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Novartis Battens Down Hatches Over Falsified Zolgensma Data

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Accused of concealing manipulated data from the US Food and Drug Administration while applying for approval of its spinal muscular atrophy drug Zolgensma, Novartis AG has moved quickly to vigorously defend the safety and efficacy of its expensive gene therapy treatment and its own corporate reputation.

Observers were stunned on 6 August by an FDA statement highlighting an investigation into data manipulation issues associated with the Swiss major's filing for Zolgensma (onasemnogene abeparvovec) which was approved in the US for type 1 SMA on 24 May. The agency noted that it would continue to investigate the matter and determine whether Novartis should face civil or criminal penalties, but clearly stated that it believed in the integrity of the human clinical trials data for Zolgensma and that the product should remain on the market.

Novartis said, "The totality of the evidence demonstrating the product's effectiveness and its safety profile continue to provide compelling evidence supporting an overall favorable benefit-risk profile." It noted that its AveXis Inc. subsidiary, acquired for $8.7bn in May 2018, "voluntarily self-disclosed to the FDA and subsequently to other health authorities" that some data previously submitted to the agency as part of the Zolgensma filing were inaccurate.

The Basel-headquartered firm added that AveXis had become aware in mid-March of allegations of data manipulation in a specific animal testing procedure used in the development of the product. However, on a conference call on 7 August, Novartis CEO Vas Narasimhan stressed that the mouse testing assays in question were used for initial product testing and had not been used since June 2018.

He said that an internal investigation was immediately undertaken and once the firm had arrived at interim conclusions from those probes, Novartis shared its findings with the FDA on 28 June. Much of the call focused on the timelines from finding out about the issue and letting the FDA and other agencies know and Narasimhan insisted that the company did not delay disclosing any of its findings to fit around the timing of the Zolgensma Biologics License Application *(Also see "Novartis CEO Calms Concerns Over Zolgensma launch" - Scrip, 18 Jul, 2019.)*

Rob Kowalski, head of global regulatory affairs, said, "What we did in this case is exactly what we do in every case, which is informing the agency once we actually understand the information that we have in hand." The only exception for how Novartis handles such issues "would have been if we felt even on early preliminary data there was some imminent harm to patients…which was not the case here."

Narasimhan also addressed the issue about how soon non-US regulators who are currently evaluating Zolgensma were informed. While the US was told on 28 June, regulators in Europe and Japan were contacted on 1 and 2 July respectively, he said, noting that the difference "was just based on weekends and time zones so we tried to do all of the notifications concurrently."

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from the executive editor

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Trust in the pharma industry is hard won and easily lost, and Novartis, with the revelation it had been sitting on the knowledge that data used for approval of its gene therapy Zolgensma were manipulated, has become the latest firm to find itself under an unwelcome spotlight (see cover story). No matter that the mouse testing assays in question were limited to only a small portion of the product testing data, and that the safety, efficacy and quality of the product were not an issue, the optics are what's important, and they are not good.

The reverberations will be felt beyond Basel's boardrooms. A number of US Democrat senators (and presidential hopefuls) are on the case, framing in a 9 August letter to the acting FDA Commissioner Ned Sharpless the data falsification issue for what is a high-profile and very high-priced product as part of a larger story about pharmaceutical price gouging. Some say this is likely to lead to a legislative showdown on drug pricing later this year and Novartis's peers will not thank it for adding further grist to the mill.

There was more heartening news for Allergan and Novo Nordisk, which both reported better than expected sales for their key products in their second quarter results. This made pleasant reading for AbbVie in particular as Allergan's Botox-fueled revenue stream is a primary incentive for its planned $63bn acquisition of the firm. Even so, observers still have concerns that the top-selling wrinkle reducer's sales will sag over time. See all the details on p4-7.

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Gilead's Marketing Of Descovy For HIV Prevention Should Not Suggest Superiority To Truvada

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Gilead Sciences Inc. has emphasized the renal and bone safety benefits of Descovy (emtricitabine/tenofovir alafenamide or FTC/TAF) relative to Truvada (emtricitabine/tenofovir disoproxil fumarate or FTC/TDF) as it works to convert patients ahead of generic competition to the older HIV fixed-dose combination therapy in 2020.

However, those efforts hit strong resistance at a US Food and Drug Administration advisory committee review of a pre-exposure prophylaxis (PrEP) indication for Descovy.

At the 7 August meeting, members of the Antimicrobial Drugs Advisory Committee urged the agency to hold a firm line against labeling, promotional or educational materials that suggest Descovy is superior in any way to the older drug, at least when it comes to preventing HIV infection. Panelists said any potential advantages with Descovy on renal and bone biomarkers may or may not have clinical benefits and could be outweighed by unfavorable changes in lipids and weight gain with the newer drug.

"The labeling and advertising for Descovy, if approved, should only speak to the noninferiority, not the superiority, of both the effectiveness as well as the safety," said Sarah Read, deputy director of the National Institute of Allergy and Infectious Diseases' Division of AIDS.

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To read the rest of this story go to: https://bit.ly/2yScO3n

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Dave Lennon, president of AveXis, spoke about the company's discussions with the European Medicines Agency which last month reverted its initial accelerated assessment on Zolgensma to a standard review. He admitted that Novartis has been preparing "a large volume of responses" from the EMA's second set of questions on the drug and they require "additional time for us to submit as well as for them to review it and therefore we've moved out of the accelerated assessment process but we are on track for a Q4 approval." *(Also see "Novartis's Zolgensma Loses EU Accelerated Assessment" - Scrip, 26 Jul, 2019.)*

What is still unclear is whether or not the information about historic data manipulation was a key factor in the EMA's move to revoke accelerated assessment on Zolgensma. The agency had not yet responded to requests for clarification from *Scrip*'s sister publication *Pink Sheet* at time of going to press.

With regards to the actual falsified data, Narasimhan said, "We are now in the process of exiting the small number of AveXis scientists involved in these data inaccuracies. We do not believe this issue extends beyond these individuals and does not impact our clinical data or gene therapy platform." Lennon agreed, saying that "this was an issue that was historic in nature and relegated to a few individuals within the company."

He went on to say that over the last year since the acquisition, "almost the entire management team of AveXis" has changed and it has hired close to over 1,000 people into an organization "that is much more dependent on integrity of process and quality systems than on individual actions…we will continue to work to make sure that we are operating at the standards that we would expect in the industry, and from Novartis as a company."

Despite his insistence that "we are committed to ensuring the highest levels of transparency and integrity with health agencies, as well as with the patients and providers we serve, news of the falsified data has raised some uncomfortable issues for Narasimhan, who has repeatedly spoken about prioritizing compliance and ethics and improving the Swiss drugmaker's corporate reputation. The latter has taken quite a bashing of late, with ongoing bribery allegations in the US, Greece and South Korea and the damaging revelation that Novartis signed a $1.2m contract with Donald Trump's former lawyer Michael Cohen to get access to the US president. *(Also see "Narasimhan Promises To Improve Novartis' Image As Top Lawyer Exits " - Scrip, 16 May, 2018.)*

Narasimhan did not suffer much from the Cohen controversy given that former CEO Joe Jimenez was in charge but the AveXis data manipulation comes on his watch. He said he wanted to emphasize again that "we are committed to rebuilding trust with society, for me personally all the way through the leadership team and the broader organization. It's a long road and sometimes it's bumpy.

"We investigated it thoroughly, aggressively, to try to get to the bottom answer. We informed the agency as soon as we had a technical assessment. We did that of our own accord proactively…and I think that's why I think everyone in our organization can stand proud that we tried to do the right things in this instance."

Narasimhan added that "we understand the agency has a different perspective which we respect, but we've tried to be transparent." He said that "we'll never be perfect but we'll be relentless in trying to keep improving and being the most highly respected company in our industry."

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Good News For AbbVie: Allergan's Q2 Sales Exceed Expectations, Including Behemoth Botox

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Allergan PLC posted better than expected product sales for the second quarter on 6 August with its blockbusters Botox (onabotulinumtoxinA) and Restasis (cyclosporine) holding up well versus competitive pressures. Yet despite the good news for AbbVie Inc., which is paying $63bn for Allergan primarily for its Botox-fueled revenue stream, the companies still can't shake external concerns that the top-selling wrinkle reducer's sales won't hold up over time.

Investors have good reason to worry, since Botox is facing new competition in its two biggest categories – medical aesthetics and migraine headache prevention. And the dry eye drug Restasis, which has yet to see anticipated generics launch in the US, eventually will be hit by lower-cost versions. Also, several smaller Allergan products, with 2018 sales totaling $2bn, will lose patent exclusivity between now and 2023 when AbbVie's Humira (adalimumab) will face US biosimilars that aim to grab some of the anti-inflammatory injectable's nearly $20bn in annual sales.

For now, however, Botox, Restasis and certain Allergan drugs are seeing sales gains, and launches for multiple new indications and products are anticipated over the next year and a half, despite setbacks for various development programs.

Allergan's new and existing assets won't completely fill AbbVie's revenue hole once Humira biosimilars hit. *(Also see "AbbVie Pounces On Chance To Buy Revenues In $63bn Mega-Deal For Allergan" - Scrip, 25 Jun, 2019.)* However, the company anticipates using revenues from Allergan's products to support its own research and development, including business development, for drugs that may help reverse the coming sales decline.

ALLERGAN'S PRODUCT SALES BEAT CONSENSUS

Allergan reported $4.09bn in second quarter non-GAAP revenue, which was down 1.1% year-over-year from $4.1bn, but the April-to-June period beat analyst consensus expectations of $3.9bn. Botox sales grew 4.2% to $974m in the quarter, in-

cluding a 3.6% increase for therapeutic indications to $545.8m and a 5% rise in cosmetic uses to $428.2m.

