleared for use in patients with different levels of SMA, Cumbo noted that "both ambulatory and non-ambulatory [DMD] patients are obtaining access" to Exondys.

> 'It's a battle every day, and we are not yet where we want to be'

Cumbo also said that Sarepta has not observed issues with reauthorizations for access to the drug, which are a standard part of the reimbursement process.

Awareness matters: Sarepta reported genetic testing has been increasing and will help make for a successful launch. Biogen execs noted that a key element for Spinraza will be newborn screening for SMA.

Thinking globally, where market access can be even more difficult, Sarepta is working on distribution agreements and a managed access program in territories outside the US and expects those agreements to be finalized in the coming months.

CEO Edward Kaye announced during the call that he is resigning as president and CEO when his current employment term ends this year in order to "focus on the next series of key initiatives for Sarepta." These include approval of Exondys in Europe and development of next-generation therapies for DMD, such as gene therapy – a category of treatment that's also likely to ring pricing alarms.

Kaye said that he will be helping recruit a candidate for the position of president and CEO, and will then serve as an active board member and special regulatory and scientific advisor.

Of course BioMarin, a pioneer of enzyme replacement therapies, is no stranger to rare diseases or high cost therapies. The company helped establish the orphan drug business model, giving presentations over the years about the financial benefits of low development costs relative to pricing for rare disease drugs. But even though there's experience and evidence behind Brineura, it's not just the payer climate that sponsors must be wary of – the political climate is still poised for change.

President Donald Trump has repeatedly called out the biopharma industry for high drug prices, notably accusing pharma companies in January of "getting away with murder," and the populist president is expected to return to the issue at some point during his term.

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For details of the Brineura approval, see BioMarin Expects 30% Markdown For Orphan Pediatric Drug Brineura

Almirall To Position Oral DMF For Psoriasis Ahead Of EU Biologics Use

STEN STOVALL sten.stovall@informa.com

Almirall aims to start selling its unpatented fumaric acid derivative throughout Europe in the third quarter for treating plaque psoriasis, but will not seek approval for the medicine in the US.

Spain-based Almirall SA will roll out its as-yet unpatented fumaric acid derivative throughout Europe in the third quarter of 2017 as a first-line induction and long-term treatment for adults with moderate-to-severe chronic plaque psoriasis, offering, it says, a much cheaper option than new, highly-priced biologic therapies.

The Barcelona-based drug maker is readying plans for EU commercialization of its oral dimethyl fumarate (DMF) treatment after winning backing from the European Medicines Agency's (EMA) top advisory drug panel, the Committee for Medicinal Products for Human Use (CHMP). The expected final approval by the EU Commission in coming months will allow the medium-sized pharma to sell its fumaric acid derivative – branded as Skilarence and currently only available in Germany in a different composition – to the rest of the European Union.

Almirall believes it will be welcomed as a moderately priced, effective product in the region where healthcare budgets are under extreme pressure.

"This is a very good product. It's not expensive. So we expect broad take-up of this product by European healthcare systems, and therefore big market share," Almirall investor relations spokesperson Pablo Divasson del Fraile told *Scrip* in an interview.

He said that's because Skilarence will be much cheaper than any biologic drugs, such as Novartis AG's *Cosentyx* (secukinumab). "We estimate that, in some cases, it will be between 60% and 70% cheaper than an available biologic alternative," Divasson del Fraile said, adding: "Healthcare systems in the EU will like that. It's an affordable molecule, not an expensive biologic." He declined to give price details or outline Almirall's commercialization plans.

NO PATENT PROTECTION

The Spanish company has no patent yet on its dimethyl fumarate pill at the moment but Almirall has filed a patent application in Europe and other territories which covers the specific pharmaceutical composition of Silarence. If granted, this patent would expire in December 2034.

Almirall says it is nonetheless confident the IP underpinning the therapy will be safe on grounds that, once it receives marketing authorization, Skilarence will have ten years of regulatory data protection in the EU.

Divasson del Fraile also said the Spanish company is also confident it won't face rival equivalent copies in any case, due to practical hurdles. "Our assumption is that it will cost too much and take too long for a potential copycat of Skilarence to be made from scratch," he told *Scrip*.

