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Pfizer Hits Pause On M&A To See How US Tax Reform Plays

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Pfizer Inc. isn't likely to make any big M&A moves soon given that Congress might shortly take up potential changes to US tax policy. CEO Ian Read said large-scale M&A is largely on hold until there is more clarity around tax reform.

"Tax reform will change the net value of assets in the marketplace in various ways, and we think it's prudent to wait for a decision on tax reform so that we can really understand the valuation of our assets as we do these reviews," Read said during the company's second quarter sales and earnings call on Aug. 1.

Some investors are eager to see Pfizer make a big acquisition as the focus on near-term growth drivers intensifies.

"We will look at the circumstances and the asset prices and determine the appropriate capital allocation when we feel that we have a realistic handle on what asset prices truly represent," he said. "Right now, we need to see tax reform or the absence of tax reform to understand the market values."

Pfizer's chief executive has been a big proponent of tax reform and has talked for many years about how elements of the US tax system prevent US drug companies from competing on a level playing field with their international rivals. Since 2014, the New York-based company made two tax-motivated acquisition attempts as part of an effort to relocate the big pharma to a friendlier tax domicile. The first was **AstraZeneca PLC** in 2014 and the second was **Allergan PLC** in 2015.

Both deals fell apart, the second one spectacularly in 2016 when the US Treasury stepped in at the eleventh hour with new rules to reduce the economic benefits of tax-motivated inversion deals. *(Also see "It's The End Of Pfizergan, So Pfizer Will Have To Grow It Alone" Scrip, 7 Apr, 2016.)*

Now that congressional leaders say they are turning attention to tax reform, Pfizer isn't planning any big shakeups until it can see what gets done. There is no guarantee Congress will be able to reach an agreement on tax reform and in a timely manner, particularly after the way health care reform has unfolded. The general thinking has been that broad tax reform or even a tax holiday on cash held overseas could usher in an M&A boom in the sector.

Many US-based multinational pharmaceutical companies hold the majority of their cash overseas to avoid paying the high 35% corporate tax rate, limiting the way it can be used. *(Also see "Pharma Is Ready And Waiting For A Tax Holiday Under Trump" Scrip, 9 Nov, 2016.)*

Pfizer has a tax reform wish list, chief financial officer Frank D'Amelio revealed. The company's top priority for tax reform is a territorial tax system, whereby taxes would only be levied on domestic income. Second is repatriation, he said, referring to cash held overseas that could be brought to the US at a lower tax rate. The third priority is lower corporate taxes, he said.

The call for Pfizer to complete a big merger have been growing since the company decided against a break up last year. But finding a good target at a fair value isn't easy. Pfizer has received a lot of push back from investors after buying **Medivation Inc.** last year for $14bn, especially after sales of the

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from the editor

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For pharma, smiling and waiting has been a pretty effective tactic for enduring/enjoying the Trump presidency thus far. President Trump repeatedly promises master strokes to advance reforms in health care provision, drug pricing, regulations and corporate taxation, but then splashes noisily, apparently unable to move forward.

Trump's threats to stop the industry "getting away with murder" on medicine pricing, after a knee-jerk and transitory wobble in investor confidence in the sector, look unlikely to inflict severe pain on drug makers. If a leaked draft executive order on the matter is anything to go by (and who knows if it is), action means cutting back on regulations that are seen as adding cost, reining in price-inflating intermediate actors in the supply chain, and turning the screws in international trade relations, including attempting to apply upward pressure to drug pricing outside the US. Not raiding pharma firms' profits by imposing mandatory drug price cuts or capping price rises or forcing through a radical competitive bidding process in the US. All this without pharma raising its voice to defend its corner.

Nor has pharma got noisy against Trump's threats to immigration, and to date his bark has proven louder than his bite on this too.

Meanwhile, Pfizer's Ian Read continues to hold his breath also regarding M&A, postponing big deals while he awaits more clarity on tax reform (see cover story). Where Read is explicit, others are quietly observing the same stasis, leaving the long-expected boom in biopharma acquisitions still unrealized. This probably hurts bankers and lawyers more than big pharma.

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Shaky Q1 For Lupin But Upbeat On FDA Generics Reform, Biosimilars
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Lupin reported a weak first quarter, but the management sees "tremendous upside" in opportunities arising from the US FDA's recent initiatives to encourage generic competition. A build-up also appears on the cards for biosimilars, where the company now has a "financing partner" for a project.

Horama's Gene Therapies For Retinal Diseases: Fast Followers?
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French biotech Horama has built-up its executive team and has two potential gene therapies for retinitis pigmentosa nearing the clinic.

Spark Therapeutics' Vision Loss Gene Therapy Heads For EU Market
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A gene therapy for inherited retinal conditions leading to blindness could be marketed in Europe in 2018, but needs to avoid the setbacks dealt to UniQure's gene therapy, *Glybera*, that is being withdrawn from the EU market.

Finance Watch: Canaan Closes New VC Fund; CARB-X Backs More Antibiotics
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Canaan raised $800m for tech and health care investments. Also, six companies closed VC rounds, CARB-X backed more antibiotics, CIRM funded BrainStorm and Sarepta led recent offerings.

Tymlos Inclusion Stands Out As Express Scripts Reveals 2018 Formulary
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Radius Health's pricing and reimbursement strategy has been successful, at least with Express Scripts, which included its bone-builder Tymlos on a 2018 formulary that excludes several brand-name drugs.

inside:

GSK To Overhaul Emerging Markets Model

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GlaxoSmithKline PLC plans sharp changes to its emerging market business model with an eye on long-term profitable growth and being "better" at rolling out innovations in the region, its new CEO Emma Walmsley said.

"We are focusing our commercial efforts on driving an improved performance in the US which is, without doubt, the priority market but the biggest change geographically in fact is going to be about being more competitive in our emerging markets business," she said at the second quarter earnings conference call that saw the announcement of a significant business overhaul.

Global and local competition has impacted GSK's returns in emerging markets and the company needs to structure more effectively and efficiently for long-term profitable growth.

"We need a model that can competitively drive what is today a largely classic branded product business with brands like *Augmentin* (amoxicillin/clavulanate), but also one that can successfully launch more new innovations such as the *Ellipta* portfolio or *Nucala* (mepolizumab). To do this we are going to create a new, single, dedicated, end-to-end operating model for emerging markets spanning commercial, supply and R&D for life-cycle management," she said.

The group will have its own dedicated governance model and the right commercial structure for each market whether that is a standalone business, a cluster of similar markets or a distributor-led model. Each market will be resourced accordingly and the company remains very committed to access of its medicines, the CEO said.

Although GSK had some difficult times in recent years in certain countries in emerging markets, it expects the region to continue to contribute to growth for the company.

"We just need to have a much more fit-for-purpose - particularly from a cost structure point of view - operation there, because 90% of the business is still in branded generics, it is also noticeable that we haven't been as good as we should have been at launching some of our innovations, so I want us to be better at rolling out innovation," she said.

GSK is going to be making some meaningful shifts there as well as running it on, basically, an integrated P&L with supply chain.

"This is an area where, frankly, our supply chain both in terms of service levels and probably flow and number of factories has not been where it should be, so we are going to be doing a lot of work on that," she said.

CHINA HIT

Although GSK has taken a big hit in China, it will continue to invest in the market.

"For obvious reasons, it is important that we participate not just commercially but from a manufacturing point of view, and from an R&D point of view, in China, with China, for China. We have to be patient in terms of seeing materiality of the contribution, but we are still very much supporting our progress there," she said.

During the second quarter, the group's turnover in emerging markets grew 11% AER and 2% CER, while its pharmaceuticals turnover grew 10% AER and 4% CER.

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Kite First Off The Blocks For EU CAR-T Filing

Kite Pharma Inc. has staked a claim to be the first to file a chimeric antigen receptor T cell (CAR-T) therapy in the EU, having submitted a marketing authorization application for axicabtagene ciloleucel (KTE-C19) ahead of **Novartis AG**'s leading product CTL019 (tisagenlecleucel).

The submission, based on the ZUMA-1 trial, is for its use as a treatment for patients with relapsed/refractory diffuse large B-cell lymphoma (DLBCL), transformed follicular lymphoma and primary mediastinal B-cell lymphoma who are ineligible for autologous stem cell transplant.

The application will beat a relatively quick path to EU approval based on its inclusion in the European Medicines Agency's (EMA's) newly established Priority Medicines (PRIME) regulatory initiative for patients with refractory DLBCL. PRIME aims to support the development and accelerate the review of new therapies to treat patients with a high unmet need. Axicabtagene ciloleucel is already under review by the US FDA, with a Nov. 29 PDUFA action date.

The application should be buoyed by the positive sentiment surrounding this innovative field following the smooth sailing Novartis's CTL019 recently enjoyed at its FDA advisory committee meeting on July 12. The panel unanimously voted in favor of its approval for pediatric relapsed/refractory B-cell acute lymphoblastic leukemia (ALL). However, some said the positive assessment was likely aided by the high level of unmet need in pediatric ALL, and that the risk/benefit analysis may be trickier to dissect for other therapies in different indications. The Kite product did face bumps in development when one very ill NHL patient died from cerebral edema in the extension phase of ZUMA-1 – the same severe side effect that derailed another competitor in the field, **Juno Therapeutics Inc.**'s JCAR015. Nevertheless, analysts also are confident of success for Kite's product.

alex.shimmings@informa.com 1 August 2017

GSK Closes China Neuroscience Center In Latest R&D Reorganization

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Emma Walmsley

Once hailed as the global center for **GlaxoSmithKline PLC** in the central nervous systems therapeutic area, the research hub in China is now being wound up.

Located in Shanghai's sleek Zhangjiang Hitech zone in Pudong New District, the center was opened in 2007 with much fanfare and an ambitious goal to tackle neurodegeneration disorders, including multiple sclerosis, Parkinson's disease and Alzheimer's disease.

Along with the opening, the company announced a plan to staff the center with roughly 50-60 people and "with some years, we'd hope it would be one of our largest R&D centers".

A decade later, though, GSK has decided to throw in the towel, closing the center in its latest global R&D structure reorganization, under the new leadership of CEO Emma Walmsley.

The new direction is aimed to make GSK's R&D and emerging markets business more competitive, said the CEO in her first public appearance since taking over in April.

"So, it is a portfolio of therapy areas, assets and markets – unashamedly putting the US front and center, while putting in fit-for-purpose operating model for the emerging markets to drive the access that we have the responsibility to deliver," she said at the July 26 investor call to release the second quarterly results.

PROJECTS BEING TRANSFERRED

Since the opening, the Shanghai center has had its shares of ups and downs. In 2013, GSK retracted a research paper authored by the China R&D center team led by then head Jingwu Zang.

The reason for the retraction of the paper, published in 2010 by the journal *Nature Medicine*, was incorrect data, said the company. The scandal was at the center of a controversy that directly led to the dismissal of Zang, GSK's top scientist in China at the time.

In a response to *Scrip*, GSK spokesperson acknowledged some projects in the center are being transferred to its R&D center in the US.

"As a part of a focused R&D strategy, we will reduce global neuroscience R&D scope, including closing some projects. Some priority projects among neuroscience researches at the Shanghai Center will continue and be transferred to R&D center in Upper Province, USA. That will ensure we continue to work on key projects, and integrate with R&D teams working on future drug development." said the spokesperson in a written response, translated from Chinese.

GSK, meanwhile, plans to continue expanding drug development in other therapeutic areas in China, added the company.

