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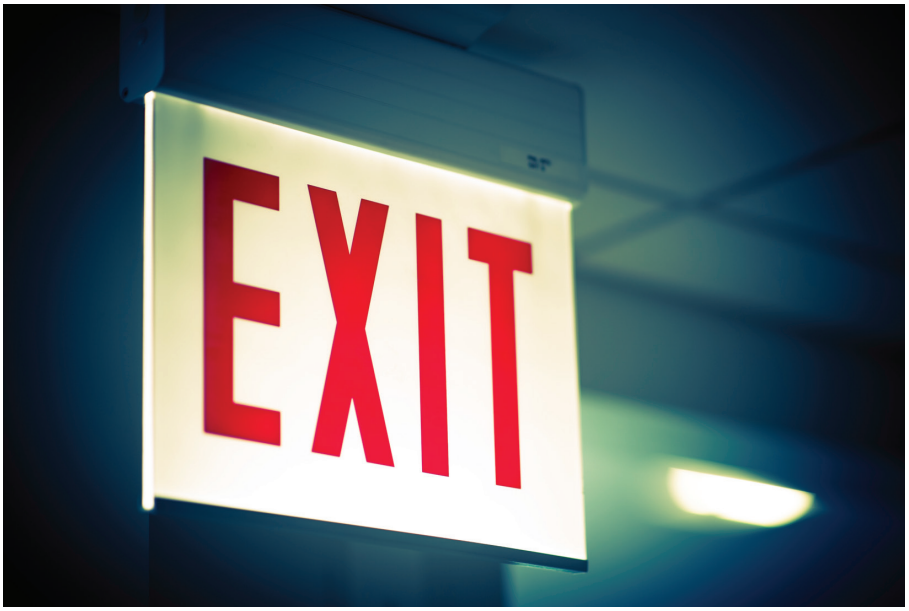

Sanofi Plans More Job Cuts, This Time In R&D

ELEANOR MALONE eleanor.malone@informa.com

Sanofi plans to cut 466 R&D positions in France and Germany under a "voluntary departure program." The company said it would "sharpen its research focus" in key areas and shift resources to priorities like gene therapy and antibody engineering.

While oncology, immunology, rare diseases and vaccines are priority areas, the firm will rein in its cardiovascular and diabetes R&D. Although these were once key revenue drivers for the French group, they are increasingly challenged by generic competition and price pressures.

The company said it would limit cardiovascular R&D to the development of its current pipeline and seek to license clinical stage programs from external partners. Future diabetes research, meanwhile, will focus on the discovery of treatments that treat the underlying causes of the disease, and the development of the current pipeline. The shift in R&D focus had previously been flagged up in February.

According to French trade union CFE-CFDT, the cuts will affect all of its French R&D sites.

In France, some research resources will be shifted to immuno-oncology. Sanofi will also reallocate resources towards biologics in France, Germany and the US, with increased investments in gene therapy in France and the US, and in antibody engineering in Germany. The company added that it had "identified areas where it can more efficiently apply its resources" which would include shifting R&D activities among its sites in France.

"The transformation of our R&D organization would enable us to focus on the therapeutic areas and platforms where we believe we have the greatest opportunity to make a meaningful difference for patients and to maximize the productivity of our research engine," said John Reed, Sanofi's global head of R&D. "We are committed to making these proposed changes responsibly both for colleagues who will stay and those who may leave the company. We look forward to working with our Works Council and trade union partners to maintain and enhance our cutting-edge research capabilities in France and Germany."

According to French trade union CFE-CFDT, the cuts will affect all of its French R&D sites – Vitry-Sur-Seine, Alfortville and Chilly-Mazarin near Paris, Montpellier in the south and Strasbourg in the north-east – with the loss of 299 jobs, the closure of the Alfortville site and the transfer of 189 posts between sites. The union condemned what it called "this umpteenth restructuring plan" and deplored "yet again, a reorganization carried out without having taken stock of the previous ones." Sanofi employs about 25,000 people in France, out of a total of around 104,000 employees worldwide as reported at the end of 2018. Around 15,000 people globally work in R&D.

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Allergan merger will fund combined R&D pot (p5)

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Bayer brings out the big guns to litigate in US (p9)

Bring Them On
China releases generics list to encourage competition (p19)

from the executive editor

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Things tend to get a bit quiet as we approach the US Independence Day holiday but that gives more time to digest the broader implications of major news events.