The CHMP recommendation backing Skilarence was based on research that had been in part already generated, he said. The underlying reference was positive results from a randomized, double-blind, placebo-controlled Phase III trial called BRIDGE.

Biomedtracker Analyst Sara LaFever told *Scrip* that "there were some very strong top-line results from BRIDGE that showed both superiority to placebo and non-inferiority to Fumaderm, so the CHMP opinion is not surprising. We would expect a positive approval decision from the EU Commission by mid-2017."

Biogen Inc. markets dimethyl fumarate and three monoethyl hydrogen fumarates – calcium, magnesium and zinc salts – as Fumaderm in Europe, where it has been widely prescribed for the systemic treatment of moderate-to-severe plaque psoriasis, a condition manifested by inflamed, red skin with silvery scales. Systemic drugs affect the entire body, and are typically used when the skin condition covers more than 3% to 10% of the patient's body and other methods haven't worked, such as phototherapy and treatments applied to the skin, such as creams, ointments, solutions and foam.

Almirall has said it expects Skilarence to be positioned where other oral systemic therapies – acitretin, methotrexate. and ciclosporin – are clinically inappropriate for patients, due to lack of efficacy, contraindications, tolerability and/or toxicity issues, or patient preference, and prior to treatment with biologics. The company believes Skilarence will therefore postpone use of systemic biologic therapies.

NO US FILING PLANNED

Almirall says it expects annual sales of Skilarence in the EU to reach at least €50m within a few years. Divasson del Fraile would not divulge exactly when that would be achieved, though.

Skilarence will only be sold in Europe, however, because Almirall doesn't intend to file the treatment for approval in the US, on grounds the process would be too expensive and time-consuming.

"The studies that have been done and which we used for applying for marketing authorization only applied for Europe. In order to file for the US market, that would necessitate other studies which would take much more time," Divasson del Fraile said.

"We felt this product could be approved more quickly in Europe. When we started to study this product's possibilities we initially thought it would be best to launch first in Europe and then move it to the US market but we're now not planning to do that. We're not going to launch similar studies in the US. It would be too expensive to do that for a company our size – and they were probably going to be more difficult to do if we did."

"In Europe, we were using some studies which had already been conducted and available in Europe. Studies in the US would need to be done from scratch. In the case of the US, we would have needed to develop those studies solely by ourselves," he explained.

Announcing the CHMP recommendation, EMA said Skilarence will be available as 30mg and 120mg gastro-resistant tablets.

"Further details behind the CHMP recommendation will be published once the EU Commission makes its final decision on the therapy's European marketing status," he said.

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Novartis Claims New Drugs Will Fuel Growth, Not M&A

Novartis sees itself engaging in only modest M&A activity to avoid over-paying for targets – and will rely on newly launched drugs and promising external targets to grow sales.

STEN STOVALL sten.stovall@informa.com

Novartis AG says its investments in innovative growth drivers are paying off and should lead to resumed sales growth next year - but don't expect the Swiss group to make a big acquisition to help achieve that, because prices for potential targets don't offer adequate value.

That was the message from Novartis' management April 25 when outlining the group first-quarter 2017 sales and profit figures, which were broadly in line with market forecasts despite weakness at its Alcon Inc. eye care division and Sandoz Inc. generics unit, and continued competition from generic versions of its one-time oncology blockbuster *Glivec/Gleevec* (imatinib mesylate).

"Our growth drivers, including *Cosentyx* (secukinumab) and *Entresto* (sacubitril/valsartan), more than offset the impact of generic erosion … In total, sales from our key innovative medicines growth drivers increased 27% in the quarter," Novartis' finance director Harry Kirsch told analysts when presenting the first-quarter update. The company currently has six main therapeutic areas of interest: oncology, cardiology, neuroscience, immunology and dermatology, respiratory, and ophthalmology.

GUIDANCE UNCHANGED

Its solid performance in the first quarter allowed the group to leave its 2017 guidance for continuing operations unchanged. Novartis is forecasting net sales to be broadly in line with 2016 when measured at constant exchange rates.