"Our research in China will focus on projects that generate real impact to the patients, promoting public health in China, through our Infectious Disease and Public Health Institute in Beijing, and innovative clinical research and investment in China's grassroots medical infrastructure."

> GSK has decided to throw in the towel, closing the center in its latest global R&D structure reorganization, under the new leadership of CEO Emma Walmsley

In an effort to refocus its R&D strategy, the UK drug maker recently announced that more than 30 R&D projects will be terminated *(Also see "Walmsley Shakes Up GSK; Cuts More Than 30 Drug Development Programs" Scrip, 26 Jul, 2017.)*.

GSK has been hit hard in China and was fined a record amount of CNY3bn ($486m) in 2014 after being found guilty of bribery.

When asked during the July 26 presentation whether China remains a key growth driver for GSK, Walmsley said the plan in China is to align its R&D with the company's overall commercial and manufacturing strategy, and closely with China's local needs.

"For obvious reasons, it is important that we participate not just commercially but from a manufacturing point of view, and from an R&D point of view, in China, with China, for China. We have to be patient in terms of seeing materiality of the contribution, but we are still very much supporting our progress there." said the CEO.

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Pfizer's Goettler On What Partners Look For In Orphan Drug Deals

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South Korean pharmaceutical companies should seek early collaborations with global companies to develop orphan drugs that meet global regulatory and compliance standards. They have the framework in place to ensure these standards are met as the drug moves along its journey to commercialization, according to a top executive at **Pfizer Inc.**

"Korean pharma companies are seeking to expand into the global market based on innovative treatments and I believe everyone, in particular patients, will see greater results if we combine this breakthrough innovation with the resources, expertise and global reach of a pharmaceutical partner like Pfizer," said Michael Goettler, global president of Pfizer's rare disease global innovative pharma business, in an email interview with *Scrip*.

He believes that the Korean government's support and Pfizer's capabilities in Korea provide a favorable environment for collaboration and partnerships, and can make a meaningful impact for rare disease patient populations.

WILLING PARTNER

Goettler underscored that for Pfizer, it is all about the significant and unique unmet needs of rare diseases patients.

The company is willing to collaborate if it finds research areas that can gain synergy by combining with advanced technologies or candidate compounds that can supplement Pfizer's Rare Diseases pipeline. Companies which can demonstrate this will find willing partners like Pfizer, he said.

"Right now, we have a global portfolio of multiple medicines in preclinical and clinical development and we are investing in addressing the unique challenges of rare disease within a number of disease areas of focus, including hematology, neuroscience, and inherited metabolic disorders," he explained.

Pfizer's Rare Disease Research Unit is tasked with identifying potential new therapies and bringing them through the early drug discovery process to proof-of-concept clinical trials, both through internal investments and unique collaborations with academic and research institutions. It uses an end-to-end approach including involvement from patients, caregivers and advocates to provide critical insights and faster learnings from different drug development phases, ultimately contributing to accelerated R&D efforts.

GENE THERAPY

Goettler also indicated that Pfizer is paying "close attention" the top specialists in Korea who are creating various breakthrough innovations in key areas such as gene research.

"We applaud the Korean government's policies that encourage biopharmaceutical innovation, accelerate the approval process of new medicines and enhance the quality of medicines available to patients," said Goettler who has recently visited Seoul to attend a bio conference.

Pfizer Rare Disease aims to become a leader in gene therapy by bringing together the foremost scientific expertise, resources and promising technologies to develop new, potentially transformative approaches to treating genetic diseases.

Specifically, Pfizer is looking to optimize gene therapy via recombinant adeno-associated viral vectors (rAAV), including rAAV vector design, analytics and manufacturing. rAAV gene therapy has the potential to directly target the underlying genetic cause of the disease. It is a technology that can be standardized, simplifying the manufacturing and regulatory path to medicine approval, he explained.

In May, Pfizer has agreed to license in **Sangamo BioSciences Inc.**'s hemophilia A gene therapy program to beef up its gene therapy research pipeline and its interests in next generation hemophilia therapies.

"At Pfizer, we know we can't go it alone and are actively supporting the development of an emerging, highly networked ecosystem that will catalyze tomorrow's health innovation...Prioritizing collaborations with patient advocacy organizations, academia and industry is critical to expediting new medical breakthroughs and we are committed to doing so openly and transparently to drive breakthrough innovation and improve the lives of people with rare diseases," Goettler maintained.

KOREAN ORPHAN DRUG SCENARIO

Korean pharmas and biotechs are emerging as active developers of orphan drugs, capitalizing on relatively low development cost and hefty incentives that come with orphan drug designations. Increasing orphan drug interest from multinational pharmas is also working favorably for Korean companies which are seeking global partnerships for their drug candidates.

Several Korean companies such as **Dong-A ST Co. Ltd.**, **Green Cross Corp.**, **ViroMed Co. Ltd.**, Gtree BNT and **Genexine Inc.** are already conducting or seeking clinical trials as well as orphan designations in the US with ambitions to develop novel global drugs.

Their robust orphan drug drive is largely in line with global trends as the US FDA and many other countries offer various incentives. The area has become a major focus for big global pharmas as the companies can raise stable earnings from these high margin drugs with state support.

"There are similar incentives to encourage the development of drugs for rare diseases in the US and other countries. These include additional market exclusivity, expedited review periods, and greater flexibility around clinical trial design and evidence requirements. In some markets, there are also rules around automatic reimbursement for orphan drugs, which removes a commercial barrier. The development of orphan drugs is therefore happening globally, not just in the US," says Daniel Chancellor, analyst at Datamonitor Healthcare.

In February last year, South Korea's drug ministry revised rules to ease the designation and approval of orphan drugs. The changes will allow high-priced drugs to be designated as orphan drugs and extended the validity of marketing approvals granted to orphan drugs.

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CONTINUED FROM COVER

prostate cancer drug *Xtandi* (enzalutamide), the driver behind the deal, disappointed in the first quarter. *(Also see "Xtandi Sales Disappoint Pfizer, Returning Focus To The High-Priced Deal" Scrip, 2 May, 2017.)* The issue is related to reimbursement coming from charitable foundations and is expected to resolve moving into 2018.

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'We certainly feel we have a good PD-L1 partnership with Merck'

IBRANCE GROWS AND GROWS

Pfizer reported $141m in Xtandi alliance revenues in the second quarter, below analyst estimates. Under a partnership with **Astellas Pharma Inc.**, Pfizer markets Xtandi in the US while Astellas is responsible for ex-US market.

The company's big new growth driver is the breast cancer drug *Ibrance* (palbociclib), which continued to perform strongly despite new competition from **Novartis AG**'s *Kisqali* (ribociclib). Sales of Ibrance were $853m, up 66%, beating analyst expectations.

The oral JAK inhibitor *Xeljanz* (tofacitinib) also continued to gain steam. After a slow start, Xeljanz is on track to have a blockbuster year. *(Also see "Pfizer's Xeljanz: The Slow Road To Blockbuster Status" Scrip, 4 May, 2017.)* Sales continued to impress in the second quarter, up 55% to $336m.

Pfizer has two sNDAs pending for Xeljanz at the FDA to expand the drug's indications further, one for ulcerative colitis with a March 2018 PDUFA date, and the other for psoriatic arthritis, with a December 2017 PDUFA date.

The company did not break out sales of *Bavencio* (avelumab), the PD-L1 inhibitor partnered with **Merck KGAA** and approved by the FDA in March for the rare skin cancer Merkle cell carcinoma. *(Also see "Pfizer's Avelumab Makes Its Debut, In Rare Form Of Skin Cancer" Scrip, 23 Mar, 2017.)* Management was pressed by analysts about its commitment to avelumab because of some speculation Pfizer might be interested in buying **Bristol-Myers Squibb Co.**, a leader in the PD-1 space that has also experienced some setbacks and related stock deflation.

On the commitment to avelumab, where Pfizer has some 30 clinical trials ongoing including multiple combinations, Read didn't sound like he would rule anything out.

"We certainly feel we have a good PD-L1 partnership with Merck, but undoubtedly the depth of our clinical experience is not the size of our two major competitors," he said. *(Also see "Is BMS The Must Have Immuno-Oncology Accessory Of The Season?" Scrip, 19 Jun, 2017.)*

At the same time, it sounds like a big merger like one with Bristol-Myers wouldn't be on the table anytime soon, unless Congress figures out a tax reform plan quickly.

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AbbVie's Mavyret Claims HCV First

AbbVie Inc.'s next-generation combination therapy for hepatitis C, *Mavyret* (glecaprevir/pibrentasvir), will be the first eight-week regimen to treat all non-cirrhotic genotypes of the virus, narrowing the treatment window from what previously was 12 weeks. Marvyret could help AbbVie fill a gap left by declining sales of its first HCV combination Viekira Pak and challenge rival **Gilead Sciences Inc.**'s near-monopoly, particularly in genotypes 2 and 3 of the virus.

The FDA announced the approval of Mavyret on Aug. 3 to treat HCV virus genotypes 1-6 without cirrhosis or with mild cirrhosis including patients with moderate-to-severe kidney disease who are on dialysis. It is also approved for genotype 1 patients who might have failed prior treatment. In that case, it is cleared for adult patients with HCV genotype 1 infection who have been previously treated with a regimen containing either an NS5A inhibitor or an NS3/4A protease inhibitor but not both.

There will be a price advantage as well. Mavyret's wholesale acquisition cost will be $26,400 for an eight-week treatment duration, $39,600 per 12 weeks and $52,800 per 16 weeks. By comparison, the monthly WAC for *Epclusa* (sofosbuvir/velpatasvir) and *Vosevi* (sofosbuvir/velpatasvir/voxilaprevir) is $24,920, or $74,760 for a full 12 weeks of treatment.

Glecaprevir is a next-generation protease inhibitor and pibrentasvir is a non-structural 5A protein inhibitor. The combination was approved just days earlier in Europe, where it will be marketed as Mavyret. Mavyret is expected to level the HCV playing field in the EU, thanks to label advantages compared to Gilead's combos.

AbbVie sees an opportunity for patients who previously faced limited treatment options, including those with genotype 3 HCV.

jessica.merrill@informa.com 3 August 2017

Teva SOS: Troubled Drug Maker Seeks Audacious Captain To Take The Wheel

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Teva Pharmaceutical Industries Ltd.'s investors have run out of patience as the company's generic drug business continues to struggle, even after the completion of an expensive acquisition last year, and as financial targets were missed again in the second quarter – all without a permanent CEO at the helm.

Teva reported second quarter financial results on Aug. 3 that were lower than expected, including a $6bn net loss as the result of an impairment charge, and lowered guidance for the full year. The company announced it will slash its dividend by 75%.

The result was that the stock opened 18% lower at $25.75. The stock closed the day down even lower, 24% to $23.75.

Even as the company's finances slide, a clearly defined turnaround strategy remains elusive, because the board of directors is continuing its search for a CEO to replace Erez Vigodman, who stepped down in February as the challenges mounted. *(Also see "Teva CEO Steps Down While An Integration Hangs In The Balance" Scrip, 7 Feb, 2017.)* **AstraZeneca PLC** CEO Pascal Soriot was rumored to be considering the position, but he put that speculation to rest during AstraZeneca's second quarter call. *(Also see "Soriot Stands By His Post-Pfizer Sales Pledge For AstraZeneca" Scrip, 30 Jul, 2017.)*

The big challenge for Teva is the US generic drug business, which is experiencing accelerated price erosion. Annual generic price erosion in the US has been in the range of 10% to 15% since 2015, versus historical levels of 5% to 10%, driven by customer consolidation and an initiative at the FDA to reduce the backlog of ANDAs at the agency, flooding the market with new competition.