The proposed AbbVie takeover of Allergan M&A news is a case in point. Looking to the future, AbbVie says it is confident that Allergan's major product Botox will be rather easier to defend from biosimilar competition than its own cash cow, Humira. AbbVie CEO Richard Gonzalez says the Botox molecule is technically very difficult to copy and that generic competition will be some time coming, and may even never materialize. Biosimilar developers think otherwise. See page 8 for all the details.

Meanwhile on pages 5-8, Mandy Jackson has taken a deep dive into the combined firm's potential pipeline. The proposed deal may have ascribed little value to Allergan's development portfolio but AbbVie executives say they are looking to the revenues from Allergan – that is Botox, in the main – to fund and expand the new entity's pipeline. Neuroscience, immunology and oncology will remain at the fore.

Meanwhile, fellow US major Bristol-Myers Squibb is still wrestling with US Federal Trade Commission's concerns in order to effect its takeover of Celgene. BMS needs to find a buyer for Celgene's blockbuster therapy Otezla to address FTC competitive concerns in psoriasis, a development that took some investors aback as there is little overlap in the two companies' immunological portfolios. As a result, the deal is not now expected to close until late 2019 or early next year. Jessica Merrill has all the details on page 4.

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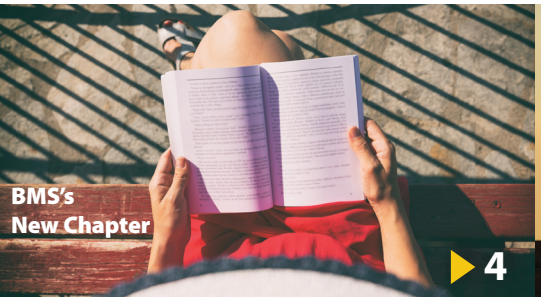

exclusive online content

Lupin Boss On Getting Biosimilar Manufacturing Right, Albuterol Outlook

ANJU GHANGURDE anju.ghangurde@informa.com

Lupin Ltd. isn't fretting about not being among the early movers in the biosimilars space and believes that those who can get the manufacturing of these products right could potentially hold a distinct edge.

In an interview with Scrip, the Indian company's managing director Nilesh Gupta reiterated that being early in the biosimilars sector "would not have been an advantage," noting that while products such as granulocyte colony-stimulating factor (G-CSF) became a "nice opportunity" for some, there have also been "casualties" along the way for pegylated G-CSF.

"I think now is the time to be able to do the right kind/range of products, be in time for patent expiry as well," Gupta said.

The US biosimilar market for Amgen Inc.'s short-acting neutropenia drug Neupogen (filgrastim) has seen significant uptake for Teva Pharmaceutical Industries Ltd.'s Granix (tbo-filgrastim) and Sandoz's Zarxio (filgrastim-sndz), the first biosimilars approved under the new regulatory pathway in the US.

In July last year, Mylan NV commenced commercial US sales of Fulphila (pegfilgrastim-jmdb), the first-to-market biosimilar version of Amgen's Neulasta, co-developed with Biocon Ltd.

Published online 21 June 2019

To read the rest of this story go to: https://bit.ly/2xo9U5C

inside:

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In December 2018 the firm had announced a separate round of cuts in France, with 670 lay-offs in HR, IT and finance to take place by 2020. After finalizing an agreement on this plan with French labor unions in March 2019, the company in April unveiled plans to shift support service roles in France in part to external partners and in part to its own platform in Hungary. But after an outcry in France, later that month CEO Olivier Brandicourt told the annual shareholders' meeting that the planned relocation of functions to Hungary would no longer take place.

The latest organizational restructuring announcement comes during a period of marked change and upheaval for the French group. In 2018, Sanofi spent nearly €13bn on acquiring blood disorder specialists Bioverativ and Ablynx. At the end of June 2018, Elias Zerhouni retired after eight years as head of global R&D, to be replaced by John Reed, formerly global head of Roche's pharma research and early development. Then from September 2018 a new CFO was appointed, replacing Jérôme Contamine after his nine years in the role. Jean-Baptiste Chasseloup de Chatillon joined from automotive group PSA Group, where he was credited with helping turn around the company.

Meanwhile, also in 2018, head of human resources Roberto Pucci retired after nine years, to be replaced by Caroline Luscombe, and Bayer's former head of pharma Dieter Weinand joined Sanofi as head of a new primary care business unit combining diabetes, cardiovascular and established products. Earlier in the year, Sanofi's deputy CFO Dominique Carouge had been appointed executive vice-president head of business transformation. In February 2019, chief medical officer Ameet Nathwani was given the additional title of chief digital officer.