The company's top-seller continued to grow despite perceived competition from new products, such as injectable CGRP inhibitors for migraine headache prevention – Amgen Inc./Novartis AG's Aimovig (erenumab), Eli Lilly & Co.'s Emgality (galcanezumab) and Teva Pharmaceutical Industries Ltd.'s Ajovy (fremanezumab) – and Evolus Inc.'s recently launched Jeuveau (prabotulinumtoxinA). *(Also see "With Jeuveau Approval, Evolus Will Focus On The Beauty Business To Gain Market Share" - Scrip, 5 Feb, 2019.)*

Cowen analyst Ken Cacciatore said in a 6 August note that Allergan's "core portfolio appears to be performing well despite investor fear of perceptual weakness in a few critical franchises (specifically in the Botox line)," and pointed out that key opinion leaders in the aesthetics space don't see new neurotoxins from Evolus and Revance Therapeutics Inc. as material threats to Botox. *(Also see "Another Botox Competitor: Revance Prepares Longer-Lasting RT002 For BLA Submission" - Scrip, 22 Feb, 2019.)*

"Although Botox has been on the US market for well over a decade (with Dysport and Xeomin just a bit shorter), our consultants believe that the [medical aesthetics] market is actually still nascent, and that strong growth is expected to persist for the foreseeable future," Cacciatore wrote.

Meanwhile, Restasis sales fell just 3.4% to $322.8m for the quarter versus analyst consensus of $209m and William Blair analyst Tim Lugo's forecast of $231m, since would-be manufacturers of generics for the dry eye drug apparently continue to have problems gaining regulatory approval. Restasis is considered a complex generic. *(Also see "FDA Urges Development Of Generic Alternatives To Bring Down Prices Of Complex Drugs " - Pink Sheet, 18 Sep, 2018.)*

"Although we don't want to begin to set unrealistic expectations, we would simply note that obviously Mylan's action date on generic Restasis is now well past and we would assume they received another [complete response letter (CRL)]," Cacciatore said. "Additionally, we believe that Teva's action date has also passed, and therefore they may have likely received a CRL. This now limits the potential set of competitors, meaning if those unidentified other potential generic challengers also stumble, Restasis might have more durability than we and management are assuming."

> "Allergan's core portfolio appears to be performing well despite investor fear of perceptual weakness in a few critical franchises."
> – Ken Cacciatore

Allergan didn't host a conference call to discuss its second quarter earnings with analysts and investors, deferring to AbbVie while the companies' merger is pending. However, Allergan said in a Q&A that accompanied its earnings report that it expects to have patent exclusivity for Restasis through at least 31 August of this year. The company also said it increased its overall revenue guidance for 2019 to reflect higher-than-expected revenue from the drug and other products. Allergan now forecasts total non-GAAP revenue of $15.4bn-$15.6bn this year versus prior guidance of $15.1bn-$15.4bn.

Vraylar (cariprazine) also was a big contributor to second quarter growth with sales of $196.1m, up 71.7% year-over-year, and is expected to become a blockbuster following recent US Food and Drug Administration approval for bipolar depression. *(Also see "Allergan Confident Data Support Bipolar Depression Addition To Vraylar's Label " - Scrip, 5 Apr, 2018.)*

Cacciatore said the new indication adds $500m-plus in sales for Vraylar, so that the product will generate more than $2bn in annual sales.

NEVERTHELESS, SALES ARE DECLINING FOR SOME DRUGS

Despite big gains for Botox, Vraylar and other products plus Restasis's holding power, Allergan's overall revenue declined due to generic competition for certain brands with help from big drops in sales for two device franchises in the company's medical aesthetics business.

Among the company's now-generic drugs, Canasa (mesalamine) for ulcerative proctitis, Namenda XR (memantine extended-release) for Alzheimer's disease symptoms, Rapaflo (silodosin) to improve urination for men with benign prostatic hyperplasia and Estrace (estradiol vaginal cream) lost patent exclusivity in 2018. Sales for the four products totaled $395.1m in 2018, while sales in the first half of 2019 totaled $59.8m for Canasa, Namenda and Rapaflo – a fraction of last year's total on an annualized basis. This year's Estrace sales were not broken out from "other product revenues."

And in addition to the impending Restasis generics later this year, the main patent for Delzicol (mesalamine) expires in 2020. Delzicol and the now-generic Asacol (mesalamine), both used to treat ulcerative colitis, generated $76.3m in the first half of 2019, which was down 19.6% from the first two quarters of 2018.

Among Allergan's medical aesthetics devices, sales of CoolSculpting for body contouring fell 38.9% to $29.8m in the second quarter, but the US FDA cleared the brand's related contouring product CoolTone on June 24, which Allergan intends to launch during the second half of 2019. Also, the company's breast implant sales plunged 68.7% to $36.2m due to a worldwide recall of textured implants. *(Also see "Worldwide Recall On Allergan Textured Breast Implants" - Medtech Insight, 24 Jul, 2019.)*

Allergan said that growth in its underlying business and the longer patent exclusivity for Restasis will allow the company to absorb the financial impact of its textured breast implant recall.

UPCOMING LOES IMPERIL $2BN IN REVENUE

Five other major Allergan franchises with sales totaling $2bn last year also are expected to lose patent exclusivity over the next four years:

- the atypical antipsychotic Saphris (asenapine; $139.7m in 2018 sales) in 2020,
- the depression drug Viibryd (vilazodone; $349.m) in 2021,
- high blood pressure drug Bystolic [(nebivolol); $585.5m combined with Byvalson (nebivolol and valsartan)] in 2021,
- the glaucoma drugs Combigan/Alphagan (brimonidine; $551.4m) in 2022 and 2023, and
- Ozurdex (dexamethasone intravitreal implant; $298.7m) for macular edema and non-infectious uveitis in 2023.

Sales in the second quarter of 2019 declined 3.6% year over year for Saphris to $32.6m, rose 25.1% for Viibryd to $110.5m, increased 1.5% for Bystolic/Byvalson to $151m, fell 7.1% for Alphagan and Combigan to $132.5m, and gained 16.1% for Ozurdex, totaling $110.9m.

AbbVie CEO Richard Gonzalez was clear in announcing the Allergan deal that Botox was a main focus of the companies' merger, but $2bn in potential sales declines through 2023 is significant on top of the loss of patent protection in the nearer term for the $1bn-plus product Restasis. AbbVie's R&D pipeline alone isn't likely to make up for Humira sales declines in the US starting in 2023, yet the company is buying Allergan with billions of dollars in future branded product sales declines and an R&D pipeline that's seen several failures. *(Also see "Allergan's Big Deal: A Buyout, Not A Split, Appeases Wary Investors" - Scrip, 25 Jun, 2019.)*

However, some pipeline programs in Allergan's portfolio are nearing the finish line. The company expects an FDA decision in December for its acute migraine drug, the oral CGRP inhibitor ubrogepant, with a launch planned for the first half of 2020. *(Also see "US Product Launches To Plan For In 2020" - Scrip, 30 May, 2019.)*

In ophthalmology, bimatoprost SR, an implant for the treatment of glaucoma, also is under FDA review with a first half 2020 launch anticipated. And, despite safety concerns, abicipar for age-related macular degeneration is under review with a mid-2020 US launch planned. *(Also see "Allergan Improves Safety Of Abicipar, But Not Enough Compared To Lucentis, Eylea" - Scrip, 2 Apr, 2019.)*

No major products in development or already approved are expected to hold up clearance of the AbbVie-Allergan merger due to anti-competitive reasons; the companies expect their transaction to close in the first quarter of 2020. *(Also see "AbbVie's Five Biggest Priorities, Apart From Allergan" - Scrip, 26 Jul, 2019.)*

William Blair's Tim Lugo said in a 6 August note that he expects the deal to close in early 2020, as expected, without the kinds of major delays from the US Federal Trade Commission (FTC) that have put the timing of other big pharma mergers in doubt.

"We will await announcement of any required divestitures before close considering the Federal Trade Commission (FTC) has been actively policing mega-mergers and product acquisitions (Bristol-Myers/Celgene and Roche/Spark), but see minimal product overlap with Allergan and AbbVie," Lugo wrote.

AbbVie anticipates a divestiture of Allergan's Phase II/III inflammatory bowel disease candidate brazikumab, which Allergan confirmed in its second quarter Q&A, noting that it also expects to sell off Zenpep (pancrelipase) for exocrine pancreatic insufficiency due to cystic fibrosis and other conditions. Zenpep sales totaled $70m in the second quarter, up 26.1% year over year.

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Novo's Ozempic Soars As Focus Shifts To Oral Semaglutide

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Novo Nordisk AS has posted a healthy set of financials for the second quarter, helped by the strong launch of the injectable Ozempic (semaglutide) but all eyes are now on the third quarter and the expected US approval of the closely-watched oral version of the once-weekly GLP-1 type 2 diabetes drug.

Ozempic Q2 sales came in at DKK2.33bn ($349m), topping analyst consensus by 26%, and on a conference call, CEO Lars Fruergaard Jørgensen said Novo was pleased with the positive market reception in Europe and North America. He noted that Ozempic, which was approved in the US in February 2018, has now obtained broad formulary coverage and the weekly new-to-brand prescription (NBRx) market share for the drug has now reached 35%, bringing the Danish company's combined GLP-1 NBRx slice of the market to 53%, including the older GLP-1 therapy Victoza (liraglutide).

Novo Nordisk expecting a call soon from the FDA on oral semaglutide

The success of Ozempic is partly offsetting declining sales of Victoza, which Novo said was due to a negative impact from changes in the channel and payer mix, as well as coverage gap legislation that have hit prices negatively. Mylan NV filed an abbreviated new drug application (ANDA) for Victoza last month and while Novo previously settled with Teva Pharmaceutical

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Industries Ltd. which is licensed to launch a generic in December 2023 (June 2024 if Novo is granted a pediatric extension), analysts at Morgan Stanley issued a note on 9 August saying they do not expect a launch before 2023.

Jørgensen said Novo will likely use the same tactics with Mylan as it did with Teva "because it's really not anything different from that, it is pretty much as one would expect, I would say, and we know what to do to defend ourselves."

Back with Ozempic and chief science officer Mads Krogsgaard Thomsen talked about three new Phase IIIb trials initiated in Q2. The five-year 1,500-patient FOCUS study will assess the long-term effects of the drug on diabetic retinopathy, while the 1,000-patient SUSTAIN FORTE trial was initiated. The objective of the trial is to look at the efficacy and safety of semaglutide 2mg versus semaglutide 1mg subcutaneous in type 2 diabetics; the 3,000-patient FLOW trial will assess the effect of Ozempic versus placebo on the progression of renal impairment in people with type 2 diabetes and chronic kidney disease.

However, much of Novo's focus now is on oral semaglutide, which was filed in Japan last month and is currently under review at the US Food and Drug Administration. Analysts expect the agency to give the thumbs-up next month based on the extensive PIONEER clinical development program, which is composed of 10 evaluations of the oral version.