The challenges have hit generic drug makers across the board, but Teva, as the number one generic drug company in the world, has a lot of exposure. Teva completed the $40.5bn acquisition of **Allergan PLC**'s generic drug business last year, further solidifying its leadership position in generics. Generic medicines comprised 54% of Teva's sales in the second quarter versus 51% in the second quarter of 2016.

The deal was supposed to help Teva better compete in a consolidating market, but some investors were displeased with the high price of the deal.

Investors are also concerned about a looming threat on the specialty side of the business, the eventual launch of **Sandoz Inc./Momenta Pharmaceuticals Inc.**'s 40mg version of *Copaxone* (glatiramer), although it has been delayed by a third-party manufacturing issue. *(Also see "Pfizer Warning Letter Trips Up Sandoz/Momenta's Expected Glatopa Launch" Pink Sheet, 23 Feb, 2017.)*

And the most acute challenges and leadership changes are part of a longer history of inconsistent management at Teva.

The leadership changes underway at Teva extend a long way down the bench. The company is also hiring a new chief financial officer and saw the head of generic medicines, Sigurdur Olsafsson, step down in December, succeeded by Dipankar Bhattacharjee. Former chair Yitzhak Peterburg has stepped into the interim chief executive role.

During the second quarter conference call, chair Sol Barer insisted hiring a permanent CEO is his number one personal priority, but not something he will rush.

"I live, eat and sleep this," he said. "While it is always great to do this in a rapid time…six months is not a long time to look for a CEO." He said the board has met with a number of highly-qualified candidates. Finding someone with the right qualifications to take on the challenge of turning around Teva could be the issue.

Credit Suisse analyst Vamil Divan, in a same-day note, said it will be difficult for the stock to recover unless a permanent CEO and CFO are appointed. "Until those individuals are named, we believe it will be difficult for investors to become more constructive on Teva's longer-term outlook."

CUTTING PEOPLE, PLANTS AND FOOTPRINT

Peterburg insisted, however, that the company is not waiting for a permanent replacement to take steps to fix the struggling business. "Although I am in an interim position as CEO, given the current environment dynamics, I have had to take decisive actions," he said during the conference call. "Significant change is required at an accelerated pace. To this end, the board and management team are continuing to take action to aggressively confront our challenges."

Teva is focused on streamlining the business to reduce costs. Peterburg said the company is ahead of cost savings projections coming from the Allergan acquisition. The company has delivered over $800m in cost savings on a pro forma basis and expects to reduce costs by $1.6bn by the end of the year, $100m more than originally expected.

The company has reduced headcount by 7,000 people, roughly 2,000 more than originally planned. The firm is also reducing its manufacturing networks with plans to close or divest six plants in 2017 and nine plants in 2018, he said. Teva also plans to reduce its geographic footprint in markets that are not run to full scale. "By the end of 2017, we expect to exit 45 markets globally," Peterburg said.

Teva already announced plans to divest its global women's health business and European oncology and pain businesses to help pay down debt. *(Also see "Teva To Divest Women's Health, Some Oncology As CEO Search Proceeds" Scrip, 11 May, 2017.)* Peterburg said agreements could be finalized within months.

Teva reported second quarter sales of $5.7bn, up 13% compared to the second quarter of 2016, driven by the addition of the Allergan generics business. US generic medicines revenues were $3.1bn, up 20% as a result of the acquisition. Specialty medicines revenues declined 9% to $2.1bn, with US revenues down 13% to $1.5bn. The company's blockbuster Copaxone franchise experienced a 10% decline in revenues, generating $1.02bn, while facing pricing pressure and generic competition to its daily 20mg formulation.

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An Inflammatory Deal: Bristol Commits Up To $2.3bn To Buy IFM Therapeutics

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A few billion dollars paid over several years in the grand scheme of **Bristol-Myers Squibb Co.**'s massive immuno-oncology portfolio isn't such a huge thing, but more than $2bn in potential milestone fees is a big deal for the recent startup **IFM Therapeutics** and its investors – and it shows the importance of being able to inflame a tumor with T cells, otherwise known as turning a "cold" tumor "hot."

Nothing about the acquisition of IFM is small, including the $300m upfront fee that Bristol is paying to buy the Boston-based company, which is more than 10 times IFM's $27m Series A venture capital round barely more than a year ago. The firm's investors stand to earn up to $1.01bn in milestone fees for each of the two molecules that IFM has in preclinical development against key targets in the innate immune system – stimulator of interferon genes (STING) and NLRP3 – as well as other undisclosed payments for any additional compounds coming from IFM's immuno-oncology platform.

STING has been of interest to biopharmaceutical companies pursuing immuno-oncology strategies for at least a few years, but IFM's program targeting NLRP3 in cancer may be a first-in-class molecule. Drugs that enhance the innate immune system's response against tumors may complement therapies against targets in the adaptive immune system, such as PD-1 and CTLA4, the immune checkpoints inhibited by the Bristol blockbuster *Opdivo* (nivolumab) and *Yervoy* (ipilimumab), respectively.

"We have generated, preclinically, very exciting data with Opdivo and we are looking at Yervoy as well," Bristol Head of Discovery Carl Decicco told *Scrip*, noting that the company plans to test the IFM molecules in combination with both Bristol drugs, but the specifics are still being reviewed.

The STING compound is expected to enter clinical trials in 2018, but the timing of human trials for the NLRP3 molecule has not been disclosed.

BRISTOL EMERGED AS OPTION A

The immuno-oncology field has evolved so fast that it's hard to keep up with what's working, what's not and which drug targets are next big thing, even for companies in the middle of it all, like IFM.

"When the company got started, there was no express strategy to sell," IFM Co-Founder and CEO Gary Glick said in an interview just hours after signing the deal with Bristol. Glick left **Lycera Corp.**, which is focused on immunotherapies for autoimmune diseases and cancer, to start IFM under investor Atlas Venture's system for incubating new companies in 2015. IFM emerged from stealth mode with its Series A round in June 2016, which was co-led by Atlas and Abingworth with participation from **Novartis AG**. *(Also see "VC Roundup: Annexon, Mersana Benefit As Investors Favor Private Over Public Biotechs" Scrip, 25 Jun, 2016.)*

But with the constant shifts in the immunotherapy space, Glick said, "it became apparent at the beginning of 2017 that the ability to develop an immunotherapeutic on its own is quite challenging."

IFM spoke with 17 companies in January during the J.P. Morgan Healthcare Conference in San Francisco that were interested in the company's pipeline – either certain programs or all of them.

"We wanted to partner with a company with the appropriate checkpoint inhibitors and experience to develop them," Glick said. "There were just a handful of companies that could exploit these assets. When looked at Bristol-Myers and their experience in immuno-oncology, and the fact that they had both PD-1 and CTLA4 … they were the best partner for us."

Bristol is acquiring IFM's NLRP3 agonist, but the company also has an NLRP3 antagonist program to curb immune responses that lead to inflammatory diseases and fibrosis, which IFM is keeping in a spinout company known as **IFM Therapeutics LLC** that retains the existing 17-person IFM team. The pharma, however, gets certain rights to the autoimmune disease program, including a first right of refusal. "There is quite a bit of interesting biology there in areas we're interested in, like fibrosis," Decicco said of Bristol's interest in the third IFM asset. "We hope to take advantage of our knowledge with Gary and bring those forward in different diseases."

Glick noted that IFM and its investors wanted to generate some clinical data for the NLRP3 antagonist before selling the autoimmune disease program, which may be enter the clinic around the end of 2018 or in early 2019.

THE FUTURE OF STING, NLRP3

There are some patent applications filed and research ongoing outside of IFM related to NLRP3 agonism in immuno-oncology, but IFM has the most advanced drug development program. There are multiple STING programs in development, however, but IFM thinks it has a best-in-class molecule.

"We really assessed what we believed to be the strengths and benefits of what was in the clinic, like the **Aduro Biotech Inc.** compound, and our data are quite compelling," Glick said.

Biomedtracker lists four STING programs in development, including the IFM asset. Almost all of them are in preclinical development except for the Phase I drug ADU-S100 from Aduro. *(Also see "Immuno-Oncology Attracts Big Deal Dollars For Biotechs" Scrip, 27 Jun, 2016.)* That is being developed in partnership with Novartis in a monotherapy solid tumor trial, but the companies plan to initiate a second Phase I solid tumor study combining ADU-S100 with a PD-1 inhibitor. *(Also see "Aduro gets $200m as Novartis steps up immuno-oncology" Scrip, 30 Mar, 2015.)*

The Belgian firm **iTeos Therapeutics SA** also has a program targeting STING in lead optimization. *(Also see "iTeos: Developing IO Therapeutics For Hot And Cold Tumors" Scrip, 15 Mar, 2017.)*

"We've advanced a lot of programs and now have a lot of information about

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things like how active checkpoint inhibitors are in different tumors," Decicco said. "There appears to be a subset where tumors are simply not responsive. But there are two sides to the immune system – the part we've been focused on, which is the adaptive side, and the innate side. We have shown that if you activate the innate side of the immune system you can inflame the tumor. If this work pays off, we will see a response in tumors where you haven't before."

STING and NLRP3 appear to be important receptors that activate the inflammasome, and Bristol intends to "hijack" those receptors to boost the innate immune response, he said. Combining drugs targeting those receptors with drugs working in the adaptive immune system could increase, deepen or lengthen cancer patients' responses to immunotherapy.

"Some potentially best-in-class types of chemical compounds have been generated for both of these [IFM] programs," Decicco said. He noted that the combinations of molecules targeting the innate and adaptive immune system that Bristol has tested preclinically appear to carry an acceptable level of toxicity, but the company is eager to understand the safety of the compounds in humans. The executive also pointed out that there has been a lot of competition to acquire drugs targeting innate immune system pathways, like STING, and now any reluctance to do deals due to a lack of safety information is starting to go away.

"We did very thorough diligence on these [IFM] programs and we're very happy with the quality of these molecules and these programs and the people, quite frankly," Decicco said.

Bristol plans to move forward fairly quickly, as it did with the preclinical IDO inhibitor it acquired in early 2015 through the acquisition of **Flexus Biosciences Inc.** for up to $1.25bn. *(Also see "Flexus flips IDO inhibitors to Bristol-Myers for up to $1.25bn" Scrip, 24 Feb, 2015.)* That drug, F001287, moved into Phase I development last year. *(Also see "Scrip's Rough Guide To IDO" Scrip, 18 May, 2017.)*

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Safety Issues Not Dampening AbbVie Optimism For Humira Successors

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AbbVie Inc. remains optimistic, despite some outside safety concerns, that its late-stage immunology drug candidates can increase its market share in autoimmune disease at a time when its top-selling powerhouse *Humira* (adalimumab) is facing increased competition from both biosimilars and new branded agents.