Later this year, the group will also get a new CEO, with Paul Hudson, current head of Novartis Pharmaceuticals, arriving in September to replace Brandicourt. *(Also see "The Challenges Facing Paul Hudson At the Helm of Sanofi " - Scrip, 7 Jun, 2019.)* Brandicourt will leave before the completion of his five-year 2015-2020 strategic road map for the company, laid out after his appointment in 2015.

Published online 23 June 2019

In Merger Plot Twist, BMS Needs A Buyer For Celgene's Otezla, Raising New Questions

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Bristol-Myers Squibb Co. is seeking a buyer for Celgene Corp.'s blockbuster psoriasis pill Otezla (apremilast) to address concerns by the US Federal Trade Commission around the planned merger related to competition in psoriasis. The news surprised some investors given that BMS and Celgene don't currently have a significant amount of overlap in the immunology space, and while Otezla was not a main driver of the merger, it is still a significant revenue-generating growth driver.

Otezla is approved for the treatment of moderate-to-severe plaque psoriasis and psoriatic arthritis and generated $1.61bn in 2018, on year-over-year growth of 26%.

BMS has some portfolio overlap in immunology with Orencia (abatacept), which is approved for rheumatoid arthritis and psoriatic arthritis, but confirmed that the FTC's concerns were related to overlap with a BMS-owned pipeline drug, an oral selective tyrosine kinase 2 (TYK2) inhibitor BMS-986165, in late-stage development for moderate to severe plaque psoriasis. BMS presumably sees more long-term value in the pipeline asset than in Otezla.

The company announced the planned divestiture on 24 June and said the merger would be delayed several months while it enters into a consent decree with the FTC. The deal is now expected to close in late 2019 or early 2020 rather than in the third quarter, BMS said. BMS' stock opened 4.3% lower at $47.22, although the company also announced disappointing data on Opdivo in first-line liver cancer.

BMS unveiled plans to buy Celgene for $74bn in January as part of a strategy to reduce its dependence on the cancer blockbuster Opdivo (nivolumab). But some BMS investors were already questioning the value of the deal with Celgene's big seller Revlimid (lenalidomide) maturing and a limited market exclusivity. *(Also see "Bristol Values Celgene's Hematology, Immunology Portfolio At $74bn, But Does It Price In Risk?" - Scrip, 3 Jan, 2019.)* Despite some investor challenges, shareholders in both companies voted in favor of the merger in April. *(Also see "As Expected: Shareholders Back Bristol's $74bn Celgene Buy" - Scrip, 12 Apr, 2019.)*

Celgene had already extricated itself from some existing partnerships in the cancer space, including with BeiGene Ltd. and Mereo BioPharma Group PLC, ahead of the deal closing. *(Also see "Deal Watch: Sanofi Further Opts Out Of CNS Tie-Up With Voyager" - Scrip, 20 Jun, 2019.)*

Otezla is a significantly smaller brand compared to Revlimid, a backbone regimen for the treatment of multiple myeloma that generated $9.69bn in 2018. But it is still one of only a handful of marketed drugs Celgene would have brought to BMS, along with two other cancer medicines, Pomalyst (pomalidomide) and Abraxane (paclitaxel protein-bound particles).

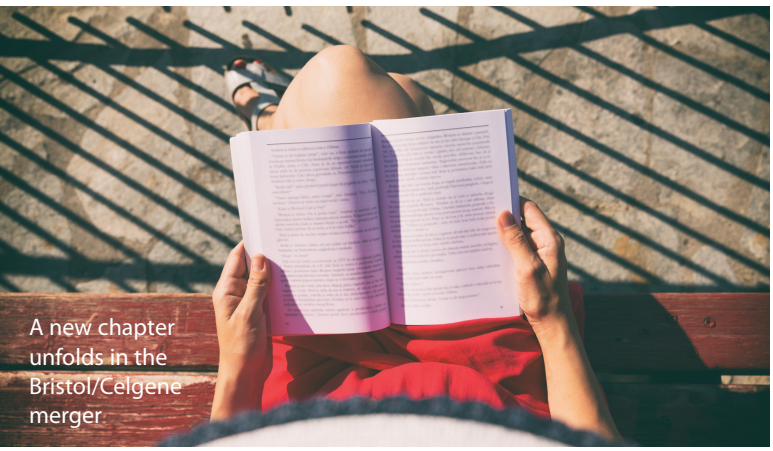
FTC'S CONCERNS RAISE QUESTIONS FOR THE INDUSTRY

Otezla is also expected to continue to grow, with some analyst estimates forecasting around $2.5bn in sales of the product in 2023. Another attractive aspect of the drug is that it would have given BMS a foundation in the intensely competitive psoriasis space ahead of the launch of the TYK2 inhibitor.