Thomsen said, "We're having a really constructive dialog with the agency and we do believe we are on track to meeting the Prescription Drug User Fee Act action date of 20 September in the case of the diabetes indication." He added that progress is being made on Novo's applications for Ozempic and oral semaglutide to get cardiovascular indications, saying that while the FDA may call an advisory committee meeting to discuss those two cases, "we have not heard that there should be one, but there is always the possibility, that is the prerogative of the agency."

Thomsen went on to say Novo does not think its submission strategy of a six-month fast track application for oral semaglutide for diabetes and then, two 10-month standard reviews for the cardiovascular indications for the two versions of semaglutide is a problem. "The agency is clearly diligent in reviewing the dossiers as evidenced from the questions that are flowing to and from the company," he said, "and I have no reason to believe anything else but the PDUFA action dates" of 20 September and 20 January, 2020.

Jørgensen declined to talk about launch plans for oral semaglutide, likely in 2020, because "we do not have approval by the FDA so we cannot go into a specific contracting discussion." He added that Novo is "medical-type discussions where we are making sure that payers have a good insight into profile of the product and those are being conducted as we speak and we believe they are going very well."

He stated that the company has confidence in the drug's profile "and also that we can obtain access to have a meaningful launch when we get to that." Novo also confirmed the initiation of SOUL, a cardiovascular outcomes trial for oral semaglutide. The trial is expected to enrol 9,600 people in 34 countries.

As for the Q2 numbers, analysts were reasonably impressed as operating profits rose 10% to DKK13.45bn and sales increased 9.6% to DKK30.04bn. Wimal Kapadia at Bernstein issued a note on 9 August saying the results were "strong in all the right places… all eyes were on the GLP-1s following a weak 1Q19 and Novo delivered." He added that "a shift to Ozempic from Victoza is a clear positive" and highlighted the outperformance of the obesity therapy Saxenda (liraglutide), up 66% to DKK1.46bn.

Kapadia went on to claim that "the only thing holding Novo back is US pricing," adding that while oral semaglutide "is not bullet proof," investors should look at the stock "to capture the transition to Ozempic and oral sema and the potential from obesity." He said that "we may not care about obesity much today, but we will and soon," citing possible Phase III semaglutide data in the first quarter of 2020 and also a Phase II trial that has just started looking at combining semaglutide and Gilead Sciences Inc.'s cilofexor (an FXR agonist) and firsocostat (an ACC inhibitor) for the treatment of patients with nonalcoholic steatohepatitis (NASH).

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Vifor Plots Veltassa Growth In Face Of Emerging AstraZeneca Threat

Zurich, Switzerland-based Vifor Pharma Group has set out how it plans to grow sales of its hyperkalaemia treatment Veltassa (patiromer) in the face of competition from AstraZeneca PLC.

Vifor got a headstart on AstraZeneca in the hyperkalaemia market as its competitor hit a series of barriers that stopped it getting to market. AstraZeneca finally won approval for its product, Lokelma(formerly ZS-9, sodium zirconium cyclosilicate), last year and set about trying to generate a belated return on the $2.7bn it spent to acquire the drug in its takeover of ZS Pharma.

Lokelma got off to a slow start, generating sales of $2m in the first half of the year, but Vifor is alert to the risk that AstraZeneca could pose to the upward trend in sales of its sodium-free potassium binder, Veltassa.

"We don't see any deviation in the trend but of course Lokelma is in the market," Colin Bond, Vifor's chief financial officer, said on an 8 August first-half results conference call with analysts.

Veltassa, which was approved in the US in 2015 and Europe two years later, made a similarly slow commercial start. Sales in the first half came in at CHF62.6m ($63.6m), up 70% on the prior period but still a slight return on the $1.53bn Vifor paid to acquire the drug and its developer Relypsa.

Vifor has run up against a European market access environment that it thinks has gradually become more and more challenging in recent years. Those challenges have slowed the rate at which Veltassa has

secured coverage in European markets but there are signs of progress: Vifor secured coverage for the drug in Germany, Spain and Belgium in the first half of 2019 at satisfactory prices.

"We are quite happy with the results we are seeing so far," Stefan Schulze, chief operating officer at Vifor, said. Schulze expects Vifor to get positive coverage decisions in other markets over the second half of the year but cautioned that progress in some of the bigger European countries, such as Italy, France and the UK, is more likely to happen in 2020.

Vifor sees the day it secures broad coverage for Veltassa in Europe as the likely inflection point for sales of the product but it is also working on other potential growth drivers. The pursuit of one of those growth drivers led Vifor to increase R&D spending by 19% in the first half of the year.

The additional money funded the initiation of a Phase IIIb trial of Veltassa in heart failure patients with reduced ejection fraction who are hyperkalemic. The roughly 2,400 participants in the trial will take Veltassa or placebo on top of renin-angiotensin-aldosterone system inhibitor medications. Vifor hopes to link Veltassa to a reduction in cardiovascular deaths or hospitalizations.

"The DIAMOND study initiated in May will definitely be key to uptake in cardiology," Vifor's executive chairman, Etienne Jornod, said. Currently, 90% of Veltassa prescriptions are in nephrology, making cardiology a largely untapped opportunity for Vifor. Top-line data from DIAMOND are due in 2022. Vifor can afford to invest in Veltassa in part because of the success of other products. Ferinject (ferric carboxymaltose), a treatment for iron deficiency, is on track to achieve blockbuster status a year ahead of schedule on the back of another period of double-digit growth. Vifor Fresenius Medical Care Renal Pharma, a joint venture between Vifor and Fresenius Medical Care, also achieved double-digit growth.

Going into 2019, Vifor predicted it would enter into one in-licensing, product acquisition or corporate transaction in the year. The deal is yet to materialize but Vifor affirmed the plan in the most recent set of results, while remaining non-committal about the likely nature of the transaction.

"It could be a commercial deal, it could be a pipeline deal, it could be both," Bond said.

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Opioid Litigation Clouds Loom Over Teva's Turnaround

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Lack of clarity over Teva Pharmaceutical Industries Ltd.'s liability in ongoing opioid litigation continues to weigh on the generic drug manufacturer as it works toward a financial turnaround. Despite executing on a sweeping cost savings program, continuing to pay down on a mountain of debt and progress stabilizing its North American generic drug business, the company's growth trajectory remains unclear.

Teva announced second quarter sales and earnings on 7 August and, despite financial improvements in the underlying business, management could not alleviate investor concerns on the opioid front.

> "I'm not the kind of guy who ever quits unless the job is done, so of course I'll see it through." - Kare Schultz

Adding to the uncertainty, chief financial officer Michael McClellan announced his intention to leave the company, with Teva initiating a search for a new CFO. McClellan said he was leaving for personal reasons and will remain through the third quarter results announcement, but analysts felt the move added to uncertainty around the company's outlook.

Some analysts, during the same-day call, pressed leadership on their commitment to seeing Teva through the turnaround. The current management team led by CEO Kare Schultz have been viewed relatively favorably by investors given the financial headwinds the company is facing.

Suntrust Robinson Humphrey analyst Gregg Gilbert asked Schultz outright about his intentions, commenting, "When you took the job, you knew you were signing up for a major turnaround that would be painful in many ways, but I suspect you did not sign up for a massive opioid story that could take years to resolve and create investor concern about bankruptcies."

Schultz, who is nearing two years into his turnaround plan for Teva, responded that he has a five-year contract and would stay longer if it is required. "I'm not the kind of guy who ever quits unless the job is done, so of course I'll see it through."

He downplayed the impact of the opioid litigation, noting that managing potential litigation is a standard part of the job description for a pharmaceutical CEO.

"I think it's remarkable that actually apart from Mike, who for personal family-related reasons is leaving now, I have exactly the same management team as I appointed now nearly two years ago," Schultz added.

HOW MUCH TO RESERVE FOR LIABILITY EXPOSURE?

In May, Teva agreed to pay $85m to settle claims brought by Oklahoma over the company's role in the US state's opioid epidemic as a result of marketing both generic opioids and the fentanyl brands Actiq and Fentora. *(Also see "Teva Stresses Stability In Settling Oklahoma Opioids Case" - Generics Bulletin, 28 May, 2019.)*

Several other states have filed independent suits against opioid manufacturers that could result in large payouts. *(Also see "Opioid Litigation Avalanche: New York's Expanded Suit Puts More Pressure On Makers And Distributors " - Pink Sheet, 28 Mar, 2019.)* The bulk of civil actions against opioid makers and distributors have been consolidated in the US District Court for the Northern District of Ohio, where a trial is slated to begin in October.

Teva has an accrual of $646m in the second quarter for legal settlements, which it said were mainly for the Oklahoma settlement and estimated provisions for other certain opi-

oid cases. Teva separately faces financial exposure from a criminal investigation by the US Department of Justice into generics industry price-fixing.

"With all of the evidence that we have in our hands, we deny any liability, because we have not seen any evidence of us having any misconduct in the opioid situation or any misconduct in the pricing area," Schultz told investors. In the Oklahoma state settlement, Teva was able to avoid claiming any wrongdoing.

Some analysts questioned the amount of money Teva has accrued for legal liability as being too low, given the amount of outstanding litigation.

McLellan said the company had built the estimate at the "low-end of the range" based on understanding from the Oklahoma settlement and estimates for future settlements.

"We still don't see that we have a huge liability in this case in terms of causing the epidemic, but we do know there's a lot of cases going on and there is a likelihood that some of these could settle in the future, so that's where the number comes up," he said.

But investors clearly are seeking more clarity on the amount of liability. The company's stock price has lost about half of its value since May, opening on 7 August at $6.59. One year ago, the stock was trading at $22.50 – and the company was already in the midst of financial upheaval.

NORTH AMERICAN GENERICS STABILIZE

Schultz has been guiding investors that 2019 will be a trough year for Teva, with the company on track to return to growth in 2020. He recommitted to that forecast during the mid-year earnings call.

"It's not that there will be a dramatic turnaround in the coming years, but the trend lines will slowly change, and we'll start to see a moderate increase in revenues and moderate increases in EPS going forward," he said. The current year will be the lowest in terms of operating profit and in terms of average earnings per share, he assured investors.