AbbVie talked up a number of pipeline milestones expected in the second half of 2017 during its July 28 second quarter earnings call – data from the second and third Phase III studies of JAK1 inhibitor upadacitinib (ABT-494) in rheumatoid arthritis (RA) as well as Phase IIb trial results for IL-23 inhibitor risankizumab in Crohn's disease, psoriatic arthritis and atopic dermatitis along with Phase III data in psoriasis. The Chicago-area pharma has been pointing to these two drugs for some time as critical planks in its strategy to diversify beyond Humira, which represents roughly 60% of its annual revenues. *(Also see "Beyond Humira: How AbbVie Plans To Hold Its Immunology Leadership Reign" Scrip, 6 Jun, 2016.)*

Chair and CEO Rick Gonzalez said while Humira sales continue to grow for now, upadacitinib and risankizumab could still fill some gaps in the market following their anticipated launches in 2019. The tumor necrosis factor (TNF) inhibitor is the best-selling drug in the world; sales were $4.72bn during the second quarter, up 15% year-over-year. *(Also see "AbbVie Hopes Imbruvica, Marivet Build Momentum Before Humira Downturn" Scrip, 28 Jul, 2017.)* The threat of biosimilars is looming, however, especially after FDA approved the first biosimilar of adalimumab and EU approval is expected soon. *(Also see "EU CHMP OKs Imraldi, Samsung Bioepis' Biosimilar Of AbbVie's Humira" Scrip, 23 Jun, 2017.)*

> Gonzalez said AbbVie had been working for several years on a strategy to augment Humira with new drugs

"Certainly, we have the gold-standard product in Humira," Gonzalez said July 28 after being asked to outline AbbVie's longer-term autoimmune strategy. "In these areas [RA, psoriasis, irritable bowel syndrome (IBS)], it's really the flagship product. It will play an important role over the long term, as we've said. Even when we see biosimilars in this market, it will be our goal to maintain our leadership position within this market.

"But Humira doesn't work on every single patient," he continued, noting that roughly one-third of the market is still not addressed by Humira.

"When you add these other two agents into the mix of our portfolio, it should give us the opportunity to significantly grow our market share position, because we will then have a set of assets that should give us much broader coverage from a clinical standpoint across the patient groups in these areas," he said.

Gonzalez said AbbVie had been working for several years on a strategy to augment Humira with new drugs that will "restate the standard of care in all the areas that we have a leadership position in." Adding the JAK1 inhibitor and anti-IL-23 mechanisms to anti-TNF will give AbbVie's portfolio much broader therapeutic coverage in the autoimmune arena, he added.

But in the already crowded autoimmune categories, rivals also are focused on similar mechanisms.

AbbVie believes upadacitinib can play an important role in treating RA patients who've responded inadequately to anti-TNF

therapy, the exec said. Likewise, in Phase II studies, risankizumab has demonstrated potentially important differentiation in psoriasis compared to drugs currently improved for that disease, he asserted. Meanwhile, in IBS, AbbVie hopes both drugs will provide additional patient choice, important in an area where "patients tend to rotate through therapies, because they do lose effect over time," Gonzalez pointed out.

AbbVie narrowed its development approach for Humira successors late last year when it elected not to exercise its option to license a Phase II candidate – vobarilizumab, an anti-IL-6 receptor nanobody – from partner **Ablynx NV**. The Belgian biotech, which claimed AbbVie's decision was not data-driven but due to an increasing focus on oncology, announced in January that it plans to move vobarilizumab into Phase III in RA before the end of 2017. *(Also see "AbbVie Knocks Back Ablynx's Vobarilizumab In RA" Scrip, 20 Oct, 2016.)* The antibody also is in Phase II in systemic lupus erythematosus.

Morningstar analyst Damien Conover shares some of AbbVie's optimism for its autoimmune pipeline, saying in a recent note that the pharma "looks well-positioned with the next-generation immunology drugs." They have shown improved efficacy and safety in some instances compared to Humira and other drugs in the space, he added.

SAFETY CONCERNS COULD DOG JAK INHIBITOR CLASS

However, a dark cloud hangs over the JAK inhibitor class due to post-market reports of thromboembolic adverse events in patients taking **Pfizer Inc.**'s *Xeljanz* (tofacitinib) and FDA's complete response letter earlier this year, which pushed back potential approval of **Eli Lilly & Co.**'s baricitinib. *(Also see "Baricitinib Complete Response May Put Lilly/Incyte Behind IL-6 Blockers In RA" Scrip, 14 Apr, 2017.)* Lilly said during its second quarter earnings call on July 25 that the FDA asked for an additional study demonstrating the baricitinib's risk/benefit profile, potentially delaying the refiling of the new drug application (NDA) by 18 months. *(Also see "Lilly Hopes To Revitalize Its Cancer Brand With 'Foundational' Agents" Scrip, 25 Jul, 2017.)*

AbbVie said July 28 that it has been monitoring studies of upadacitinib for signals of deep venous thromboembolism (DVT) and pulmonary embolism (PE) and so far has seen nothing indicating a risk profile greater than would be expected for any RA therapy, since such patients generally face greater risk than the population at-large for thromboembolic events. Chief scientific officer Michael Severino said the CRL for baricitinib seems to be driven by an imbalance of DVT and PE event rates between the treatment and placebo arms of Lilly's studies, but expressed doubt there is any evidence of JAK inhibitor class effect.

"We … know that RA patients start out with increased risk of DVT and PE, and that these events are observed in virtually all Phase III programs in RA regardless of the mechanism of action," the exec noted. "We also know that there had been a number, I think it's something like 18 post-marketing reports of PE, with Xeljanz. Since RA patients are at increased risk and Xeljanz has been in the market for several years, I don't think that that is necessarily surprising. When we think about what we don't know, there are a number of things in that column. For starters, we don't know whether baricitinib does in fact increase risk. Here, the FDA has just asked for more data."

Pressed for details, Severino said AbbVie has seen two cases of PE in clinical trial patients receiving upadacitinib, and each patient had a number of risk factors. One was a recurrent case, he said.

"Given the background rates that I talked about, it really isn't surprising to see a small number of cases like this, particularly in Phase II where the large majority of patients are on active drug," Severino explained. "With respect to our ongoing trials, what we've said is that we're monitoring our data closely. We have a good understanding of the background rate, which is between about 0.3 and 0.8 events per 100 patient years. And we're not seeing anything that's elevated above that rate."

Some analysts worry that the FDA won't see it that way, however. BMO Capital Markets analyst Alex Arfaei said in a July 30 note that an otherwise strong quarter for AbbVie was overshadowed by uncertainty about upadacitinib's regulatory prospects.

"We believe the potential risk of thromboembolic events with the JAK1s and the FDA's cautious stance on seemingly small imbalances has increased uncertainty about the class, including AbbVie's upadacitinib," Arfaei wrote. Citing AbbVie's argument that event rates in clinical trials track with background rates, he said Lilly has made basically the same argument.

"There was no mention of a numerical imbalance like that reported with baricitinib," he added. "However, Lilly's argument is similar and our concern is that FDA may again interpret the data differently; until its review is complete, some uncertainty will likely persist. AbbVie's [Phase III] program is comprehensive, and based on what we know, we expect US and EU launches in 2019; however, upadacitinib also could be delayed."

US, EU FILINGS EXPECTED IN 2018

AbbVie has guided that it expects to file both upadacitinib and risankizumab for approval in 2018 and anticipates approval in 2019. It reported top-line data in June from the Phase III SELECT-NEXT study of upadacitinib in RA, showing that two oral, daily doses of the drug met primary endpoints for improvement from baseline on disease scale and low disease activity. *(Also see "AbbVie May Be Poised For An Oral RA Smack Down" Scrip, 7 Jun, 2017.)*

That was the first of six studies testing the JAK1 inhibitor in RA – SELECT-NEXT and SELECT-BEYOND, which are slated to produce data during this quarter, are testing the drug in combination with disease-modifying therapies. Two other trials will investigate upadacitinib monotherapy against a control regimen of methotrexate and the other two will test the candidate in combination therapy against Humira and **Bristol-Myers Squibb Co.**'s *Orencia* (abatacept), an anti-CD80/86 therapy.

For risankizumab, Severino told the earnings call that AbbVie is nearing completion of three registrational trials in psoriasis. He said the drug offers best-in-class potential with the benefit of quarterly dosing. In Phase II data presented earlier this year, the anti-IL23 compound demonstrated the ability to maintain clinical and endoscopic remission of Crohn's disease after 52 weeks of maintenance treatment.

AbbVie will begin Phase III testing with risankizumab in both Crohn's and ulcerative colitis later this year, the exec said, and expects to produce Phase II data before year's end in psoriatic arthritis. It plans to launch a Phase III study for that indication in 2018.

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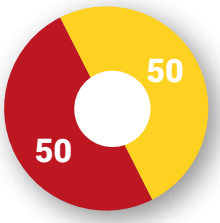
Snapshot of the Opioid Crisis



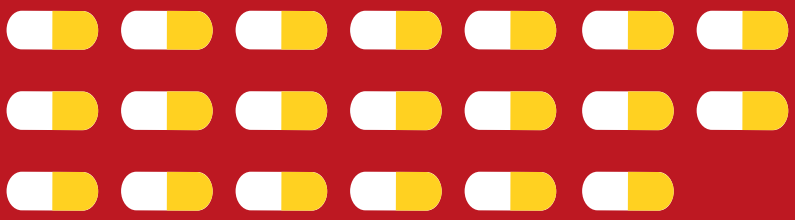
Opioid prescriptions constitute **more than half** of the total prescription pain market.[1]

$18.4B

The anticipated annual market size for opioid drugs in the US by 2020.

Pfizer leads the industry for opioid R&D.[1]

20 The number of potentially abuse-deterrent opioid candidates in Phase II or later stages of development, according to Biomedtracker.



Biomedtracker lists two opioid receptor-targeting drugs candidates for pain indications filed at FDA:

- AcelRx's **Dsuvia** for moderate-to-severe pain
- Intellipharmaceutics' **Rexista** for chronic pain

Professional Perspectives

Informa Pharma Intelligence's Biomedtracker and SERMO surveyed 30 US primary care physicians treating patients with chronic pain who prescribe opioids to better understand first-hand how these controversial drugs are perceived. Findings suggest:

1/2 of the physicians surveyed think abuse-deterrent opioids will play no or only a slightly impactful role in combatting the opioids epidemic in the US.[1]

The majority of physicians surveyed don't know if legislation has been adopted in their state requiring that abuse-deterrent opioids be covered by insurers.[1]

1/2 of the physicians prescribe opioids to just 0–20% of their patients to treat chronic pain.[1]

Timeline of Key Drug Approvals During the Opioid Drug Crisis

December 1995:
Oxycontin becomes the first long-acting opioid therapy widely marketed with a lower potential for abuse only to see the initial formulation eventually withdrawn from the market.[1]

December 1995 – July 2009:
10 major branded opioid therapies for pain in the US are approved, fueling the growing opioid abuse crisis spurred by Oxycontin and its widespread promotion and availability for a range of chronic pain.[1]

August 2009:
Embeda, a morphine product containing naltrexone components that biologically counteract abuse potential, is the first Abuse-Deterrent Formula (ADF) drug to hit the market. However, it is withdrawn in 2011 and reinstated with the addition of an anti-abuse label claim in October 2014.[1, 2, 3, 4]

February 2016:
The FDA revises and outlines its strategy to combat the growing epidemic of opioid abuse, dependence and overdose in the US, with the goal of enforcing an action plan to reduce the abuse and ensure access for patients who need relief.[6]

April 2010:
Oxycontin receives approval of an abuse-deterrent formulation, which replaced the older tablets. (specific label claim not awarded until 2013)[5]

June 2017:
The FDA comes down on Opana ER after widespread abuse and requests company pull its drug from the market.[7]

July 2017:
FDA holds two-day public meeting to determine the impact of ADF opioids, which will help establish a regulatory framework for continued development of these formulations. FDA updates risk management plan for extended-release and long-acting opioids to include immediate-release products.[8, 9]

Sources: [1] Pressures and Opportunities in Pain (Pharma Intelligence, 2016); [2] US FDA approves King's Embeda as abuse-resistant painkiller, Scrip, Aug. 14, 2009; [3] Pfizer recalls newly acquired pain drug Embeda, Scrip, March 17, 2011; [4] Pfizer's Embeda Joins Abuse-Deterrent Club, But FDA Wants Assurances, Pink Sheet, Oct. 20, 2014; [5] FDA Okays Purdue's Newer OxyContin; Payors And Physicians Chew On Drug's Benefit, Pink Sheet, April 6, 2010; [6] FDA's Opioid Policy Reboot: New Risk-Benefit Model, Real-World Data, Pink Sheet, March 4, 2016; [7] Curtain Falls On Opana ER As Endo Agrees To US FDA Withdrawal Request, Pink Sheet, July 6, 2017; [8] Abuse Deterrent Opioids: Which Studies Will Show Real World Effect?, Pink Sheet, July 19, 2017; [9] FDA Expanding Opioid REMS To Immediate Release Formulations, Pink Sheet, July 10, 2017

Shire May Spin Out Neuroscience Unit To Tighten Rare Disease Focus

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Shire PLC seems ready to make the move toward a pure focus on rare diseases. During its second quarter earnings call, the specialty pharma announced it had begun a strategic review of its neuroscience franchise – with all options on the table, including being spun out into a new publicly traded entity.