The FTC's concerns raise two big questions for the industry. First, what drug maker that might be interested in buying Otezla could do so without also raising FTC anti-competitive concerns?

Secondly, does the decision suggest the FTC is becoming more stringent when it comes to pipeline overlap and could that have implications for other mergers?

Roche's planned acquisition of Spark Therapeutics Inc., for example, has been extended twice due to the FTC's ongoing review, without a lot of clarity from Roche as to why, and with the two companies having substantial overlap in hemophilia. Roche's $4.8bn acquisition of Spark was


A new chapter unfolds in the Bristol/Celgene merger

announced in February, with the company originally expecting the deal to close in the first half of the year. *(Also see "Roche Confident Spark Therapeutics Acquisition Will Complete In First Half" - Scrip, 3 Apr, 2019.)* Roche's tender offer has most recently been extended until 31 July.

While the divestiture of Otezla could bring in significant amount for BMS – which said the proceeds from the sale would allow the company to accelerate its post-closing deleveraging plans – a sale by necessity puts the pressure on BMS to unload it quickly.

The value of the drug could be as much as $9.3bn, Credit Suisse analyst Vamil Divan speculated in a same-day research note. "The key for Otezla now will be what Bristol can obtain for the asset," he said. "We believe sellers are often at disadvantage when potential buyers know they need to divest a given asset, but there are many companies with drugs in the dermatology space that may look to bid on the asset."

Mizuho Securities analyst Salim Sayed calculated the net present value as much lower, however, pointing out in a same-day note that the TYK2 launch would be expected to put pressure on Otezla long-term, putting the value of the drug in the "high $6bn to low $7bn range."

A BUYER WITHOUT OVERLAP

Finding a buyer who can pay that much for a single asset and with commercial synergies in dermatology could prove challenging, however, if the FTC was to subject the transaction to a similar standard as applied to BMS. Big pharmas with a substantial commercial presence in psoriasis like AbbVie Inc., Novartis AG and Johnson & Johnson would presumably also present regulatory concerns, though in the case of BMS, Otezla and BMS-986165 are both oral drugs, which may have raised a specific concern. Drug companies that don't have experience in the fiercely competitive space may be reluctant to take on the commercial challenge, especially if they can't take advantage of existing commercial infrastructure.

Otezla could be a compelling opportunity for a company with a commercial presence in dermatology, but not specifically psoriasis. A company like Sanofi could be a possible contender, with a presence in dermatology with Dupixent (dupilumab) for atopic dermatitis, but no late-stage programs or marketed drugs for psoriasis. Pfizer Inc. has been building up in dermatology, beginning with the launch of Eucrisa (crisaborole) in 2017 for atopic dermatitis, but while it doesn't sell any drugs for psoriasis, it does have a TYK2/JAK inhibitor in Phase II development for psoriasis.

Biotech investors will now be keeping a close eye on any other signs that the FTC is taking a more aggressive approach to pipeline overlap, and particularly waiting to see what happens next with the ongoing Roche/Spark review.

"Bulls say FTC is merely erring on the side of timing caution as they review other healthcare transactions, owing to criticism related to lax enforcement and fears that they allow a deal to go through that removes a potential disrupter from the market," Jefferies analyst Michael Yee said. "We continue to be mindful and are carefully watching to get a better handle on if we are in a more aggressive FTC era for biotech."

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AbbVie Will Use Allergan Revenue To Fund Combined Firm's Large R&D Pipeline

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AbbVie Inc. CEO Richard Gonzalez said repeatedly when describing the company's rationale for buying Allergan PLC for $63bn that very little value was ascribed to Allergan's research and development pipeline. However, the pharmaceutical firms combined have 62 drugs in clinical development – with 38 in Phase II and III or awaiting regulatory approvals, including new indications for marketed products – requiring substantial ongoing investment.

Allergan also markets the dry eye drug Restasis (cyclosporine ophthalmic emulsion), which generated $1.26bn in 2018 sales, but is poised to face generics this year, and Lumigan (bimatoprost ophthalmic solution) to reduce eye intraocular pressure in glaucoma. *(Also see "Going Generic: Big Brands Poised To Lose Marketing Exclusivity In The US In 2019 " - Scrip, 15 Mar, 2019.)* Allergan also sells Linzess (linaclotide) for irritable bowel syndrome under a partnership with Ironwood Pharmaceuticals Inc., and some women's health products, like the birth control pill Lo Loestrin.