Analysts used much of their call with management to ask whether the revamped company would engage in a major M&A transaction. The company said it continues to look primarily at bolt-ons ranging between $2bn to $5bn in size - and is having a difficulty finding targets, due to upward valuation trends for likely assets.

"We're having a hard time finding value-generating acquisitions even in that range … So what you've seen us do is move upstream a bit," chief executive Joe Jimenez said. "These are nice assets that are supplementing our pipeline; we're structuring them in a way that somewhat share the risk given that they're earlier stage assets, but we're finding that we can create a significant amount of additional value that way," Jimenez added, referring to recent asset deals.

SEG101 PLANS ADVANCE

One such acquisition – the December purchase of Selexys Pharmaceuticals Corp. – brought with it the monoclonal antibody *SEG101* (crizanlizumab; formerly SelG1) which inhibits p-selectin and showed a statistically significant reduction in sickle cell pain crises at the antibody's highest dose in the Phase II SUSTAIN clinical trial, data of which was presented at ASH in December 2016.

Based on that study's results, Novartis announced it will submit an approval application for SEG101 in the US during the second half of next year and in the EU sometime in 2019. But the company expects to conduct an additional PK/PD (pharmacokinetic/pharmacodynamic) bridging study beforehand.

"We've been able to accelerate the filing from 2020 to 2018 based on a single Phase IIb study," explained Vas Narasimhan, Novartis' chief medical officer, adding: "we need to transfer the manufacturing and then upscale the final manufacturing process [of SEG101] … You have to remember that this was a small biotech that was developing this product. So as soon as we have the material available we then do a standard PK/PD bridging study which the FDA often requires when you move to final manufacturing for a biologic and based on the timeline of the read-out for that study, we will file," Narasimhan said, adding: "There's nothing abnormal about SEG101."

BAF31 FILING DATE

Novartis also used the quarterly update to confirm it will not file new multiple sclerosis drug BAF312 (siponimod) until 2018. This is later than some optimistic scenarios foresaw, but still ahead of a more conservative case for 2019. The filing is to be in relapsing MS as opposed to secondary progressive MS. That indication "is suggestive of more modest differentiation from current therapies than was originally assumed," analysts at Deutsche Bank said in a reaction note.

Explaining the timing rationale, Narasimhan said: "This is a more complex manufacturing process than you'd typically see in a small molecule. There are a few steps in the chemical synthesis that are unique, and so we just have to get this finalized. We'll then file [BAF312] in the first part of next year."

ENTRESTO'S $500M TARGET

Another clear message conveyed by management was the apparent resurgence of heart drug Entresto which, after a lacklustre launch, has begun to accelerate, clocking up $84m in global sales in this year's first quarter, and compared with just $17m in the year-ago quarter.

Management reaffirmed the $500m sales aspiration for the therapy.

Asked whether the drug can hit that target without further acceleration, Paul Hudson, who heads Novartis' pharmaceuticals operations, replied: "Our trend is good. The global number of $500m is definitely achievable."

Hudson said the full deployment of the Novartis sales force for the product "happened at the beginning of the year and the true operational impact will come late summer or autumn. So we feel good about that progression." Entresto is now approved in 78 countries and launched in more than 35 countries to date.

"It's also worth adding that we recently just came on line in Italy and Canada with Entresto. We'll get entrance into France hopefully on the back end of the summer," he said, adding that HTA authorities in Germany recently gave the green light for reimbursement there, Europe's biggest national economy.