In an interview, CEO Flemming Ornskov said he would not speculate right now on what the outcome of the strategic review will be – the purpose is to determine if the neuroscience franchise and the remainder of Shire, mainly centered on rare disease therapeutics, can each stand on their own financially. During Shire's second quarter earnings call on Aug. 3, he said the company hopes to provide an update on the findings of its neuroscience strategic review by the end of 2017.

"If I look at the rare disease business, which is approximately 80% of our total revenue, and the neuroscience business, which is 20%, they are both characterized now with strong growth, they have diverse portfolios, they are increasingly – more so for the rare disease business than the neuroscience business – globalizing, they have pipelines and I think they have significant opportunities over the coming years to build growth with strong portfolios and generate significant cash flows and profitability," he told *Scrip*.

INSIDE THE NEUROSCIENCE BUSINESS

The company's neuroscience franchise rests on its mature attention-deficit/hyperactivity disorder drugs *Vyvanse* (lisdexamfetamine) and *Adderall XR* (amphetamine and dextroamphetamine), but has been newly invigorated with the US approval of the new ADHD drug *Mydayis* in June. *(Also see "FDA's NDA And BLA Approvals: Cotempla XR-ODT, Baxdela, Mydayis, Rituxan Hycela, Haegarda" Scrip, 23 Jun, 2017.)*

Although Vyvanse is slated to lose US patent protection in 2023, Ornskov talked up the neuroscience unit's growth potential going forward, almost as if appealing to a potential acquirer. Still Shire's top-selling product after a decade on the market, Vyvanse revenue grew 10% last year but was flat during the second quarter, bringing in $518m, with $460m of that from US sales. Adderall XR declined 30% year-over-year to $71m on the quarter, as the unit's net sales dropped 3% from second-quarter 2016.

Overall, the franchise yielded sales of $635m during the second quarter, with the decline due primarily to generic competition for Adderall XR, chief financial officer Jeffrey Poulton told the earnings call, although that impact was offset somewhat by launch stocking of Mydayis.

Since 2010, Shire's ADHD portfolio has posted 12% compound annual growth and offers growth potential going forward, mainly on the basis of adult patients and ex-US markets, Ornskov said. Shire increased global ADHD market share from 24% to 33% from 2014 to 2016 and is the sector leader in six of the 10 largest ADHD markets, he added. Mydayis (mixed salts of single-entity amphetamine) will launch in September and is expected to provide longer-lasting therapy for ADHD patients, many of whom now take a combination of two extended-release products or one extended-release and one immediate-release product each day, the exec pointed out. *(Also see "Shire CEO: Mydayis To Be Big ADHD Drug, But No Ex-US Launch Planned (Yet)" Scrip, 21 Jun, 2017.)*

SHARPENING RARE DISEASE FOCUS

Shire is still settling from the merger with **Baxalta Inc.** last year, which grew Shire's revenues substantially and increased its focus on rare diseases. But Ornskov indicated that now might be the optimal time to focus the company almost solely on rare disease business. *(Also see "Shire's Record Year Bolstered By Baxalta, But Shows Across-The-Board Growth" Scrip, 16 Feb, 2017.)*

"I think we've have come to a point where we have two businesses that are very distinct," he said. The rare disease business focuses on small patient groups, often pediatric, with treatment in hospitals or highly specialized clinics, Ornskov noted, whereas the neuroscience business requires "much larger sales forces" to target psychiatrists, neurologists and primary care physicians. "So [these are] very distinct businesses all the way down to commercial model, target audience, research and development profile. I think we've come to a point where [it could be] a great option to consider both businesses as viable if they were listed as two independent units."

Asked if spinning out or divesting neuroscience would benefit Shire by making its R&D focus tighter and potentially more economical, Ornskov pointed out that the rare diseases business "has a very rich pipeline." By contrast, there are one or two promising neuroscience pipeline candidates behind Mydayis, he said. The neuroscience unit "probably need[s] to strengthen the pipeline both organically and inorganically through some business development deals," the exec added.

Asked who might be interested in acquiring Shire's ADHD business, Datamonitor Healthcare analyst Daniel Chancellor noted that several big pharma companies – such as **Johnson & Johnson** (*Concerta*), **Eli Lilly & Co.** (*Strattera*) and **Novartis AG** (*Focalin*) – have ADHD products on the market. He also mentioned **Pfizer Inc.** as a possibility. A smaller firm, **Noven Pharmaceuticals Inc.**, has *Daytrana* (methylphenidate) on market for ADHD, as well.

"Shire is the ADHD company, so there isn't necessarily an obvious buyer of this business – you would expect any deal making to be going in Shire's direction, rather than against," Chancellor told *Scrip*. "Perhaps more likely would be a spin-off in the style of **Bioverativ Inc.**, or a diversified company already in CNS looking to expand its Rx offering such as **Teva Pharmaceutical Industries Ltd.** or **Valeant Pharmaceuticals International Inc.**"

Big biotech **Biogen Inc.** spun out Bioverativ earlier this year as a standalone entity fo-

cused on hematology. *(Also see "Bioverativ Fills Gap In Pipeline With $400m True North Buy" Scrip, 23 May, 2017.)*

In a same-day noted lauding Shire for a strong quarterly report and maintaining a "buy" rating for its stock, Deutsche Bank analyst Richard Parkes indicated the decision to review all strategic options for the neuroscience business is not a big surprise.

"This shouldn't shock investors given: (1) prior company commentary over potential for further portfolio optimization; (2) that the division is outside Shire's core focus in rare diseases; and (3) the division will experience a major headwind from patent expiry of Vyvanse in 2023," he wrote on Aug. 3. "However, there is likely to be a debate over possible use of proceeds should any cash be generated and management of any earnings dilution (i.e., deleveraging versus M&A)."

BAXALTA SYNERGIES AHEAD OF SCHEDULE

Other highlights for the second quarter included news that the Baxalta merger is yielding synergies ahead of schedule – $400m to date against an expected $300m, Ornskov said. Shire remains on track to produce $700m in synergies by year three of the transaction, he added. *(Also see "Shire's Ornskov On Goals And Accomplishments One Year After Baxalta Merger" Scrip, 20 Jun, 2017.)*

Noting that R&D chief Phil Vickers left the company in June, Ornskov said Shire will hold off on finding a successor while it is undertaking a reorganization of its R&D apparatus. The revamp is focused on platforms to support a rare disease emphasis, with hubs to be located in Switzerland, Austria and Cambridge, Mass. *(Also see "Shire's Sales, R&D Heads Shed Light On The Post-Baxalta Road Ahead" Scrip, 14 Feb, 2017.)*

Shire posted product sales of nearly $3.6bn during the quarter, of which nearly $1.9bn represents legacy Shire business prior to the acquisition of Baxalta. The Shire business grew 7% year-over-year, while the Baxalta business was up 8%. When comparing the integrated business to Shire total product sales for second quarter 2016, revenues increased 55%.

Growth leaders during the quarter were the immunology business, up 18% to $683m, and internal medicine, up 15% to $484m. While not declining like neuroscience, the genetic diseases unit experienced an off quarter, with total sales of $705m, a 2% increase year-over-year.

Shire attributed the genetic disease flatness to increasing competition in the hereditary angioedema space, where **CSL Behring** obtained FDA approval June 22 for a new prophylactic therapy, *Haegarda* (C1 esterase inhibitor subcutaneous (human)). Poulton said Shire projects that its HAE products will continue to be affected negatively by the Haegarda launch, with *Cinryze* (C1 esterase inhibitor (human)) revenues expected to decrease during the second half of 2017 and *Firazyr* (icatibant) approximately level with 2016 sales.

Outside of HAE, Ornskov said Shire's plan is to continue growing sales for its genetic disease drugs – primarily enzyme-replacement therapies – through increased screening and diagnosis of new patients outside the US.

Dry eye disease drug *Xiidra* (lifitegrast) brought in $57m in sales during the quarter, a 13% sequential increase over the first quarter, which itself saw a 10% uptick from the previous quarter. Poulton noted that the drug, competing against Allergan's *Restasis*, now holds 23% market share in dry eye.

Shire's strategy in this space has centered on increasing awareness and growing the overall category. *(Also see "Shire Plays Up Xiidra Launch, Downplays Missed Sales Expectations" Scrip, 1 Nov, 2016.)* The dry eye business was largely flat before the Xiidra approval, but has risen 24% since, Ornskov said. Future growth prospects for the drug in the US hinge on making progress with Medicare Part D providers, he added, which cover about 40% of the dry eye patient base.

"The market is basically 60/40, so 60% commercial in the US, 40% Medicare," Ornskov said. "We only have access mainly to the 60% right now, so I think if you look at our market share, 23%, only having access to about half the market I think after a year or so is a very strong performance. The brand continues to grow week over week, month over month, the total number of prescriptions, number of patients treated. We capture an increasing portion of new patients," he said, "almost half of new patients go onto Xiidra."

Shire could obtain Canadian approval of Xiidra before the end of the year and is preparing a regulatory filing for Europe, he said.

Published online 3 August 2017

PellePharm's Topical Patidegib Nears Phase III

The US biotech **PellePharm** has announced positive top-line results from a UK-based Phase II trial of its novel topical hedgehog signaling pathway inhibitor, patidegib, in Gorlin syndrome and basal cell carcinoma. The company says it is aiming to start a Phase III study of the compound in the first half of 2018, following discussions with the US FDA, and supported by a planned Series C round of funding.

Topical patidegib is designed to tackle one of the major drawbacks of hedgehog signaling inhibitors, namely that they are associated with adverse systemic side effects when administered orally, even though they are clinically effective. Patidegib, licensed exclusively from **Infinity Pharmaceuticals Inc.**, is stable in a gel formulation for at least two years.

The search for an effective and well tolerated therapy for Gorlin syndrome, in which patients develop multiple basal cell carcinomas, has been underway for a considerable length of time. "The search for safe and effective chronic mitigation of the tumor burden for patients suffering from Gorlin syndrome has been my life's work," remarked Ervin Epstein, a co-founder, president and director of PellePharm.