AbbVie executives admitted on 25 June when the mega-deal was announced that the company is buying Allergan to add its nearly $16bn in annual sales to AbbVie's own $33bn in revenue before its $20bn in Humira (adalimumab) sales are whittled away by biosimilar competitors, which will launch in the US starting in 2023. However, the executives

also noted that revenue from Allergan's products, including its top-seller Botox (onabotulinumtoxinA), will help fund and expand AbbVie's pipeline.

"This transaction is not a transaction that's highly dependent on pipeline," Gonzalez said during AbbVie's same-day conference call to discuss the deal with analysts and investors.

He described any successes in Allergan's pipeline after the deal closes in early 2020 as "upside" – value on top of what AbbVie priced into the acquisition.

"We're not betting on pipeline," Gonzalez said. "So, if some of their pipeline assets were to work out, there would be an upside to our model. We've built in very, very modest assumptions in this."

But while it plans to eliminate $2bn in costs after the companies merge, including $1bn in overlapping R&D expenses, AbbVie also believes that combining the firms' revenue streams will give it more revenue to fund R&D, including additional deals to bring in outside assets.

"The revenue scale that Allergan brings to AbbVie will enable enhanced funding of our innovative R&D platform and provides ample resources for additional pipeline expansion," Gonzalez said.

While AbbVie already has its sights set on expanding its R&D programs, despite bringing in 20 Phase II through registrational programs from Allergan, it's not alone in discounting the value of the programs it will take on in 2020 when the deal closes. Analysts and investors also don't see a lot of added value in the acquired pipeline, especially after several high-profile, late-stage R&D setbacks at Allergan.

"In terms of R&D abilities, Allergan has been wanting, and it will bring little to the table," Wolfe Research analyst Tim Anderson said in a 25 June note.

SVB Leerink's Geoffrey Porges said in a 25 June note that "Allergan has been dogged by disappointing R&D performance and unrealistic expectations for pipeline programs, and AbbVie has suffered from some of the same issues," pointing out the disappointing performance of the cancer drug candidate Rova-T, which was acquired in the $5.8bn purchase of Stemcentrx Inc. in 2016. *(Also see "AbbVie's Rova-T Disappoints As Second-Line SCLC Trial Halted" - Scrip, 6 Dec, 2018.)*

"Diversifying the business is obviously important strategically, but we tend to prefer our companies focusing their business development efforts on filling their pipelines with unique, innovative assets and that does not seem to be the case here," Credit Suisse analyst Vamil Divan said in a 26 June report.

NEUROSCIENCE PRESENTS BIG ALLERGAN R&D OPPORTUNITIES

One of the most highly valued programs in Allergan's pipeline isn't particularly novel – there already are three CGRP inhibitors on the market for migraine headaches – but it could be the first oral drug and the first on-demand treatment for migraines. Ubrogepant, in-licensed from Merck & Co. Inc., is under review at the US Food and Drug Administration with a decision expected in late 2019.

While "the large majority of the value of this transaction comes from Allergan's strong portfolio of on-market products," AbbVie president and vice chairman Michael Severino said during the company's conference call, "there are areas in the pipeline that look interesting, such as their [central nervous system (CNS)] programs."

Severino noted the CGRP inhibitors, which include the Phase III drug atogepant for migraine prevention; the antipsychotic Vraylar (cariprazine), which won supplemental FDA approval in May for bipolar depression; and Botox, which has several cosmetic and therapeutic indications, including chronic migraine prophylaxis. Vraylar's sales in its previously approved indications of schizophrenia and bipolar I disorder totaled $487m in 2018 and analyst consensus foresees $1.17bn in sales in 2023.

When Allergan's CNS portfolio is added to AbbVie's Duodopa (levodopa/carbidopa) for Parkinson's disease and the company's own pipeline programs, "we see neuroscience as an important area for long-term growth potential," Gonzalez said.