North America segment revenues declined 8% versus the prior-year quarter to $2.07bn, due to lower sales of Copaxone (glatiramer), Treanda (bendamustine) and other specialty products. Generic revenues notably stabilized in the quarter, with revenues flat at $946m. US revenues, Teva's largest market, declined 10% to $1.93bn. Revenues in Europe declined by 11% to $1.18bn.

Consolidated revenues decreased 8% in the quarter to $4.34bn, with lower sales of Copaxone offsetting growth from new products like Austedo (deutetrabenazine) and Ajovy (fremanezumab). The company reported an operating loss of $644m in the quarter compared to $14m in the second quarter of 2018.

Ajovy, a calcitonin gene-related peptide (CGRP) inhibitor for migraine headache prevention, is expected to be a big future growth driver for Teva, but it brought in only $23m in the quarter after generating $20m in the first quarter. Teva previously targeted revenues of $150m for Ajvoy in 2019, but has had to scale back forecasts.

"I think it's likely that we will be slightly shy of the $150m on Ajovy," Schultz said, but he indicated that higher than expected sales of Austedo will make up the shortfall. Austedo for tardive dyskinesia generated $96m.

Ajovy brought in lower revenues than either of its two competitors, Amgen Inc./Novartis AG's Aimovig (erenumab), which generated $83m in the second quarter, and Eli Lilly & Co.'s Emgality (galcanezumab), which generated $34.3m.

Exec VP-North America commercial Brendan O'Grady said Teva is focusing on profitability with Ajovy and stopped buying down the copay for plans that have Ajovy on an exclusion list.

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Sage's Zulresso Launch Is Off, But Not Running

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Sage Therapeutics Inc. advised investors not to expect the launch of Zulresso (brexanolone) to pick up momentum until late in the year and into early 2020, as it prepares for a slow ramp of the first ever treatment for postpartum depression. Management updated investors on the launch of Zulresso during a second quarter earnings call on 6 August.

The drug is administered through a 60-hour I.V. infusion and requires continuous inpatient monitoring for sedation and sudden loss of consciousness, which could present commercial hurdles. It was approved by the US Food and Drug Administration in March with a Risk Evaluation and Mitigation Strategy that will take time for Sage to implement. *(Also see "Zulresso Is Sage's First Step In Postpartum Depression Treatment" - Scrip, 19 Mar, 2019.)*

It also had to go through scheduling by the Drug Enforcement Administration, which can take about 90 days. Zulresso officially launched the week of 24 June as Sage's first commercial drug, CEO Jeff Jonas told the call.

"Six weeks into the launch, we are right were we expected to be," Jonas said. Given the timeline, the company obviously did not generate any substantial revenues in the second quarter, just $519,000 coming from channel stocking ahead of the launch. The first patient was treated in July, Sage reported. The company has been focused on certifying health care facilities to administer

Zulresso under the REMS program and establishing formulary access. More than 100 hospitals, infusion centers, wellness centers and fertility centers have been certified under the REMS, Sage said. Those centers – most of which are hospitals – cover 55 of the top 140 Metropolitan Statistical Areas (MSAs) in the US and about 45% of potential patients.

"Over time, our goal is to have at least one site of care in all 140 MSAs to provide treatment options for women with PPD across the US," chief business officer Mike Cloonan said.

As of 1 August, the company said plans representing 65% of covered lives have committed to favorable coverage of Zulresso with either light or no restrictions, Cloonan said. Other plans, covering approximately 30% of covered lives, are still reviewing Zulresso. Typical policies require a prior authorization with a diagnosis of PPD for moderate to severe patients, he added.

Sage also opened a patient support organization in Raleigh, North Carolina in June. "We are taking a family-centric approach to our go-to-market strategy, and Sage Central is integral to our efforts to provide a range of patient support resources to assist women with PPD and their families," Cloonan said. Sage Central connects patients to case managers who can provide information about navigating treatment with Zulresso, including finding certified sites and understanding insurance coverage.

The commercial experience Sage gains with the launch of Zulresso is expected to give the company a leg up when it launches an up-and-coming oral drug for PPD and major depressive disorder, SAGE-217, which investors view as the larger commercial opportunity.

SAGE-217 is a next-generation positive allosteric modulator optimized for selectivity to synaptic and extrasynaptic GABA-A receptors that showed a significant effect on PPD in the Phase III ROBIN trial, without loss of consciousness. The company also has completed one Phase III trial in MDD and is on track for another data read from a second Phase III trial, MOUNTAIN, in MDD in the fourth quarter or early 2020.

As Jefferies analyst Andrew Tsai said in a same-day research note, "While Zulresso isn't a core part of our thesis, its more important aspect is to pave the path for '217."

On Sage, the Jefferies team is decidedly bullish. "Sage represents one of the cleaner, de-risked growth stories in biotech as its two novel depression drugs could potentially generate a cumulative $4bn-$6bn in peak sales over time."

Sage is planning a far-reaching development plan for '217, which it outlined during an R&D overview on 24 July. In addition to PPD and MDD, the company is evaluating opportunities in bipolar depression, generalized anxiety disorder and treatment-resistant depression.

Sage reported cash and equivalents of $1.2bn as of 30 June and forecast a cash balance of at least $950m at the end of the year.

Published online 6 August 2019

Bayer Eyes Indications Beyond BlueRock's Initial Focus With $240m-Plus Buyout

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Bayer AG already held a majority stake in BlueRock Therapeutics, but now says it will pay $240m up front and up to $360m in milestone fees to own the cell therapy developer outright and potentially expand its focus beyond neurology, cardiology and immunology.

While Bayer is eyeing new disease areas for BlueRock's induced pluripotent stem cell (iPSC)-based Cell+Gene technology platform, the biotechnology firm will operate autonomously with some input from its parent company to maintain an entrepreneurial spirit of innovation. The deal is in line with Bayer's strategic interest in cell and gene therapy, in which the company has made significant investments, including the creation of its Leaps by Bayer unit for advancing innovative technologies in specific areas of interest.

Bayer supplied a majority of the funding for BlueRock's $225m series A venture capital round in 2016 through its Leaps initiative under a joint venture with Versant Ventures Between that financing, the up-front fee involved in Bayer's buyout of the company, and future payments contingent on preclinical and clinical milestones, the companies said BlueRock's valuation is about $1bn.

> "We now can execute upon our vision and strategy more aggressively as part of Bayer," – Emile Nuwaysir

BlueRock also entered into a collaboration agreement with the CRISPR gene editing specialist Editas Medicine Inc. in April, but the financial details of that transaction were not disclosed. *(Also see "Deal Watch: Editas, BlueRock Ink Cross-Licensing Technology Collaboration" - Scrip, 3 Apr, 2019.)*

BAYER CONSIDERED MULTIPLE DEAL OPTIONS

Sasha Doumani, spokeswoman for Bayer's pharmaceuticals group in the US, said the company considered a variety of deal types and structures to incorporate BlueRock's engineered cell therapies into its research and development pipeline before it decided an acquisition was the best option.

"The acquisition will allow Bayer to acquire full rights to BlueRock's broad IP portfolio and the entire technology platform with the possibility to extend the platform to other indications beyond the current development programs," Doumani told *Scrip*. "Bayer had considered alternative transaction structures, including licensing of one of the existing development programs, but determined that the platform nature of the technology provided great potential and therefore owning full rights provided better long-term value creation. Bayer would have the full benefit of the upside of the BlueRock platform and the opportunity to steer the future strategy and overall direction of the company."

BlueRock will report to Bayer for financial purposes and the firm will be overseen by a board that includes BlueRock CEO Emile Nuwaysir, representatives from Bayer and external advisors. However, BlueRock will have its own executive team to manage day-to-day operations in line with its strategic objectives.

Also, Doumani explained, "A Bayer alliance manager safeguards BlueRock's autonomy and freedom to operate within the Bayer governance framework and interacts with the BlueRock executive team to ensure mission and strategy are appropriately supported by Bayer."

"We now can execute upon our vision and strategy more aggressively as part of Bayer," Nuwaysir told *Scrip*, noting that much of BlueRock's operation will remain unchanged.

STRATEGY TO FACE FIRST TEST THIS YEAR

The executive team will oversee initiation of BlueRock's first clinical trial for its Parkinson's disease candidate before the end of 2019. That candidate will be the first to demonstrate the potential of the company's Cell+Gene technology platform.

The platform begins with healthy donor cells that are transformed into iPSCs that BlueRock can expand and differentiate into nearly any cell type within the body. The company's technology includes native cell replacement to switch out disease-specific cells with engineered iPSCs and *ex vivo* gene editing of cells to augment and enhance their function and improve safety. Through gene editing, additional functions can be engineered into the cells, including protein production, antibody or cytokine secretion, or local enzyme replacement.

The cells developed to treat Parkinson's disease are dopaminergic neurons created with BlueRock's native cell replacement technology to re-innervate the brain and reverse degeneration to potentially restore motor control and function.

Other programs in preclinical development include engineered microglia to treat neurodegeneration, oligodendrocytes using the native cell replacement technology to treat demyelinating disorders, enteric neurons for Hirschsprung's disease, cardiomyocytes for heart failure, macrophages engineered for tolerance and to treat fibrosis, and engineered T-regulatory cells for graft-versus-host disease.

Nuwaysir said BlueRock has about 130 employees, but that number will grow as more development programs move into the clinic.

Published online 8 August 2019

Multiple Firsts As Pexidartinib Approved In US – With Warning

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The US approval of Daiichi Sankyo Co. Ltd.'s Turalio (pexidartinib) brings with it a number of firsts, both for the company and in the wider oncology space, where the major Japanese firm is mounting a strategic push to build substantially its market presence over the next few years.

For patients, the FDA nod marks the first for a drug therapy specifically for adults with symptomatic tenosynovial giant cell tumor (TGCT). For Daiichi, the approval is the first in the US for its oncology pipeline, and the first globally for a first-in-class co-inhibitor of CSF1R, KIT and FLT3.

The path to the marketing clearance has not been entirely smooth, however, complicated mainly by the hepatotoxicity risks around pexidartinib, which led to two partial clinical holds during development. Two irreversible cases of cholestatic liver injury, out of 768 patients receiving the drug in clinical trials, occurred via an unknown mechanism in Phase III trials.