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

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Selected clinical trial developments for the week 21–27 April 2017

LEAD COMPANY/PARTNER	COMPOUND	INDICATION	COMMENTS
Updated Phase III Results			
Roche	*Ocrevus* (ocrelizumab)	relapsing and primary progressive multiple sclerosis	OPERA I, II, ORATORIO; outcomes continue to be favourable.
GW Pharmaceuticals PLC	*Epidiolex* (cannabidiol)	Dravet syndrome, Lennox-Gastaut syndrome	GWPCARE1,4: convulsions reduced.
Sanofi	*Aubagio* (teriflunomide)	first-episode multiple sclerosis	TOPIC; positive effects on cortical gray matter atrophy.
Pfizer Inc. /AstraZeneca PLC	*Zavicefta* (ceftazidime plus avibactam)	hospital-acquired pneumonia	REPROVE1; first detailed data in this indication.
Merck & Co. Inc./AiCuris GMBH & Co. KG	letermovir	CMV infections	Significantly reduced infection.
Paratek Pharmaceuticals Inc.	omadacycline	skin and skin structure infections	OASIS; confirmed efficacy.
Sumitomo Dainippon Pharma Co. Ltd.	dasotraline (SEP-225289)	attention deficit hyperactivity disorder	Study 305; positive results in children.
Phase III Completed			
Biogen	*Spinraza* (nusinersen)	spinal muscular atrophy	CHERISH; improved motor function in later-onset disease.
The Medicines Co.	*Carbavance* (meropenem plus vaborbactam)	urinary and respiratory tract infections	TANGO1; non inferior to active comparator.
Phase III Interim/Top-line Results			
Auris Medical Holding AG	*Keyzilen* (esketamine)	tinnitus	AMPACT2; positive safety profile in chronic intermittent use.
Eli Lilly & Co.	abemaciclib	breast cancer	MONARCH 3; improved PFS .
Eli Lilly & Co.	*Cyramza* (ramucirumab)	first-line gastric cancer	RAINFALL; improved PFS.
AbbVie Inc./Enanta Pharmaceuticals Inc.	glecaprevir/pibrentasvir	hepatitis C	Endurance 3; high SVR12 rates after eight weeks of therapy.
Jazz Pharmaceuticals PLC	JZP-110	narcolepsy	TONES 2; positive results.
Phase III Initiated			
ObsEva SA/Kissei Pharmaceutical Co. Ltd.	OBE2109	uterine fibroids	PRIMROSE 1, 2; an oral GnRH receptor antagonist.
Kyowa Hakko Kirin Co. Ltd.	*Siliq* (brodalumab)	axial spondyloarthritis	Study 006; in Asia.
Pfizer Inc.	lorlatinib (a ALK/ROS1 inhibitor)	non-small cell lung cancer (NSCLC)	CROWN; versus crizotinib in ALK-positive/ROS1 patients.
Ultragenyx Pharmaceutical Inc.	triheptanoin	glut1 DS movement disorder	Paroxysmal movement disorders.
Acorda Therapeutics Inc.	tozadenant	Parkinson's disease	TOZ-CL-06 long-term safety study.
Aldeyra Therapeutics Inc.	ADX-102	non-infectious anterior uveitis	Sequesters free aldehydes.
Phase III Announced			
Acceleron Pharma Inc./ Celgene Corp.	luspatercept	first-line lower-risk myelodysplastic syndromes	To start in early 2018.
Can-Fite BioPharma Ltd.	piclidenosan	rheumatoid arthritis	ACRobat; to replace methotrexate.

Source: Biomedtracker

Genfit's Enrollment Delay In NASH May Aid Intercept's First-To-Market Goal

JOSEPH HAAS joseph.haas@informa.com

Firm cites heavy competition for NASH patients, as well as desire for balanced enrollment in elafibranor pivotal study. Competitor Intercept pushed back its Phase III enrollment timeline this past February.

Genfit SA's announcement April 24 that it will need more time to enroll the first 1,000 patients in a Phase III study for its non-alcoholic steatohepatitis (NASH) candidate elafibranor likely increases the edge Intercept Pharmaceuticals Inc. already had in reaching the market first with its own Phase III candidate, Ocaliva (obeticholic acid).

First to market probably won't determine the ultimate winner in the NASH sweepstakes, but both companies, the first to reach Phase III in the indication, covet the possibility. Numerous companies are targeting the unmet medical need, as evidenced by the clinical trial and biomarker data in NASH presented during the European Association for the Study of the Liver conference in Amsterdam, April 20-23. (See related article.