IMMUNOLOGY, ONCOLOGY REMAIN KEY FOR ABBVIE

Allergan's neuroscience pipeline will add several programs in areas where AbbVie's

AbbVie/Allergan CNS Pipelines

ABBVIE'S CNS R&D PROGRAMS	ALLERGAN'S CNS R&D PROGRAMS
ABBV-951, a subcutaneous injection of levodopa and carbidopa, is in Phase III for Parkinson's disease (PD)	A new drug application (NDA) is pending at the US FDA for the oral CGRP inhibitor ubrogepant for acute treatment of migraine headaches
ABBV-8E12, a monoclonal antibody targeting tau proteins in the brain, is in Phase II for Alzheimer's disease (AD) and progressive supranuclear palsy (PSP)	The oral CGRP inhibitor atogepant is in Phase III for migraine prevention
Elezanumab targeting repulsive guidance molecule A (RGMa) is in Phase II for multiple sclerosis	Vraylar, an oral antipsychotic, is in Phase III for major depressive disorder (MDD) and Phase I for autism spectrum disorder
ABBV-0805, a monoclonal antibody that removes or inactivates alpha-synuclein, is in Phase I for PD	The NMDA receptor modulator AGN-241751 is in Phase II for MDD
	AGN-151607, a neurotoxin, is a next-generation botulinumtoxinA in Phase I for MDD and Phase II for atrial fibrillation
	AGN-242626, an oral muscarinic acetylcholine receptor (M4) agonist, is in Phase I for AD
	The M1 agonist AGN-242701 also is in Phase I for AD

Source: AbbVie, Allergan, Biomedtracker

not active currently, but immunology and oncology will remain AbbVie's bread and butter, anchored by Humira until it loses patent exclusivity in the US and the hematological cancer therapies Venclexta (venetoclax) and Imbruvica (ibrutinib).

AbbVie and its partners will add more indications to the Venclexta and Imbruvica labels over the next few years, helping to grow the products' revenues substantially by the time Humira goes off-patent. Analyst consensus sees Venclexta sales rising from $344m in 2018 to $2.66bn in 2023, with Imbruvica soaring from $3.59bn last year to $7.13bn in 2023.

Allergan does not have any cancer drugs, but its gastrointestinal franchise anchored by the irritable bowel syndrome (IBS) products Linzess (linaclotide) and Viberzi (eluxadoline) has an R&D program that could overlap with inflammatory bowel disease (IBD) indications – ulcerative colitis (UC) and Crohn's disease (CD) – approved for Humira and under investigation for AbbVie's interleukin-23 (IL-23) inhibitor Skyrizi (risankizumab), which was approved to treat psoriasis in April.

AbbVie does not expect any major snags in its Allergan acquisition related to anti-competitive concerns that could be flagged by the Federal Trade Commission, but one exception could be Allergan's IL-23 inhibitor brazikumab (MEDI2070), which is in Phase II for UC and Phase II/III for CD under a license with AstraZeneca PLC. Skyrizi is in Phase III for both IBD indications and other candidates in AbbVie's pipeline are being developed for these diseases as well.

Gastrointestinal disease R&D programs at Allergan also include two drugs for non-alcoholic steatohepatitis (NASH) – the Phase III CCR2/5 receptor antagonist cenicriviroc and FXR agonist AGN-242266 – and the Phase III ghrelin agonist relamorelin for diabetic gastroparesis. Allergan and its Linzess partner Ironwood Pharmaceuticals Inc. also have a delayed-release version of their drug in Phase II for pain in IBS with diarrhea.

MEDICAL AESTHETICS: BOTOX AND BEYOND

The most valuable asset in Allergan's product portfolio is Botox, which generated $3.58bn across its therapeutic and cosmetic indications. The wrinkle-reducing injection is the cornerstone of the company's market-leading $4.5bn medical aesthetics portfolio and it is a key element of Allergan's R&D portfolio in aesthetics.

Gonzalez said AbbVie will leave the medical aesthetics business largely untouched and will continue to invest in that unit's existing assets while adding new products through R&D and acquisitions. The AbbVie CEO echoed Allergan's sentiments about aesthetics still being a largely untapped market with much room for growth.

With Allergan's significant global presence in medical aesthetics and its plans to launch several new indications and new products during the next several years, "we feel highly confident in the competitive position of this business," he said. "In addition, the medical aesthetics market remains highly underpenetrated. With increasing interest and acceptability of aesthetic procedures and products globally, and increasing utilization within younger demographics, the medical aesthetics market has the potential to double by 2025, making this franchise extremely attractive and durable for AbbVie."