Reductions in biomarkers of activity in the hedgehog signaling pathway correlated with complete responses, and partial responses were also seen in both treatment groups, PellePharm reported. And importantly, there were no detectable plasma levels of patidegib after its topical administration, the Menlo Park, California-based company announced on July 31.

A second Phase II study of topical patidegib, in patients with sporadic basal cell carcinomas, is being conducted by PellePharm, from which top-line results are expected in the fourth quarter of 2017.

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2 August 2017

Sanofi 2Q: Dupixent's First Set Of Sales Are On Track

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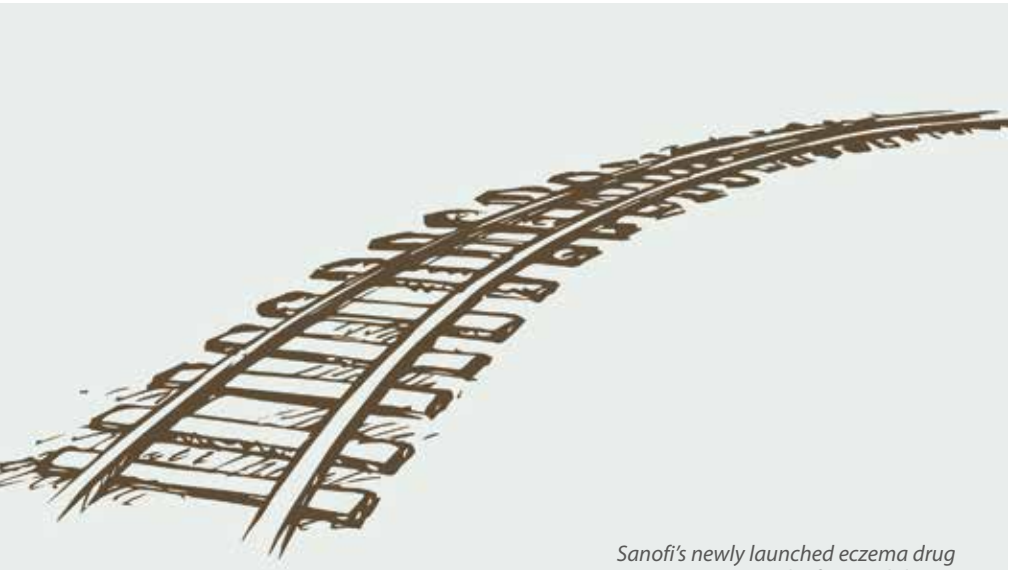

Shutterstock: ArtMari

Sanofi's newly launched eczema drug Dupixent is on track after a solid quarter

The second quarter of 2017 was a fairly quiet period for **Sanofi**, with no surprises making an appearance in the group's 2Q earnings on July 31. Diabetes remains a tough arena for the pharma company, particularly in the US, but its new biologic *Dupixent* (dupilumab) has performed well in its first few months on the market.

In the second quarter, sales of Sanofi's insulin glargine products *Lantus* and follow-on version *Toujeo*, decreased 13.5% to €1.4bn. Individually, Lantus sales were €1.2bn in 2Q, down 19.2%, and Toujeo revenue was €210m, up 46.1%.

In the US alone, insulin glargine sales of €782m were down 23.9%, reflecting the impact of exclusions from various CVS commercial formularies from Jan. 1, 2017 and from the United Health commercial formulary that became effective on Apr. 1, 2017.

In the second half of 2017, Sanofi expects an "accelerated decline" of US diabetes sales relative to the first half of the year.

Sales for Lantus decreased 14% in Europe due to biosimilar competition in several markets and patients switching to Toujeo. The fall in sales for Lantus, while a significant drop, was in-line with analyst forecasts for the second quarter.

Overall, Deutsche Bank analysts said the second quarter of 2017 was solid and noted that "Sanofi is now getting into a habit of at least meeting if not beating expectations."

2Q Figures In Brief

Net sales: €8.7bn

Operating income: €2.3bn

EPS: €1.35

Net sales for Sanofi Genzyme: €1.4bn

Sanofi has raised its full year earnings expectations modestly based on results in the second quarter. The company now expects "broadly stable" earnings per share this year compared with a previous forecast of stable to slightly lower EPS.

Meanwhile, sales of Sanofi's recently launched eczema drug Dupixent – the first biologic approved as a treatment for moderate-to-severe atopic dermatitis – were in-line with consensus estimates at €26m for the quarter. Since its US launch earlier this year, more than 13,000 patients have been prescribed Dupixent and Sanofi's product is trending ahead of other recently launched dermatology biologics.

2Q Sales For Individual Pharma Franchises

Rare diseases: €752m

Multiple sclerosis: €549m

Immunology: €27m

Oncology: €383m

Diabetes: €1.6bn

Cardiovascular (*Praluent* sales): €42m

Established products: €2.6bn

Sanofi said on its July 31 earnings call that there is great demand for the drug as the first biological option in eczema. Biological treatments for other skin conditions such as psoriasis have been available for several years.

"This is a strong first quarter of sales [for Dupixent] and we are relieved that it matches the initial prescription data trajectory, likely removing some fears that Sanofi might have been discounting to gain uptake," Deutsche Bank analysts said in a July 31 note. Deutsche Bank analysts had forecast Dupixent sales of around €35m in 2Q, but this estimate was above consensus.

Dupixent, an injectable human monoclonal antibody designed to specifically inhibit overactive signaling of two key proteins, IL-4 and IL-13, has been slated as a potential blockbuster for Sanofi. The drug, which was developed by Sanofi and its regular pharma partner **Regeneron Pharmaceuticals Inc.**, has a future in other indications and clinical trials are ongoing in asthma, nasal polyps and eosinophilic esophagitis.

In July, the drug won a positive recommendation for approval in Europe, also for moderate-to-severe atopic dermatitis.

Meanwhile, analysts at Bryan, Garnier & Co. highlighted Sanofi's MS drug *Aubagio* (teriflunomide) – which was approved in the US in 2012 – as a key product for the big pharma.

Sales of Aubagio are approaching the €2bn mark on an annual basis, with a market share at 10%. Second-quarter sales for the oral immunomodulating agent were €414m, up 33%.

Sanofi's other branded MS therapy *Lemtrada* (alemtuzumab), which was approved in 2014, saw sales of €124m in the second quarter.

Sanofi has raised its full year earnings expectations modestly based on results in the second quarter. "While the guidance raise on the surface is not a surprise, it demonstrates confidence from a management team that likes to set a conservative (beatable) target," Deutsche Bank analysts noted.

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Regeneron And Sanofi Antibody Discovery Deal To End

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The antibody drug discovery deal between **Regeneron Pharmaceuticals Inc.** and **Sanofi** that produced *Praluent*, *Dupixent* and *Kevzara* is to come to an end at the close of 2017, the US company said during its second-quarter results presentation. Regeneron reported a solid second quarter, but investors' eyes glanced over the strong performance for *Eylea* (aflibercept) to focus rather on how the recent launch of product Dupixent (dupilumab) in atopic dermatitis was faring.

Regeneron's total revenues for the three months ended June 30 were $1.47bn, up 21% on the same quarter last year. Eylea's net US sales accounted for $919m of these revenues, up by 11%, and beating consensus forecasts of $878m. Added to this was a $191m share of the net profit from partner **Bayer AG**'s Eylea sales outside the US (compared with $167m for Q2 2016) which were $542m, up from $486m the previous year.

Regeneron attributed the rise to its increasing share of a growing market (the overall branded anti-VEGF market in the US grew by 7.4% in the first half of 2017) as there was a slight decrease in inventory levels and no price hike. "This growth has been driven by new patients and new indications," CEO and president Leonard S. Schleifer told a conference call. The company has now increased its full year guidance to 10% growth year on year, up from single-digits previously.

Regeneron plans to defend the product against encroaching competition – namely, **Novartis AG**'s brolucizumab (RTH-258), which has just produced strong Phase III data – by filing an sBLA for quarterly dosing by the end of the year. A Phase III study of Eylea in non-proliferative diabetic retinopathy is also enrolling.

But it was Dupixent's performance that drew most attention. The product, which is tipped as a potential blockbuster, had global Q2 net sales, as recorded by Sanofi, of $29m (€26m) (there were no material sales outside the US). The IL-4 and IL-13 blocker was approved in March by the FDA for the treatment of moderate-to-severe atopic dermatitis in adult patients whose disease is not adequately controlled with topical prescription therapy or when therapies are not advisable. It has also just received a positive opinion from the CHMP.

Schleifer said the launch was progressing extremely well, "and most important, we have been very pleased with the positive reception that Dupixent has received from patients and physicians, along with the progress we have made with payers". He pointed to a "steady flow of both prescriptions written for new patients as well as prescriptions filled for new patients without any evidence of a bolus effect." During the past two months, approximately 500 patients per week who are new to the brand have had prescriptions filled.

Analysts at Baird said the Dupixent sales were "good but don't track with enthusiasm" and they raised some concerns about its future performance. "The drug is clearly selling well, just not as well as implied by the move up from the mid-300s [scripts/week] since April," they said in a research note. "We would also note that Pfizer reported pretty lackluster sales for the other recently launched atopic dermatitis drug, *Eucrisa* [crisaborole] … with $9m in sales, sequentially flat from 1Q17, stoking our concerns that maybe the market size isn't quite as big as originally believed."

The next catalyst for Dupixent is the Phase III data read-out in asthma, which is expected shortly with a sBLA submission slated for the fourth quarter.

PRALUENT PROGRESS

Meanwhile, Praluent (alirocumab) revenues continued to underwhelm: Sanofi has already reported net sales in the second quarter of $46m worldwide, with the US accounting for $33m.

While, admitting to disappointment with the uptake of the PCSK9 inhibitor class, Regeneron said it was encouraged by its recent discussions with payers and pointed to a recent decision by CVS that it would provide co-preferred access to Praluent through its CVS Caremark commercial formularies, which cover approximately 25 million people.

"We remain optimistic about the long-term potential for this class. The potential resolution of our patent dispute with Amgen and anticipated cardiovascular outcomes data for Praluent in early 2018 could have an impact on demand," said Robert J. Terifay, Regeneron's EVP of commercial.

NOT A PARTING BUT AN EVOLUTION

The partnership which produced Praluent and Dupixent, as well as their latest success the anti-IL6 receptor product Kevzara (sarilumab) for moderate to severe rheumatoid arthritis, is coming to an end.

Regeneron said the 2007 antibody discovery agreement between it and Sanofi would not be extended further – it was originally scheduled to terminate in 2012, but was updated by the partners in 2009 to extend to 2017. It seems, the partnership has now run its course.

But a license and collaboration agreement covering Praluent, Dupixent and Kevzara is not impacted by the expiration of the antibody discovery agreement and will continue. Sanofi is also continuing to collaborate with Regeneron on the investigational IL-33 monoclonal antibody REGN3500/SAR440340 in Phase I for the treatment of asthma and COPD.

Sanofi stressed that the end merely represents an evolution of its collaboration with Regeneron, with their attention now turning to cancer. In July 2015, Sanofi and Regeneron entered into global collaboration agreements to discover, develop and commercialize new antibody cancer treatments in immuno-oncology.

As such, the anti-PD1 product REGN2810 and the anti-LAG-3 product REGN3767, that were produced via the drug discovery partnership, will continue to be developed with Sanofi under the immuno-oncology collaboration.