The commercial roll-out of Turalio is therefore being accompanied by a black box warning from the FDA that the drug "can cause serious and potentially fatal liver injury." There is also requirement for liver monitoring prior to and during treatment, while the product will be available only through a risk evaluation and mitigation strategy (REMS) discussed earlier this year. *(Also see "Defining REMS Success An Unanswered Question For Daiichi's Pexidartinib" - Pink Sheet, 15 May, 2019.)*

Daiichi stressed that as part of this, Turalio will be available only through certified prescribers, with all patients included in a registry. Biologics by McKesson Corp. is acting as the exclusive specialty pharmacy provider in the US, where Daiichi is also running a patient financial support program.

MEDICAL NEED

Despite the precautions, the medical need for pexidartinib in TGCT is clear, albeit in what is a relatively small, highly specialized market. Turalio is approved specifically for TGCT associated with severe morbidity or functional limitations and not amenable to improvement with surgery.

Also known as pigmented villonodular synovitis or giant cell tumor of the tendon sheath, TGCT is a rare debilitating disease affecting the joints, for which there are no approved systemic therapies. The main treatment so far has been surgery, but only in suitable patients.

First Drug For TGCT Approved In US

Given the nature of this market, pexidartinib received Breakthrough Therapy and orphan designation in the US, where it was given a priority review after its submission last December.

The FDA nod was supported mainly by the placebo-controlled Phase III ENLIVEN study, which showed a tumor response rate (RECIST) of 38% versus 0% for placebo at week 25.

The oral small molecule acts as a multi-kinase inhibitor of colony stimulating factor 1 receptor (CSF1R), KIT proto-oncogene receptor tyrosine kinase (KIT) and FMS-like tyrosine kinase 3 (FLT3).

Few other drugs appear to be in active clinical development for the disorder, Biomedtracker shows, with other companies focusing on macrophage colony stimulating factors. In this class, Novartis AG's MCS110 is in Phase II and Roche's emactuzumab in Phase I, and both are non-oral antibodies.

Daiichi notes the estimated global incidence of TGCT is around 11-50 cases per million person-years, with the localized (rather than diffuse) form accounting for 90-90% of cases. But in sufferers where the tumor has wrapped around bone, tendons or ligaments, surgery is difficult or impossible, and in severe cases limb amputation may be necessary.

The recurrence rate for localized TGCT is around 15% following complete resection, where this is possible.

WIDER ONCOLOGY STRATEGY

Pexidartinib was one of the main attractions behind Daiichi's acquisition for $805m upfront in 2011 of California-based Plexxikon Inc., which now acts as the small molecule structure-guided oncology R&D center of the Japanese company.

Building on this and its other targeted acquisitions, notably of Ambit Biosciences Inc. for $410m in 2014, Daiichi is aiming to deliver to market seven pipeline oncology products by the end of fiscal 2025. The hope is to build revenues of JPY500bn ($4.5bn) in oncology revenues over the same time frame.

While the huge deal with AstraZeneca PLC in March for the antibody-drug conjugate trastuzumab deruxtecan (DS-8201) - worth up to $6.9bn in total - will boost these ambitions, pexidartinib will make a more modest contribution.

Datamonitor Healthcare sees the molecule's sales growing to $85m globally in 2023, given its highly specialist setting.

Elsewhere, it was submitted in the EU for the same TGCT indication this March and Daiichi's current pipeline also shows it in early clinical development in Asia for solid tumors, including TGCT. The company so far has opted to develop the drug independently, given its indication, which does not require a large sales force.

Elsewhere in the oncology pipeline, Daiichi's main late-stage assets include the oral FLT3 inhibitor quizartinib (from Ambit), approved in Japan for FLT3-ITD-positive acute myeloid leukemia in June.

This is also awaiting EU approval, but received an expected Complete Response Letter in the US the same month. *(Also see "Keeping Track: FDA OKs AMAG's Vyleesi, But Bronchitol And Quizartinib Draw CRLs" - Pink Sheet, 21 Jun, 2019.)*

Published online 5 August 2019

AbbVie Revs Up The Race To Market In Uterine Fibroids

JESSICA MERRILL jessica.merrill@informa.com

AbbVie Inc. and partner Neurocrine Biosciences Inc. have beat Myovant Sciences Ltd. to the US Food and Drug Administration's doorstep with a new drug application (NDA) for the first oral gonadotropin-releasing hormone (GnRH) antagonist, elagolix, for heavy menstrual bleeding associated with uterine fibroids. AbbVie announced the filing on 5 August, positioning the company to beat Myovant to market, as was expected.

AbbVie appears to be several months ahead of Myovant on the launch of elagolix for uterine fibroids if the application is approved, and has another advantage in that elagolix already is on the market and sold as Orilissa for endometriosis pain. Myovant recently announced positive Phase III data for its GnRH antagonist relugolix in July and confirmed it is on track for filing an NDA in late 2019. *(Also see "Myovant Plans Q4 Uterine Fibroid Drug Filing In A Showdown With AbbVie" - Scrip, 23 Jul, 2019.)*

The FDA review of elagolix may not be straightforward, however. Labeling for Orilissa in endometriosis carries a warning for bone loss and recommends limiting duration of use because of the safety issue. It also includes a warning on suicidal ideation. Labeling recommends using the lowest possible dose.

A HIGHER DOSE FOR UTERINE FIBROIDS

The NDA filing for elagolix for bleeding associated with uterine fibroids is for a higher dose, which is presumably why AbbVie is filing an NDA rather than a supplemental NDA (sNDA).

The recommended dosing for Orilissa currently is 150mg once daily for up to 24 months or 200mg twice daily for up to six months. The two Phase III trials on which the NDA in bleeding associated with uterine fibroids is based – ELARIS US-1 and ELARIS UF-II – evaluated the safety and tolerability of elagolix at 300mg twice daily for six months.

The studies looked at the therapy alone and in combination with low-dose hormone (add-back) therapy (estradiol 1 mg/norethindrone acetate 0.5 mg) in women for six months. Add-back therapy is in-

TURN TO PAGE 16

HOW BIG ARE PHARMA'S GOLDEN EGGS?

Pharma industry sales are heavily reliant on a relatively small number of relatively costly drugs. But what are its biggest golden eggs, how reliant are companies on those products, and how has the situation evolved over time?

HOW IMPORTANT ARE THE TOP SELLING DRUGS?

In 2018, the top 180 companies in pharma (representing > 95% of all drug sales) generated $829bn in pharma sales. Of these sales:

TOP 10
10 drugs sold by
16 companies
11% of pharma sales
$87.154bn

TOP 20
17% $142.598bn

TOP 50
29% $238.281bn

TOP 10 DRUGS IN 2018 – AND TOP 10 DRUGS A DECADE AGO, SALES ($M)

2018		RANK	2009	
20,473	Humira	1	Lipitor	12,653
9,685	Revlimid	2	Plavix	9,804
7,570	Opdivo	3	Advair Diskus	7,877
7,453	Enbrel	4	Remicade	7,103
7,263	Eylea	5	Enbrel	6,691
7,171	Keytruda	6	Abilify	6,392
7,138	Herceptin	7	Diovan/ Diovan HCT	6,112
7,002	Avastin	8	Avastin	5,747
6,903	Rituxan	9	Rituxan	5,622
6,496	Xarelto	10	Humira	5,565

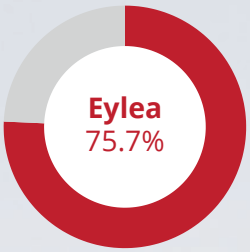
16 Drugs
had sales of
>$5bn in 2018

11 Drugs
had sales of
>$5bn in 2009

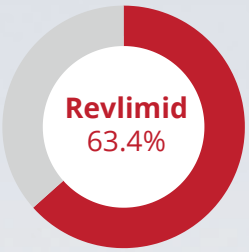
Drugs in red ranked in top 10 in 2009 & 2018

Scrip
Informa Pharma Intelligence

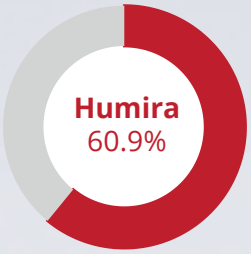
COMPANIES WHOSE REVENUES DEPENDED MOST ON TOP 10 GOLDEN EGGS IN 2018 :



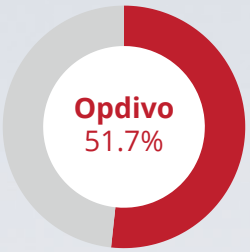
Regeneron, $6.7bn



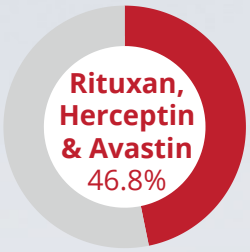
Celgene, $15.3bn



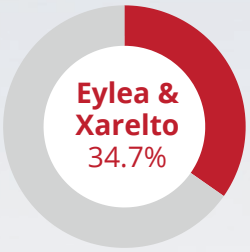
AbbVie, $32.7bn



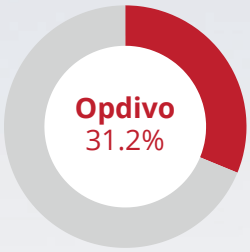
Ono Pharma, $2.7bn



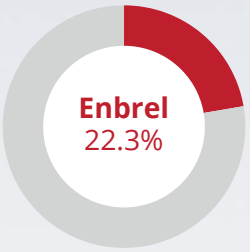
Roche, $44.8bn



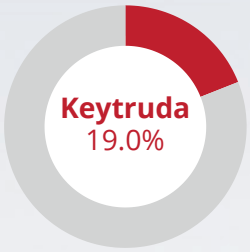
Bayer, $18.8bn



BMS, $21.6bn



Amgen, $22.5bn



Merck & Co., $37.7bn

KEY
Company Name,
Total Pharma Sales

Percentage figure = product's contribution to total pharma sales

TOP DRUGS THIS CENTURY: HOW HUMIRA STACKS UP AGAINST LIPITOR

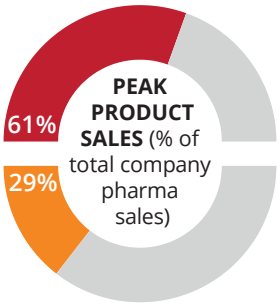
HUMIRA
Top selling drug 2012-2018

abbvie

PEAK SALES

LIPITOR
Top selling drug 2001-2011

Pfizer



BIOLOGIC

AUTOIMMUNE/ INFLAMMATORY

SMALL MOLECULE

CARDIOVASCULAR

2018 SALES FOR COMPARISON...

HUMIRA® adalimumab

$20.5bn

PHILIP MORRIS

$25.5bn[1]

Coca-Cola

$31.9bn[2]

$166.7bn[3]

Sources: [1]Philip Morris cigarettes and other combustibles, PMI corporate website; [2]Coca-Cola company global revenues, Coca-Cola corporate website; [3]Apple iPhone, Apple corporate website.