Investors have been somewhat worried about coming competitors for Botox, including a potentially longer-acting neurotoxin from Revance Therapeutics Inc., but analysts expect this business to remain fairly stable. *(Also see "Another Botox Competitor: Revance Prepares Longer-Lasting RT002 For BLA Submission" - Scrip, 22 Feb, 2019.)* Consensus estimates forecast that Botox Cosmetic sales, which totaled

AbbVie's Immunology And Oncology Pipelines

ABBVIE'S IMMUNOLOGY PIPELINE	ABBVIE'S ONCOLOGY PIPELINE
Skyrizi is in Phase III for UC, CD and psoriatic arthritis (PsA); it's in Phase II for atopic dermatitis (AD) and hidradenitis suppurativa	The BCL2 inhibitor Venclexta, partnered with Roche, is in Phase III for multiple myeloma (MM) and mantle cell lymphoma (MCL), Phase II for myelodysplastic syndrome (MDS) and Phase I for acute lymphoblastic leukemia (ALL)
The JAK1 inhibitor upadacitinib is under US FDA review for rheumatoid arthritis (RA); it's in Phase III for PsA, CD, UC, AD and giant cell arteritis, and Phase II for axial spondyloarthritis	Imbruvica, a BTK inhibitor partnered with Johnson & Johnson, is in Phase III for first-line follicular lymphoma (FL), relapsed or refractory (R/R) FL or marginal zone lymphoma (MZL) and first-line MCL.
ABBV-599, which combines a Bruton's tyrosine kinase (BTK) inhibitor and a JAK1 inhibitor, is in Phase II for RA	Empliciti (elotuzumab), partnered with Bristol-Myers Squibb Co., targets SLAMF7 and is in Phase III for first-line MM
ABBV-323 is a CD40 antagonist in Phase II for UC	The PARP inhibitor veliparib is in Phase III for non-small cell lung cancer (NSCLC), BRCA-mutated breast cancer and ovarian cancer
ABBV-3373, an anti-TNF and steroid conjugate, is in Phase Ib/IIa for RA	Rova-T is in Phase III for first-line treatment of small cell lung cancer (SCLC)
ABBV-157 targets RORyt and is in Phase I for psoriasis	The BCL2-targeting navitoclax, also developed with Roche, is in Phase II for myelofibrosis
ABBV-154 is in Phase I for RA	Telisotuzumab vedotin, a c-Met-targeting antibody-drug conjugate (ADC), is in Phase II for solid tumors
	ABT-165 targeting VEGF and DLL4 is in Phase II for solid tumors
	Another 14 assets are in Phase I, including Venetoclax for ALL

Source: AbbVie, Allergan, Biomedtracker

$1.55bn in 2018, will be about $1.57bn in 2023. Botox Therapeutic sales are expected to reach $2.3bn in 2023 versus $2.03bn in 2018.

Allergan's aesthetics R&D pipeline includes Phase II studies for Botox in reducing jawline and neck wrinkles and a Phase I study in improving skin quality. Kybella (deoxycholic acid), approved in the US to reduce the appearance of a double chin, is in Phase II for reducing jowl fat.

A next-generation neurotoxin called nivobotulinumtoxinA – available in a vial without the need for reconstitution, unlike Botox – is in Phase III for the reduction of glabellar lines (wrinkles between the eyes) and crow's feet. And BoNTE (EB-001), the short-acting toxin that Allergan acquired last year with the purchase of Bonti Inc. for $195m up front, is in Phase II for glabellar lines. *(Also see "Allergan Buys Bonti, Releases New Data In Defense Of 'Iconic' Botox Brand" - Scrip, 14 Sep, 2018.)*

EYE CARE, A PRIORITY AT ALLERGAN, DIVERSIFIES ABBVIE PORTFOLIO

Ophthalmology also has been an important therapeutic area for Allergan and will give AbbVie another means for diversifying its revenue beyond Humira. Allergan's biggest product in this category – Restasis (cyclosporine) for dry eye disease – is expected to face generics this year, but the company will maintain a presence in that indication and in glaucoma on top of new ophthalmology opportunities.