"We look forward to our continued collaboration to pioneer the next generation of cancer treatments for patients," Sanofi said. "We are proud of the accomplishments of the Sanofi and Regeneron alliance to date and believe that they demonstrate the groundbreaking impact that collaborations like this can achieve."

Once the agreement has expired, Regeneron retains the right to develop or continue to develop other product candidates discovered under it independently or with other collaborators. The $130m of 2017 annual funding from Sanofi under the agreement is expected to be fully utilized by the end of the third quarter of 2017, Regeneron added.

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Takeda-Advinus R&D Alliance 'Closed'

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It's official. **Takeda Pharmaceutical Co. Ltd.**'s multi-year, multi-project discovery collaboration with **Advinus Therapeutics** has run its course, bringing to close a much-publicized deal that put Indian discovery services on the world map some years ago. Advinus' contract research business is currently being acquired by **Eurofins Scientific**.

The Takeda-Advinus collaboration, announced in October 2012, aimed to generate IND-ready compounds for major therapeutic areas including inflammation, CNS, GI and metabolic diseases.

> The third milestone underscores the rapid progress of the programs, a result of the innovative solutions and the speed and quality of Advinus' efforts supported by Takeda's

Takeda confirmed that the alliance with Advinus "was ended", but declined to comment on further possibility of partnerships with Advinus, whose drug discovery business is being transferred to Impetis Biosciences Ltd as part of the overall Eurofins deal.

"Takeda is continuously considering various options aiming to accelerate its growth focusing on prioritized therapeutic areas of gastroenterology, oncology and central nervous system plus vaccines. At this point, we have nothing to be disclosed," Takeda told *Scrip*.

Advinus maintained that the collaboration with Takeda was a three- year alliance which was "successfully delivered upon".

"At the end of three years the alliance was successfully closed," Advinus told *Scrip*.

THIRD MILESTONE

Advinus was founded in 2005 by Rashmi Barbhaiya, a former president of R&D at Ranbaxy Laboratories Ltd., and some former executives of Ranbaxy and it was backed by India's diversified Tata group.

Last year, Advinus announced that it had reached the third milestone in its R&D collaboration with Takeda. The Indian firm's top brass was, at the time, quoted as saying that achievement of the milestone by Advinus' scientists was a clear demonstration of how an effective partnership could deliver "novel and effective" candidates for drug development in a "cost-effective manner".

Under the alliance, Advinus was responsible for carrying out the research needed to identify candidate molecules for clinical development in specific therapeutic areas while Takeda handled the development and commercialization of these candidates. Details on commercialization of assets under the alliance, if any, could not immediately be ascertained. "In each of the previous two years, Advinus has met predetermined milestones. The achievement of the third milestone underscores the rapid progress of the research programs over the past year, a result of the innovative solutions and the speed and quality of Advinus' efforts supported by Takeda's guidance and highly interactive engagement," an Advinus statement at the time said.

CO-FOUNDER'S EXIT

Significantly, much appears to have changed at Advinus since its heady days of R&D alliances with innovator firms like **Merck & Co. Inc.**, **Johnson & Johnson** and **Novartis AG**, in addition to Takeda, culminating in the recently proposed divestment deal with Eurofins.

The Indian firm has witnessed significant turbulence over the recent past, including the departure of its co-founder and former CEO and managing director Rashmi Barbhaiya. Last year Advinus was reported to have laid off several personnel from its Pune discovery services unit while some experts previously referred to a significant "mismatch" between the expectations of the Tata group and co-founder Barbhaiya.

The alliances with Merck, J&J and Novartis, among others, had delivered on various milestones previously, though latest updates, if any, on these could not immediately be got.

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BMS' Opdivo Approval In CRC Overshadowed

Following strong second quarter sales growth for **Bristol-Myers Squibb Co.'s** PD-1 inhibitor, *Opdivo* (nivolumab), the FDA has granted it an accelerated approval for the treatment of adults and children with microsatellite instability-high (MSI-H) and mismatch repair deficient (dMMR) metastatic colorectal cancer (CRC), that has progressed following previous treatment with a fluoropyrimidine, oxaliplatin and irinotecan.

However, the approved indication is narrower than for its prime rival, **Merck & Co. Inc.**'s PD-1 inhibitor *Keytruda* (pembrolizumab) which was additionally approved in May by the FDA for patients with all tumor types with these dMMR or MSI-H biomarkers. *(Also see "Keytruda Approval Opens New Routes For Immuno-Oncology" Scrip, 24 May, 2017.)* Datamonitor Healthcare analyst Hardik Patel says this means Keytruda still holds the target population advantage. Patients with dMMR or MSI-H tumors are less likely to respond to conventional chemotherapy, and CRC is the most commercially significant market segment.

Around 15% of patients suffering from metastatic colorectal cancer have dMMR or MSI-H tumors which, according to Patel, is a large subgroup considering the high prevalence of CRC. However, "the presence of a direct competitor for this patient population in Keytruda, drastically reduces Opdivo's potential in this setting," he said.

Opdivo is already launched for melanoma, non-small cell lung cancer (NSCLC), renal cell carcinoma, Hodgkin's lymphoma, head and neck, and bladder cancers. Sales for the drug were at $1.19bn this second quarter, up by 42% from the same quarter last year.

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2 August 2017

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Exclusive Remicade Contracts Are Slowing Biosimilar Uptake

JESSICA MERRILL Jessica.merrill@informa.com

Defensive tactics by **Johnson & Johnson** to protect its blockbuster *Remicade* (infliximab) from biosimilar competition are working, at least according to rival **Pfizer Inc.**, which launched the first biosimilar version of Remicade, *Inflectra* (infliximab-dyyb), in late 2016.

The launch of Inflectra has been slower than expected, Pfizer CEO Ian Read said during the company's second quarter conference call on Aug. 1. The reason, he said, was market access challenges among commercial payers, because J&J has managed to secure exclusive contracts for Remicade.

"While we achieved 100% Medicare coverage, we've experienced access challenges among national commercial payers where our lower-priced product has not received access of parity to the innovative product and remains in a disadvantaged position despite recent price increases taken by the innovative product," Read said.

Pfizer Essential Health Group President John Young further elaborated: "In the commercial insurance space, access for Inflectra has been substantially limited due to J&J's pursuit of exclusionary contracting with insurers and providers."

The suggestion runs counter to the very intention of biosimilars, which are expected to be priced below the innovative brand medicines, eventually generating substantial health care savings. To secure an exclusive contract, J&J most likely would need to offer even steeper discounts for Remicade versus the biosimilar or secure a bundled contract, offering discounts for other products on the condition that Remicade also is given preference.

Bundling is a tactic J&J CEO Alex Gorsky has discussed publicly with investors as an option to defend against biosimilar competition, but it is unclear how receptive payers would be to those kinds of bundled contracts when biosimilars are available. *(Also see "Bundled Contracts To Defend Against Biosimilars May Face Payer Skepticism" Pink Sheet, 21 Jul, 2016.)*

J&J declined to comment about what tactics it is using. In an email, the company commented, "Both Pfizer and Janssen submitted proposals and the end result is that the majority of payers have preferred Remicade over Inflectra."

The pharmacy benefit manager **Express Scripts Holding Co.** couldn't comment on specific contracts but said, "Generally speaking, biosimilars create competition in a therapy class that was previously dominated by one originator product, thus bringing down the cost of care in that therapy class, whether through a less expensive biosimilar or price concessions on the originator product."

Nonetheless, if biosimilars don't generate compelling commercial returns it's unlikely drug makers will continue investing in their development.

A TEST CASE

The US biosimilar market remains very much an experiment for now, with no certainty about how it will unfold and what the pricing or market access dynamics will look like long-term.

Inflectra, developed by **Celltrion Inc.**, was only the second biosimilar approved in the US when it was cleared by the FDA last year and the launch is being closely watched as a test case. **Merck & Co. Inc.** recently launched a second biosimilar version of the anti-TNF, **Samsung Bioepis Co. Ltd.**'s *Renflexis* (infliximab-abda), which will only increase the competitive dynamics and make the category a more interesting test of the US biosimilar market. *(Also see "Merck's Second-To-Market Renflexis Biosimilar Priced Below The First" Scrip, 24 Jul, 2017.)*

Pfizer launched Inflectra at a wholesale acquisition cost (WAC) of $946.28 per 100mg vial, which was a 15% discount to the WAC price for Remicade. *(Also see "Pfizer Will Support Inflectra Launch With Dedicated Sales Force" Scrip, 14 Nov, 2016.)* Merck set the WAC for Renflexis below Inflectra, at a 35% discount to Remicade, or $753.39. Neither price includes rebates and discounts, however, so the actual cost is not publicly known. J&J, as an example, has said the actual cost of Remicade is about 30% lower than the WAC after rebates. Pricing transparency is one of the challenges facing the drug industry as it tries to confront growing backlash over high drug prices.

Young said during the conference call that the Medicare Average Sales Price (ASP) for Inflectra and Renflexis are exactly the same.

STRONG MARKET SHARE UNDER SOME GOVERNMENT CONTRACTS

Pfizer has had better success selling Inflectra under government contracts than commercial insurance plans, Young said, such as the US Department of Veterans Affairs. "VA would be a good example of such a provider where we actually have infliximab share of 20% or more and that continues to grow," he added, but noted that Inflectra's market share was only 2.3% of the overall infliximab volume at the end of June.

Pfizer's biosimilar revenue grew a strong 60% off a small base to reach $121m in the second quarter, including worldwide Inflectra sales of $94m, though only $23m of that was generated in the US.

"We continue to see the value of biosimilars in the marketplace and expanding patient access to important high-quality, low-cost treatment options, but we know the market is still in development," Young said.

Meanwhile, US sales of Remicade were $1.06bn in the second quarter. Sales were down a substantial 13.9%, but a big portion of the decline was due to a favorable price adjustment in 2016 that created a headwind in 2017 across J&J's pharma portfolio, as well as new competition from *Stelara* (ustekinumab) in Crohn's disease. J&J acknowledged some impact from biosimilars during its second quarter earnings call in July, but noted that the effect of the competition was more muted than expected. *(Also see "Remicade: Biosimilars And Pricing Pressure Wear On J&J's Blockbuster Brand" Scrip, 18 Jul, 2017.)*

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Celgene, Agios Ready For Enasidenib Launch After Early Approval

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Celgene Corp. and partner **Agios Pharmaceuticals Inc.** are ready to quickly capitalize on the FDA approval of *Idhifa* (enasidenib), which came nearly a month earlier than its Aug. 30 priority review user fee date, for a subset of relapsed or refractory acute myeloid leukemia patients, giving Agios its first approved drug and Celgene the initial fruits of a collaboration inked in 2010.

Idhifa, an oral, targeted inhibitor of the isocitrate dehydrogenase-2 (IDH2) enzyme, was approved on Aug. 1 to treat adult AML patients with an IDH2 mutation as determined by a diagnostic test. Concurrent with the drug's approval, the FDA also okayed **Abbott Laboratories Inc.**'s *RealTime IDH2 Assay*, although Agios CEO David Schenkein noted that doctors can use a number of approved tests to ascertain a patient's appropriateness for Idhifa treatment. The partners are ready to immediately launch the product.

Agios does not anticipate that currently approved AML drugs will offer much competition to Idhifa, because this is the first drug approved specifically for patients with the IDH2 mutation. It was approved under priority review after receiving both orphan drug and fast track status from the FDA. "What we're very pleased about is that this is a full regulatory approval, rather than an accelerated approval, and it speaks to the compelling clinical benefit that we and the FDA believe Idhifa provides for patients," Schenkein said in an interview.