Drug and pharma sales figures sourced from Medtrack and pharmaceutical company corporate websites and SEC filings.

Design: Janet Haniak / Informa Pharma Intelligence Design Team

CONTINUED FROM PAGE 13

tended to counter side effects around loss of bone mineral density and hot flushes that were associated with treatment. In the Phase III studies, elagolix was associated with both side effects, and those were less frequent among women who received add-back therapy compared to elagolix alone.

Myovant is pursuing a different strategy with relugolix in that it plans to file for US FDA approval of a single combination pill with hormone therapy and has no plans to develop the drug alone as monotherapy for uterine fibroids or endometriosis. *(Also see "Myovant Plans Q4 Uterine Fibroid Drug Filing In A Showdown With AbbVie " - Scrip, 23 Jul, 2019.)*

Orilissa was approved in July 2018 for endometriosis pain but has gotten off to a relatively slow start, despite the large market opportunity, which AbbVie has attributed to the need to build the market. The company originally forecast sales of about $200m in 2019, but then revised guidance midyear to $100m. *(Also see "2018 Saw Record Launches, But No Big Splash" - Scrip, 5 Apr, 2019.)*

"We are still in the early stage of market development and while the launch ramp is slower than initially expected, we continue to believe Orilissa will be a significant long-term opportunity for AbbVie," chief financial officer Robert Michael said during the company's second quarter financial call on 26 July.

> "We continue to believe Orilissa will be a significant long-term opportunity for AbbVie." – Robert Michael

Uterine fibroids are non-cancerous tumors that can build up on the walls of the uterus and cause heavy menstrual bleeding and pain. Non-surgical treatment options for women with uterine fibroids are limited. *Published online 5 August 2019*

An AdComm After All: Amarin's Vascepa Labeling Update Now Delayed By FDA

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The US Food and Drug Administration will convene its Endocrinologic and Metabolic Drugs Advisory Committee to review a critical labeling expansion for Amarin Corp. PLC's Vascepa (icosapent ethyl) for the treatment of severely high triglycerides, likely delaying approval of a supplemental new drug application (sNDA) based on the company's REDUCE-IT cardiovascular outcomes trial.

Amarin said after the stock market closed on 8 August that the US FDA informed the company it will hold an advisory committee meeting, but 14 November is the earliest date available. The Vascepa sNDA previously had an action date of 28 September, but the company said it does not expect the FDA to meet that deadline.

"Amarin did not receive notice from the FDA of a PDUFA date extension," the company reported. "In light of the tentative AdComm date, Amarin anticipates that the PDUFA date will be extended, assuming a typical three-month extension, to a date in late December 2019."

Amarin's sNDA was granted priority review in May, which cuts the application's review time from 10 months to six, so the company pointed out that if the action date is moved to December then FDA approval still could come one month earlier than a typical review. *(Also see "Keeping Track: A Busy Week For Regenerative Medicine, A Surprise Priority Review For Vascepa, And Tazemetostat Aims For Accelerated Approval" - Pink Sheet, 1 Jun, 2019.)* Amarin said it will announce the new PDUFA date when it's revealed by the FDA.

CEO John Thero said during an 8 August conference call with investors and analysts that the FDA's formal notice about the advisory committee meeting asked the company not to publicly disclose the panel review until the date is published in the Federal Register. However, Thero said, Amarin felt a duty to inform its investors and notified the agency that it would disclose the FDA's decision.

Thero said the agency's initial communication did not indicate what topics would be discussed during the advisory panel, including whether or not the panel would cover the controversial topic of mineral oil used as a placebo in the REDUCE-IT trial. *(Also see "Amarin's REDUCE-IT Data For Vascepa May Be Game-Changing, But Not Without Controversy" - Scrip, 12 Nov, 2018.)*

The Vascepa labeling update would allow for treatment of patients with less severe hypertriglyceridemia, based on the population studied in REDUCE-IT – people with triglyceride levels between 150 mg/dL and 499 mg/dL. The current label limits treatment to individuals with triglycerides of 500 mg/dL or above. *(Also see "'That's Huge, Folks': Amarin's Vascepa Cuts CV Risk By 25% On Top Of Statins" - Scrip, 24 Sep, 2018.)*

INVESTORS STUNNED BY SURPRISE ADCOMM

The advisory committee news surprised investors who have felt increasingly confident that there would not be a panel review for the Vascepa sNDA, given the PDUFA date at the end of next month. The FDA's move to grant the application a priority review at the end of May added to investor confidence.

More recently, the company said in an update on 2 July – and Thero reiterated during Amarin's second quarter earnings conference call on 31 July – that an advisory panel was unlikely given the approaching September PDUFA date, further boosting investors' belief that the FDA would not convene a panel.

Amarin capitalized on investors' recently boosted confidence by raising $460m in a stock offering on 29 July, a few weeks after its pre-earnings update. *(Also see "Finance Watch: Amarin Raises Cash To Boost Vascepa Marketing Under Soon-To-Be Expanded Label" - Scrip, 31 Jul, 2019.)*

The offering went to market at $18.59 per share, but the company's stock has fallen this month, closing at $17.81 on 8 August. It plummeted 23.6% to $13.60 in after-hours trading following the advisory committee announcement.

"It's not totally surprising to have a panel, although we didn't think one was likely," Jefferies analyst Michael Yee said in an 8 August note. "It's reasonable to have a drug this big discussed in [a] public forum; hence, while there is some new risk today, we see the [stock price] pullback as more than reflecting that now."

Yee said the advisory committee is likely to discuss: "1) overall risk/benefit for approval, 2) evidence of applicability to various patient populations (type 2 diabetes and/or primary prevention), 3) safety/tolerability, 4) potential to discuss the placebo arm and impact on overall results." *(Also see "Amarin's Vascepa Gets ADA Recommendation For Patients With Diabetes And High Triglycerides" - Scrip, 28 Mar, 2019.)*

BIG SALES BOOST AT STAKE

At stake for Amarin and its investors is a potentially large increase in Vascepa sales. The company's proprietary fish oil formulation already has seen big increases in sales based on the REDUCE-IT results, which showed Vascepa reduced major adverse cardiovascular events (MACE), including a 20% reduction in death in patients with high triglycerides. *(Also see "Latest REDUCE-IT Results Bolster Case For Amarin's Vascepa Fish Oil Pill" - Scrip, 18 Mar, 2019.)*

Vascepa generated $100.4m in second quarter sales, up 91% from the year-ago period. Amarin now expects the drug to bring in $380m-$420m in sales this year versus earlier guidance of $350m. The company has not changed its guidance in light of the advisory committee meeting and PDUFA delay, Thero said.

If the sNDA is approved, Vascepa will become the first drug approved to treat patients with underlying cardiovascular risk beyond cholesterol management – a big potential commercial opportunity. Thero said the market size is potentially a quarter to a third of the US population.

Amarin has been considered a potential acquisition target since the positive REDUCE-IT data were announced last year, but a deal has yet to materialize, and any successful M&A would now clearly hinge on Amarin securing the sNDA approval. In the meantime, the company has been building out its commercial team – doubling the number of its sales representatives – ahead of the launch.

Amarin is moving forward with its launch planning ahead of Vascepa's potential approval in December.

"I am confident we will use all of this extra time productively," Thero said in a letter to the company's employees, which he read during Amarin's conference call about the advisory committee meeting.

The CEO noted in the letter that approval of a drug "is rarely a straight line."

Indeed, in the case of Vascepa, Amarin has had a contentious relationship with the FDA, which declined to expand the drug's label to more patients in 2015 and recommended that the company complete the REDUCE-IT trial before submitting a new sNDA.

Published online 8 August 2019

E2082 Discontinuation May Hit Eisai's Epilepsy Succession

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All clinical trials for Eisai Co. Ltd.'s E2082 have been discontinued following the death in June of a participant in a Phase I study with the investigational neurology drug.

The Japanese company said the fatality occurred after the completion of dosing in the trial, conducted in Japan in 118 healthy adult volunteers of both Japanese and Caucasian ethnicity.

E2082, a next-generation AMPA antagonist, was being progressed as a candidate for epilepsy and epileptogenesis in the placebo-controlled study, at ascending single and multiple oral doses using formulations ranging from 0.2mg to 5mg.

While extending "sincere condolences to the family of the subject," the company noted that exact causality and the link between the drug and the death remained unknown at this point; no other serious adverse reactions had been reported in the study.

DEVELOPMENT RATIONALE

Reflecting its strategic interest in both dementia and epilepsy, Eisai is investigating as part of its R&D strategy the high incidence of epilepsy observed in Alzheimer's disease patients, which in a company scientific meeting this April it noted is around seven times normal. Epilepsy patients also show significantly higher amounts of brain senile plaques with age, and epileptiform (epilepsy-like abnormal brain) activity may be involved at the earlier stages of Alzheimer's.

E2082 was being developed on the hypothesis that an observed increase in calcium-permeable AMPA receptors, and accelerated expression of the AMPA receptor GluR1 subunit, contributes to hyper-excitation in Alzheimer's patients.

Along with the synapse function modulator E2730 (which remains in development), the molecule was being investigated as a potential preventative treatment for epilepsy, given that it had shown highly selective, non-competitive inhibition of the AMPA-type glutamate receptors linked to seizures.

It had also shown a higher affinity for activated synapses than Eisai's already marketed first-in-class, once-daily oral AMPA antagonist epilepsy drug perampanel (marketed as Fycompa), and the hope was to establish clinical proof-of-concept "at an early stage," the company said in April.

Besides the Phase I Japanese trial, E2082 was in Phase II development in the US in photosensitive epilepsy.

Fycompa, approved in various indications including partial-onset and primary

generalized tonic-clonic seizures, is the main member of the AMPA antagonist class, where Biomedtracker lists the only other molecule in clinical development (Phase I) as Takeda's TAK-653, although this is for major depressive disorder.