With elafibranor, a dual agonist of PPAR alpha and delta, and obeticholic acid (OCA), a farnesoid X receptor (FXR) agonist, Genfit and Intercept have been at the forefront of a growing pack of companies targeting NASH. But that burst of developmental activity is making clinical trial enrollment difficult – both firms have now pushed back the timelines for their Phase III trials.

Intercept conceded in February that it was likely to miss its mid-2017 goal for enrolling its pivotal REGENERATE trial, but the New York-based firm is also making protocol changes to power analysis for either of two co-primary endpoints. At the time, it said it was expecting to enroll the 750 patients (of 2,000 total) needed for an interim analysis sometime mid-year, rather than during the first half of 2017; the estimated timing for interim analysis, in 2019, was unchanged. There had been concerns about the speed of enrollment in REGENERATE.

Now Genfit has announced a similar setback, pointing to heavy competition for patients among numerous drug candidates being tested in NASH as well as a desire to "ensure enrollment quality" for its RESOLVE-IT study.

While reporting its first quarter financials on April 24, Genfit said enrollment of patients with F1 fibrosis scores is proceeding ahead of schedule, but that of patients with scores of F2-F3 is occurring on "a more moderate enrollment curve compared to the initial projections." The biotech now expects to complete enrollment of 1,000 patients, needed for an interim evaluation in a trial expected eventually to enroll 2,000 participants, during the first quarter of 2018 – pushing back its timeline between four and six months. Previously, the company guided that it would reach 1,000 enrollees by mid-2017.

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APPOINTMENTS

GammaDelta Therapeutics Ltd. has appointed ***Paolo Paoletti*** CEO, ***Natalie Mount*** chief scientific officer and ***Dayle Hogg*** chief operating officer. Paoletti brings over 20 years' clinical, commercial and leadership experience in the pharma industry and previously, he was president GSK oncology and most recently, CEO of Kesios Therapeutics Ltd. Mount joins the company from cell and gene therapy focused Catapult, where she was chief clinical officer. Before this, she was at Pfizer for 16 years, where she led the developmental activities across various therapeutic areas. Hogg joins GammaDelta from Kesios Theraeutics, where he was chief operating officer. GammaDelta has also named Raj Mehta director of intellectual property, alliance management and business development following his role as commercial founder and interim CEO of the company.

UK, based **Neuro-Bio Ltd.** has appointed ***Robert Haigh*** chief operating officer. Haigh carries over 25 years of senior management and board level experience in pharmaceutical and biotech companies and joins Neuro-Bio from KalVista Pharmaceuticals Ltd. Haigh was chief operating officer at KalVista, a company he co-founded in 2011, before it merged with Carbylan Therapeutics. He started his career in 1992 at Boehringer Ingelheim, where he was a member of the team that discovered the cardiovascular drug Micardis.

Bayer has appointed ***Bhavesh Ashar*** senior vice president and head of oncology for the company's US pharmaceutical division. Ashar was vice president and general manager of US oncology Sanofi, where he spent over 14 years holding positions of increasing responsibility in sales and marketing. Before Sanofi, he was an engagement manager with McKinsey & Company.

Cardiovascular and metabolic diseases focused **Renova Therapeutics** has appointed ***Waldemar Radziszewski*** executive vice president of translational research and ***Peter Gengo*** vice president of preclinical research and pharmacology. Most recently, Radziszewski was vice president, immunology development unit and site head, biopharmaceuticals clinical development, at Sandoz. Before this, he spent 18 years holding senior leadership positions with Merck Research Laboratories and Johnson & Johnson companies, including Janssen Research & Development. Gengo is a biochemical analytical pharmacologist and brings more than 30 years of research and leadership experience to Renova from various companies, most recently the cardiovascular & metabolic disease unit at Merck & Co.

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General Enquiries:

Natalia Kay | Tel: +44 (0) 20 7017 5173 | Email: natalia.kay@informa.com

Sponsorship and Table Booking Enquiries:

Chris Keeling | Tel: +44 (20) 337 73183 | Mobile: +44 (0) 7917 647 859

Email: christopher.keeling@informa.com

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