Patients with the IDH2 mutation comprise an estimated 9%-13% of AML patients – NIH's National Cancer Institute projects that about 21,380 people will be diagnosed with AML this year. Celgene estimates that between 1,200 and 1,500 US AML patients have an IDH2 mutation.

While this is a small-market drug for Celgene, whose top-selling product *Revlimid* (lenalidomide) for multiple myeloma and other hematological malignancies generated nearly $7bn in 2016 sales, it's an important one for the prolific deal-maker – the first drug approved from its large portfolio of partnered programs. Celgene revealed a few hours after the approval that Idhifa will be priced at a wholesale acquisition cost of $24,872. Patients' median time on therapy was 4.3 months in the drug's pivotal study. The New Jersey biopharma giant said in a statement to *Scrip* that it is "proactively working with US payers on patient-centric agreements designed to provide immediate access to Idhifa with no out-of-pocket costs for eligible patients, other than those covered by federal health care programs." (Those programs have restrictions on manufacturer subsidies for out-of-pocket costs.)

Celgene and Agios will co-commercialize Idhifa in the US, with Celgene holding commercial rights in the rest of the world, under the terms of their 2010 collaboration, which gave Celgene option rights to several Agios candidates based on the concept of redirecting the metabolic networks of cancer. Schenkein said that the drug would be available to patients within a day or so of the approval.

"A third of the sales force in the United States are Agios employees and they've been training with the Celgene sales force over the past several months in anticipation of this, so they are ready to go and they're excited to try and interact with physicians and help them with their patients as quickly as possible," he told *Scrip*. He declined to specify how big the overall force or the Agios complement is, but indicated that the two companies should be able to cover the physician base with a fairly modest headcount.

"About 60% of the prescribers today who treat acute myelogenous leukemia are in the academic centers, so we know them well and will be spending a lot of time with them," Schenkein said. "We do know there is a significant fraction in the community hospitals. It'll take a little bit longer to get into that setting, but between Agios and Celgene, we've got the country covered, so we're confident that eventually we'll get to all the physicians out there who need our education and support."

BOXED WARNING FOR DIFFERENTIATION SYNDROME

Clinician education will be crucial, especially early on, because Idhifa's label includes a boxed warning explaining the risk of differentiation syndrome, which the FDA says can be fatal if not treated. The warning recommends that clinicians monitor patients receiving the drug for symptoms – which include fever, dyspnea, pleural or pericardial effusion, inflammation of the lungs, rapid weight gain, peripheral edema and dysfunction of the liver, kidneys or multiple organs – and treat symptomatic patients with corticosteroids, continuing to monitor until the symptoms subside.

Schenkein indicated that this labeling was expected and said the adverse reaction actually can be an early indication that the drug is having an effect.

"We've talked about this quite a bit and presented data at medical meetings," he explained. "Differentiation syndrome is part and parcel of the way the drug works and hematologists are very comfortable with this effect … It only occurs in a small percentage of the patients – in only 8% of the patients was it a serious side effect – and it usually means that the patients are beginning to respond. It's very manageable, but education is very important. We expect that all of the physicians will safely know how to use our drug."

Another drug already on the market – *Trisenox* (arsenic trioxide), approved in 2000 to treat acute promyelocytic leukemia and now marketed by **Teva Pharmaceutical Industries Ltd.** – also includes a boxed warning for differentiation syndrome. As a result, hematologists and oncologists already are familiar with this adverse effect and how to deal with it, Schenkein said.

Data from an ongoing Phase I trial of Idhifa were presented at the 2017 American Society of Clinical Oncology meeting showing that 13 of 109 patients (11.9%) treated with the drug had IDH-inhibitor-associated differentiation syndrome. In a poster presented at the conference, Celgene indicated that

CONTINUED ON PAGE 23

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

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Selected clinical trial developments for the week 28 July–3 August 2017

LEAD COMPANY/PARTNER	COMPOUND	INDICATION	COMMENTS
Phase III Results Published			
Roche	*Avastin* (bevacizumab)	cervical cancer	GOG-240; *The Lancet* online, July 27, 2017.
Phase III Interim/Top-line Results			
AcelRx Pharmaceuticals Inc.	*Zalviso* (sufentanil) sublingual tablets	moderate to severe pain	IAP312; high levels of patient satisfaction.
Phase III Initiated			
Biohaven Pharmaceuticals Holding Co. Ltd./Bristol-Myers Squibb Co.	rimegepant	migraine	An oral CGRP receptor antagonist.
DBV Technologies SA	*Viaskin Peanut*	peanut allergy	EPITOPE; in children aged 1-3 years.
Foamix Pharmaceuticals Ltd.	FMX101 (minocycline) foam	acne	FX2017-22; in moderate to severe disease.
Phase III Announced			
Bristol-Myers Squibb Co./ Clovis Oncology Inc.	*Opdivo* (nivolumab) with *Rubraca* (rucaparib)	breast cancer, triple negative, ovarian cancer	In patients with advanced disease.
Sumitomo Dainippon Pharma Co. Ltd.	SEP-225289 (dasotraline)	attention deficit hyperactivity disorder	In children aged six to 12 years.
Updated Phase II Results			
BioMarin Pharmaceutical Inc.	BMN-270, factor VIII gene therapy	hemophilia A	Improved Factor VIII levels, well tolerated.
Proteostasis Therapeutics Inc.	PTI-428, PTI-801	cystic fibrosis	Well tolerated.
Ritter Pharmaceuticals Inc.	RP-G28	A microbiome modulator	An oligosaccharide to improve lactose tolerance.
Phase II Interim/Top-line Results			
Spark Therapeutics Inc.	SPK-8011	hemophilia A	Well tolerated, signs of efficacy.
Theravance Biopharma Inc./ Alfasigma SpA	velusetrag	gastroparesis	Improved symptoms including gastric emptying .
Glenmark Pharmaceuticals Ltd.	GBR-830	atopic dermatitis	An anti-OX40 MAb, signs of clinical improvement.
Geron Corp./Janssen R&D LLC	imetelstat	myelodysplastic syndrome, myelofibrosis	IMerge, IMbark; signs of efficacy, more patients recruited.
Intercept Pharmaceuticals Inc./ Sumitomo Dainippon Pharma Co. Ltd.	*Ocaliva* (obeticholic acid)	non-alcoholic steatohepatitis (NASH)	CONTROL; with statins, reversed LDL increases.

Source: Biomedtracker

CONTINUED FROM PAGE 21

the side effect likely was due to the drug's mechanism of action, differentiation of leukemic cells.

The NDA was backed by a Phase I/II trial in which 199 patients with relapsed or refractory AML were given a starting dose of 100 mg of Idhifa, with dose reduction employed if necessary to manage side effects. Patients had received a median of two of previous anti-cancer regimens and 52% of the respondents were refractory to previous therapy. 23% (46/199) of patients demonstrated complete response or complete response with partial hematologic improvement in the study, with a median time to first response of 1.9 months.

In addition, of 157 patients who were dependent on red blood cell or platelet transfusions at baseline, 34% (53/157) became independent of such transfusions during any 56-day post-baseline period. Also, of 42 patients who did not require transfusions at baseline, 76% (32/42) remained transfusion-independent during any 56-day post-baseline period.

EXPANDING LABEL TO LARGER PORTION OF AML

The drug continues to be studied in the Phase III IDHENTIFY trial and Schenkein said Agios and Celgene hope to expand the label to a broader range of AML patients, including newly diagnosed patients, being enrolled in ongoing Phase I studies. Agios plans a US NDA filing before year's end for its second drug candidate, IDH1 inhibitor ivosidenib (AG120), which was part of the original collaboration with Celgene. However, when the companies signed a new collaboration agreement in 2016 focused on metabolic immuno-oncology therapies, Celgene returned full rights to AG120 to Agios, which plans to take it forward in relapsed/refractory AML on its own.

Cambridge, Mass.-based Agios is hoping ivosidenib receives a quick path forward like Idhifa, Schenkein said. It already has obtained orphan and fast track status.

"Obviously, we hope that with AG120 we get the same rapid response from the FDA that we did with Idhifa, with the priority review and … full approval or regular approval, as opposed to accelerated approval," he said. "We won't know that for a while, but we're optimistic that it will follow a similar path."

If ivosidenib is approved, Agios will use its commercial team now collaborating with Celgene on Idhifa to market it, but likely will need to add more people, Schenkein said. "The current representatives from Agios will then have two drugs that they'll be able to discuss with physicians," he noted. "We will need to expand the sales force and we'll do that next year after the NDA has been accepted by the FDA."

Schenkein noted that there are other drugs in clinical development for AML – including another IDH inhibitor, **Novartis AG**'s Phase I IDH305.

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Biotech Flex Pharma Inc. has appointed ***William McVicar*** president and CEO. He joined the company in April this year as president of research and development and was later appointed interim president and CEO. He has previously been chief scientific officer at Inotek Pharmaceuticals Corp. and held various other positions, including executive vice president of pharmaceutical development, chief scientific officer and president.

Lee Kalowski has joined **Bicycle Therapeutics Ltd.** as chief financial officer from Tokai Pharmaceuticals Inc., where he held the same position. Previously, he was vice president, global biotechnology equity research at Credit Suisse and before this, he worked in mergers and acquisitions in the pharmaceutical division of Johnson & Johnson.

SetPoint Medical Corp., a company focused on chronic inflammatory diseases, has appointed ***Terry Bevirt*** vice president of clinical affairs. Prior to joining SetPoint, Bevirt was senior director, head of clinical operations at Armagen and previously served as therapeutic area planning and operations director at Amgen. Before Amgen, she held various positions at Pharmacia Corp., Affiliated Research Centers and Abbott Laboratories Inc.

Shehnaaz Suliman has been named **Theravance Biopharma Inc.**'s senior vice president, corporate development and strategy and brings over 15 years of senior-level experience in life sciences to the company. Most recently, Suliman was vice president Roche Partnering and before this, she was group leader of portfolio management and operations for Genentech Inc. for more than four years.

Biogen Inc. has appointed ***Anabella Villalobos*** senior vice president, biotherapeutics & medicinal sciences. She joins the company from Pfizer Inc. Worldwide Research and Development, where she was vice president and head of medicinal synthesis technologies.

Reza Safaei has been elected **Nordic Nanovector** ASA's head of medical affairs. Most recently, he was head of medical affairs, Europe at Seattle Genetics Inc. He previously served as director, medical development, immuno-oncology and scientific communications, hematology at Amgen Inc. Europe.

Tony W. Ho has joined **CRISPR Therapeutics AG** as executive vice president and head of research and development from AstraZeneca PLC, where he held various roles, most recently as senior vice president and head of oncology integration and innovation. Before this position, Ho led the development and commercialization of two drugs for AstraZeneca as vice president and global medicine leader.

Todd Zavodnick joins **Revance Therapeutics Inc.** as chief commercial officer and president, aesthetics & therapeutics from Zeltiq Aesthetics Inc. At ZELTIQ, Zavodnick was president of international, before its acquisition by Allergan PLC. He previously was president and general manager, North America at Galderma Laboratories Inc.

Retinal disease-focused **NightstaRx Ltd.** has named ***Tuyen Ong*** executive vice president and chief development officer. Ong was previously chief medical officer at PTC Therapeutics Inc. and before this, vice president of global clinical development and operations at Bausch & Lomb Inc. Ong also worked as Pfizer Inc.'s global clinical lead for various therapeutic disease areas of high-unmet need.

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