Elsewhere in the novel epilepsy space, SK Biopharmaceuticals Co. Ltd.'s cenobamate - which acts on GABA and sodium channels - was accepted for review in the US in February, with a decision date of November. *(Also see "New Option For Uncontrolled Epilepsy On Horizon As US Accepts Cenobamate NDA" - Scrip, 12 Feb, 2019.)*

Eisai has a long-standing strategic interest in Alzheimer's through its now genericized former blockbuster Aricept (donepezil) and a development alliance with Biogen Inc., which includes the BACE inhibitor elenbecestat.

AGE A POSSIBLE FACTOR?

In a comment on the trial death in Biomedtracker, analysts at Sagient Research noted that the approved doses of Fycompa are actually higher than those in the Phase I study with E2082, which "raises more questions and uncertainty over how the fatality arose."

Earlier Phase I clinical studies in healthy Asian patients also found the investigational molecule to be well tolerated, but the participant age range in these was 18-54, unlike the wider 20-85 years in the E2082 study, they observed.

More broadly, "This [development discontinuation] will be a great disappointment to the company" given that Fycompa's patent is set to expire in the next few years, Sagient noted; Orange Book data show this will be in June 2021 in the US. E2082 therefore appears likely to have been part of a strategy to protect Eisai's position in epilepsy, where besides Fycompa it has other drugs including Banzel (rufinamide) in the US.

Global Fycompa sales in the current fiscal year ending next 31 March are expected by the company to be JPY25bn ($235m), and Datamonitor Healthcare sees these peaking at a substantial $723m in 2022, helped by broadened indications.

The E2082 trial death has been reported to regulators and in Japan the ministry of health, labour and welfare has launched an investigation.

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PROfound Puts Lynparza On Track For Prostate Cancer Indication

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Prospects have greatly improved for AstraZeneca PLC and Merck & Co. Inc.'s PARP inhibitor Lynparza (olaparib) winning approval in a fourth cancer type after the drug met its primary endpoint in the Phase III PROfound trial in second-line prostate cancer.

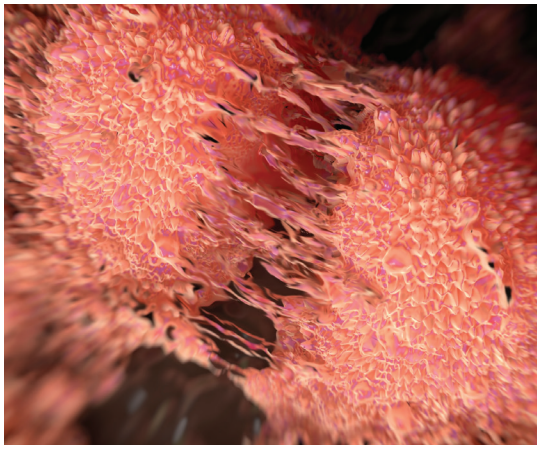
The companies hope to file the product for this additional indication by the end of the year putting it neck and neck with Clovis Oncology Inc.'s rival PARP inhibitor Rubraca (rucaparib). Clovis said in February that it hoped to file its product for BRCA-mutant advanced prostate cancer, pending data maturity, late this year following promising data from its Phase II TRITON2 study. *(Also see "Clovis In Pole Position To Be First PARP For Prostate Cancer" - Scrip, 22 Oct, 2018.)*

Catching up its rival with Phase III data would further strengthen Lynparza's position in the PARP field. It is already approved for advanced ovarian and metastatic breast cancers and is expected to gain approval in pancreatic cancer following the POLO study, which was reported in June at ASCO.

Now it has been shown in the PROfound trial to help patients with metastatic prostate cancer and certain genetic mutations to live longer without the disease worsening, compared with the standard of care.

The topline PROfound data, released on 7 August, showed a statistically significant and clinically meaningful improvement in the primary endpoint of radiographic progression-free survival (rPFS) with Lynparza, compared with Pfizer Inc.'s Xtandi (enzalutamide) or Johnson & Johnsons androgen receptor inhibitor Zytiga (abiraterone) in men with metastatic castration-resistant prostate cancer (mCRPC) selected for *BRCA* 1/2 or *ATM* gene mutations, a subpopulation of HRR gene mutations, the companies said.

The good topline data from PROfound confirmed the potential benefits of using biomarkers to help guide care for men with mCRPC; there are currently no targeted therapies available for patients with prostate cancer. HRR gene mutations occur in approximately 25% of men diagnosed with mCRPC, within which *BRCA* 1/2 and *ATM* form the majority. There is no indication as yet as to how effective Lynparza is in each of the two patient groups.



"The news suggests potential for approval in a fourth cancer type for the drug to add to existing or expected approvals in ovarian, breast and pancreatic cancers." - Deutsche Bank

The safety and tolerability profile of Lynparza was generally consistent with previous trials. Details of the PROfound data will be presented at an upcoming, but unidentified, conference. The PROfound trial is due to complete in 2021.

Lynparza was the first PARP inhibitor approved in December 2014, followed by Clovis's Rubraca in December 2016, GlaxoSmithKline PLC's Zejula (niraparib) in 2017 and Pfizer's Talzenna (talazoparib) in 2018.

While the PROfound data are a milestone in that they are the first positive

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Phase III trial data for any PARP inhibitors in mCRPC, Clovis caught the eye at ESMO in late 2018 with better than expected initial data from its Phase II TRITON2 trial of Rubraca.

In 2017, the US biotech started a Phase III trial, TRITON3, investigating Rubraca in men who have castration resistant prostate cancer. In it Clovis is comparing its PARP to standard prostate cancer treatments Zytiga, Xtandi and the chemotherapy docetaxel. Recruitment for TRITON3 began in September 2017 and will conclude in December 2020, according to Cancer Research UK. GlaxoSmithKline/Tesaro's Zejula (niraparib) is also in Phase III in this setting with initial results due in 2022.

Analysts reacted enthusiastically to the positive PROfound trial data. "The news suggests potential for approval in a fourth cancer type for the drug to add to existing or expected approvals in ovarian, breast and pancreatic cancers," analysts at Deutsche Bank said in a reaction note to investors on 7 August.

Another Phase III mCRPC trial, PROpel is ongoing and testing Lynparza in combination Zytiga compared to Zytiga alone in patients who have received no prior cytotoxic chemotherapy or new hormonal agents for mCRPC. Data from that trial, which involves 720 patients, is expected in late 2020 or early 2021.

"And with Merck having recently initiated large Phase III trials exploring use of Lynparza with its market leading PD-1 Keytruda across several cancer types, including first-line lung cancer and prostate cancer, we remain optimistic that Lynparza could remain a major growth driver for AstraZeneca well into the 2020s," the Deutsche Bank analysts concluded.

Lynparza generated sales of $520m in the first half of 2019, a rise of 93% from a year earlier. Sales of the PARP inhibitor totalled $283m in this year's second quarter, a rise of 95% from a year earlier at constant exchange rates.

Deutsche Bank currently estimates Lynparza will generate sales of $2.5bn by 2023 and potentially attain peaks sales of more than $5bn.

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Sickle Blow For Pfizer's Rivipansel At Phase III RESETs Expectations

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Pfizer Inc.'s RESET Phase III study of the selectin antagonist rivipansel in sickle cell anemia (SCA) has failed to meet its primary and key secondary endpoints.

Pfizer gained the drug after a successful Phase II read-out through its 2011 deal with Gaithersburg, MD-based GlycoMimetics Inc. that was at the time valued at up to $340m. But now the loss of future royalties and milestones sent GlycoMimetics' share price down by 60% during trading on NASDAQ on 5 August.

GlycoMimetics and Pfizer had hoped the drug would be the first therapy to disrupt the underlying cause of sickle cell anemia. The glycomimetic product acts as a pan-selectin antagonist (it binds to all three members of the selectin family – E-, P- and L-selectin) and was designed to inhibit the cell activation and cell adhesion that cause ischemia with pain so severe that sickle cell patients require several days of hospital treatment.

The multicenter trial, which started in 2015 after some delay, was testing the investigational product in 345 SCA patients aged six years and older who had been hospitalized for a vaso-occlusive crisis (VOC) and required treatment with intravenous opioids. Rivipansel was given intravenously every 21 hours up to a maximum of 15 doses.

But there was no difference in the time-to-readiness for discharge – defined as the difference between the start time and date of the first infusion of study drug and the time and date of medical staff-assessed readiness-for-discharge – with rivipansel compared with placebo, the study's primary endpoint.

> GlycoMimetics and Pfizer had hoped the drug would be the first therapy to disrupt the underlying cause of sickle cell anemia.

Secondary endpoints included cumulative opioid consumption and re-hospitalization within three months of discharge. Further data from are not yet available.

VOCs are the most common clinical manifestation of SCA, and occur when sickled red blood cells irritate the lining of blood vessels and cause an inflammatory response leading to vascular occlusion, tissue ischemia and pain. The only treatment options are pain management with analgesics including opioids and NSAIDs and hydration, leaving a significant need for new treatment options.

Both companies talked of their surprise and disappointment with the top-line data. "We recognize this is a significant setback for the SCD community, who are eagerly awaiting new treatment options," said Freda Lewis-Hall, chief patient officer and executive vice president at Pfizer Inc.

GlycoMimetics' CEO Rachel King said that the company "had strongly hoped that rivipansel would have a positive benefit for people living with sickle cell disease."

Analysts at Jefferies had been less optimistic. "Going into the trial readout, we had

leaned positive given the patient subgroups enrolled, however, also viewed it as a risky readout," they said in a 5 August reaction note.

The failure piles more pressure on GlycoMimetics' oncology portfolio. Next on the results horizon for the company is the read out for its specific E-selectin inhibitor uproleselan in relapsed/refractory acute myeloid leukemia, expected by the end of 2020. Jefferies noted that the company had $184.2m in cash and cash equivalents as of the end of the second quarter which should see it through to 2021.

SCA MARKET

Marketed drugs to treat the condition include hydroxyurea and Emmaus Life Sciences' L-glutamine, which last year became the first new drug to treat SCA in nearly two decades. *(Also see "Sickle Cell Innovators Required: Emmaus' Pending Approval Highlights Rare Disease Void" - Scrip, 25 May, 2017.)*

Other pipeline products for SCA aimed at selectins include Novartis's monoclonal antibody product crizanlizumab which acts on P-selectin and was recently filed in the US and EU for the prevention of VOCs in sickle cell patients. *(Also see "Keeping Track: Recarbrio Approval Highlights Two-Week Roundup" - Pink Sheet, 19 Jul, 2019.)*

Also approaching the market its Global Blood Therapeutics voxelotor, an allosteric modifier of hemoglobin structure that also holds a breakthrough therapy designation. The once-daily oral therapy has the potential to be disease modifying, the company says; a rolling NDA submission due to complete in the second half of 2019 will seek accelerated approval for treatment of SCD.

Datamonitor Healthcare estimates that in 2017, there were 3.2 million prevalent cases of sickle cell anemia worldwide, and forecasts that number to increase to 3.5 million prevalent cases by 2026.

Published online 5 August 2019

Getting A Good Start: Sanofi Extends Dupixent's Potential To Younger Patients

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Gaining EU approval for the use of the biologic atopic dermatitis therapy Dupixent (dupilumab) in adolescents with moderate-to-severe atopic dermatitis, and positive top-line results in children aged six to 11 years with severe atopic dermatitis, will likely cement the lead currently enjoyed by Sanofi and its collaborator, Regeneron Pharmaceuticals Inc., in developing and marketing a biologic for the condition.

However, there are a plethora of biologics in early and late-stage clinical development for atopic dermatitis, indicating the therapeutic segment is likely to become highly competitive in the not-to-distant future – a recent *Market Spotlight Report on Atopic Dermatitis* from Datamonitor Healthcare, published on 25 July, says late-clinical stage investigational products for the condition include Pfizer Inc.'s abrocitinib, Eli Lilly & Co.'s Olumiant (baricitinib), AbbVie Inc.'s upadacitinib, Incyte Corp.'s ruxolitinib, Galderma SA's nemolizumab and Dermira Inc./Almirall SA's lebrikizumab.

Dupixent is an important drug for Sanofi and Regeneron. For Sanofi, it is driving the big pharma's immunology franchise, with sales annualizing at around €2bn; in the 2019 second quarter, the big pharma reported sales of €496m for Dupixent, up by 168.2% at constant exchange rates compared with the same quarter last year and described as above consensus by "an impressive 21%" by analysts. Although some of that growth was due to increased prices, the majority of the growth was driven by strong underlying demand, the analysts added.

European sales accounted for €46m (up by 187.5%), having been approved in the EU in September 2017 for the treatment of moderate-to-severe atopic dermatitis in adults. In May, Dupixent was approved in the EU for severe asthma in adults and adolescents.

The EU approval in adolescents aged 12 and above with moderate-to-severe atopic dermatitis and who are candidates for systemic therapy, announced on 6 August, means that Dupixent, an inhibitor of IL-4 and IL-13 given every other week by subcutaneous injection, is the first biologic approved in the EU to treat adolescent patients with the condition. Atopic dermatitis is the most common form of eczema, often starting at an early age, and can prevent adolescents from fully participating in activities with their peers, Sanofi points out.

In the US, where Dupixent's indications have been extended for a number of months to include adolescents as well as adults with atopic dermatitis, and since October 2018 extended to include adults and adolescents with asthma, the sales trajectory for the biologic has been termed outstanding by Sanofi.

Itching is a distressing symptom of atopic dermatitis

In the LIBERTY AD program in adolescents with atopic dermatitis, 24% of patients who received Dupixent achieved clear or almost clear skin compared with 2% of patients treated with placebo, as measured by an investigator's global assessment score of zero or one, the co-primary endpoint of the trial. And 42% of

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PIPELINE WATCH, 2–8 AUGUST 2019

PHASE II

Event Stage	Lead Company/Partner	Drug Name	Indication	Comments	Change To LOA (%)	LOA (%)
Phase II Updated Results	Verona Pharma plc	ensifentrine (inhaled powder)	COPD	Positive Data	0	19
Phase IIb Top-Line Results	Opthea Ltd.	OPT-302	Wet AMD	w/Lucentis; Met Primary Endpoint	0	24
Phase II Top-Line Results	Allakos Inc.	AK002	Gastroenteritis, Eosinophilic	ENIGMA; Met Primary & Secondary Endpoints	4	28
Phase II Top-Line Results	Alkahest, Inc.	GRF6019	Alzheimer's Disease	Encouraging Results	1	18
Phase IIa Trial Initiation	Poxel SA	PXL770	Non-Alcoholic Steatohepatitis	Protein Kinase Activator	0	24
Phase II Trial Initiation	Eloxx Pharmaceuticals	ELX-02	Cystinosis, Nephropathic	In Patients With Nonsense Mutations	24	24
Phase II Trial Initiation	Ionis Pharmaceuticals, Inc.	IONIS PKK-LR	Hereditary Angioedema	ISIS 721744-CS2	6	20
Phase Ib/IIa Trial Initiation	89bio Ltd.	BIO89-100	Non-Alcoholic Steatohepatitis	A Glyco-Pegylated FGF-21	10	24
Phase Ib/IIa Trial Initiation	Provention Bio, Inc.	PRV-3279	Systemic Lupus Erythematosus	PREVAIL; A Humanized Diabody	6	20
Phase I/II Trial Initiation	Eureka Therapeutics, Inc.	ET1402L1, CAR Therapy	Hepatocellular Cancer	AFP Targeted Approach	4	10

PHASE III

Event Stage	Lead Company/Partner	Drug Name	Indication	Comments	Change To LOA (%)	LOA (%)
Phase III Updated Results	Evofem Biosciences, Inc.	Amphora	Contraception	AMPOWER; Quality-of-Life Improvements	0	71
Phase III Updated Results	Sesen Bio, Inc.	Vicinium	Bladder Cancer	VISTA; Positive Data	0	39
Phase III Top-Line Results	AB Science S.A.	masitinib	Melanoma	vs. dacarbazine; Activity Seen	0	35
Phase III Top-Line Results	Basilea Pharmaceutica AG	Zeftera (ceftobiprole)	Skin and Skin-Structure Infections	TARGET; Positive Results	20	68
Phase III Top-Line Results	AstraZeneca/Merck & Co	Lynparza (olaparib)	Prostate Cancer, Castration-Resistant	PROfound; Met Primary Endpoint	2	41
Phase III Top-Line Results	Athenex, Inc.	Oraxol (paclitaxel, oral)	Breast Cancer	KX-ORAX-001; Encouraging Results	37	37

Source: Biomedtracker | Informa, 2019

CONTINUED FROM PAGE 21

patients who received Dupixent achieved 75% or greater skin improvement compared with 8% of patients given placebo, as measured by the eczema area and severity index (EASI-75), the other co-primary endpoint. Dupixent also significantly reduced itch and improve patients' quality of life.

IN CHILDREN TOO

On 6 August, Sanofi released top-line data from a pivotal Phase III study in children aged six to 11 years with severe atopic dermatitis (covering more than 60% of their skin) showing that Dupixent met primary and secondary endpoints in the study, when added to topical steroids at two- or four-week intervals.

The 367-enrolled patient study found that 33% of patients who received Dupixent every four weeks and 30% of patients who received Dupixent every two weeks achieved clear or almost clear skin (an IGA score of 0 or 1), compared with 11% of patients treated with placebo ($p<0.0001$ and $p=0.0004$, respectively). 70% of patients who received Dupixent every four weeks and 67% of those who received it every two weeks, achieved 75% or greater skin improvement on the EASI-75 index, compared with 27% for placebo ($p<0.0001$ for both). Adverse events more commonly reported with Dupixent than with placebo included conjunctivitis (7-15% with Dupixent), nasopharyngitis (7-13%), and injection site reactions (10-11%).

These results will be submitted to regulatory authorities, starting with the US FDA in the fourth quarter of 2019, Sanofi said. Sanofi and Regeneron are also evaluating dupilumab for pediatric asthma (6-11 years of age, Phase III), pediatric atopic dermatitis (six months to five years of age, Phase II/III), eosinophilic esophagitis (Phase II/III), chronic obstructive pulmonary disease (Phase III) and food and environmental allergies (Phase II).

OUTSTANDING LAUNCH

Sanofi CEO Olivier Brandicourt highlighted "the continued outstanding launch of Dupixent", during its second quarter earnings call with analysts on 29 July. "We continue to see strong double-digit growth in new patient starts across all specialists and we continue to drive deeper health care professional penetration in atopic dermatitis with approximately 45% of prescribers having written prescription for at least five patients."

In Dupixent's second approved indication in the US, asthma, "new-to-brand prescriptions continue to outpace recent analog launches. Our belief that the opportunity in asthma lies in growing biologic market penetration was again confirmed with about 80% of Dupixent patients new to biologics," Brandicourt noted.

In June, the US FDA approved Dupixent's third indication, for the treatment of chronic rhinosinusitis with nasal polyposis, and launch is underway. Sanofi estimated that in this condition, there are about 55,000 patients with highest need in the US who have failed one surgery.

At the end of the second quarter, Dupixent had been launched in 28 countries, with 11 more launches in atopic dermatitis and seven in asthma planned over the remainder of 2019.

Published online 7 August 2019

APPOINTMENTS

Executive	To Company	New Role	From Company	Previous Role	Effective Date
Rafael Amado	Allogene Therapeutics	Executive Vice President, R&D and Chief Medical Officer	Adaptimmune	President, R&D	3-Sep-19
David Seiden	Avadel Pharmaceuticals plc	Senior Medical Director	Syneos Health	Senior Medical Director	1-Aug-19
Janet Dorling	CymaBay Therapeutics	Chief Commercial Officer	Achaogen	Chief Commercial Officer	5-Aug-19
Christi L. Shaw	Kite Pharma Inc	Chief Executive Officer	Eli Lilly & Co	Senior Vice President and President, Lilly Bio-Medicines	11-Jul-19
Huw Jones	Progenics Pharmaceuticals Inc	Vice President, Commercial	Advanced Accelerator Applications SA	Interim General Manager and Vice President, Marketing and Sales	8-Jul-19
Andrey E. Belous	Proteostasis Therapeutics Inc	Senior Medical Director	Galapagos NV	Medical Director	23-Jul-19
Nadja Frenzel	Tilray	Vice President, Commercial Development-Europe	Grunenthal GmbH	Senior Director, Chief of Staff	5-Jul-19
Xiaohu Deng	Viracta Therapeutics Inc	Senior Vice President, Product Development	Kura Oncology Inc	Senior Director, Head, CMC	1-Aug-19

Click here for all appointments: https://bit.ly/2oHWRYn

Source: Medtrack | Informa, 2019

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