Allergan Eye Care Pipeline

ALLERGAN'S EYE CARE R&D PORTFOLIO
Presbysol is in Phase III for presbyopia
Bimatoprost SR is an intracameral implant that provides sustained release of Lumigan (bimatoprost) for intraocular pressure (IOP) in glaucoma; it is in Phase III
In Phase III for dry eye, Optive Fusion is a multi-dose preservative-free (MDPF) formulation of an over-the-counter (OTC) eye drop
Abicipar pegol is a VEGF inhibitor in Phase III for wet AMD and Phase II for diabetic macular edema
Optive Ultra OTC drops are in Phase II for dry eye
Brimonidine DDS, an implant for sustained release of Combigan (brimonidine), is in Phase II for geographic atrophy (dry AMD) and for glaucoma
Bimatoprost ring, also in Phase II for glaucoma, is another implant
Optive Lite MDPF is in Phase I for dry eye
AGN-151597 is a gene therapy in Phase I for retinitis pigmentosa
Source: AbbVie, Allergan, Biomedtracker

Phase III asset abicipar pegol could run into regulatory concerns or commercial challenges because the potentially longer-acting VEGF inhibitor caused a fairly high rate of ocular inflammation in its Phase III wet age-related macular degeneration (AMD) studies that may limit its use, but Allergan is working on a mid-2019 US FDA submission for the biologic. *(Also see "Allergan Improves Safety Of Abicipar, But Not Enough Compared To Lucentis, Eylea" - Scrip, 2 Apr, 2019.)*

Since Allergan already has paid for and completed the abicipar development program, Severino noted during AbbVie's call that an approval with a favorable label would be added value on top of what the company has priced into its Allergan acquisition, unless the label limits uptake of the AMD drug. "We'll have to see what the label looks like to have a better sense for the opportunity," he said. "And the tradeoff we're looking at is the benefit of the longer-acting nature of this agent compared to the patients who experience ocular inflammation, which is on the order of about 8% to 10% of patients. We'll have to see what that looks like in the label and we'll have to see how that's viewed by treating physicians."

However, Leerink's Porges said in a 26 June note that he expects AbbVie to abandon abicipar if the drug receives less than favorable treatment from regulatory agencies.

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Bruised Over Humira Patent Games, AbbVie Sees Smoother Road With Botox

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AbbVie Inc. believes it will have less trouble protecting market exclusivity for Botox than it has for Humira, which would be a relief to a company whose reputation has taken a beating in the public sphere and in Congress over its approach to extending the patent life of its blockbuster. AbbVie announced on 25 June that it has reached a deal to acquire Botox marketer Allergan PLC for $63bn in an effort to reduce its reliance on Humira.

Humira has become a poster child for detractors of patent gaming aimed at blocking lower-priced competition amid the ongoing prescription drug pricing debate in the US.

Critics point to the fact that AbbVie has amassed 136 patents on Humira (adalimumab) and entered into a series of patent settlement agreements that delay biosimilar competition to the blockbuster in US until 2023, even while biosimilars launched in Europe in 2018.

CEO Richard Gonzalez fielded pointed questions over the patent estate for Humira at the high-profile Senate hearing featuring biopharma executives last Feb-

ruary. The company's actions spurred interest in bipartisan legislation to reform the practices of amassing patent "thickets" and product "hopping," or effectively extending the patent life of a product by introducing a line extension. Such practices may be addressed in a scheduled Senate Judiciary Committee markup of several patent legislation proposals.

AbbVie is not alone in its approach to extending exclusivity for its blockbuster. But the facts that it has succeeded in getting several additional years of protection in the US, and that Humira is one of the top drugs in terms of Medicare Part D spending, has made it a particular target for policymakers. The fact that it is also the top selling drug in the world with $19.94bn in revenues in 2018 also makes it a target.

Gonzalez predicted that AbbVie won't need to go to the same lengths to protect Botox (onabotulinumtoxinA) during a 25 June call on the acquisition.

"As far as it relates to a biosimilar, obviously that's an area we know well. And I would say when you look at Botox, it's a very unique molecule," he said. "And for a variety of technical reasons, I would tell you that it's highly unlikely that we would see a biosimilar against Botox for a long, long time, if ever."

His assurances are interesting given recent comments by prospective biosimilar developers Revance Therapeutics Inc. and Mylan NV, which have partnered to work on developing a follow-on for Botox.

The companies met with the US Food and Drug Administration earlier this year to see if a biosimilar can move into development via the 351k pathway and believe they will be able to move ahead, according to comments by Mylan and Revance executives in earnings calls following the meeting.

> "It's highly unlikely that we would see a biosimilar against Botox for a long, long time, if ever." – Richard Gonzalez

"Based on the agency's feedback, the companies believe that the 351k pathway for the development of the biosimilar to Botox is viable and provides the opportunity to develop and commercialize the first biosimilar to Botox," Mylan President and Executive Director Rajiv Malik said during the company's 26 February call.

Gonzalez also noted that Allergan has been successful in deflecting competition to Botox from other botulinum toxin-based treatments with savvy marketing efforts.

ALLERGAN'S MOHAWK DEAL

Allergan has been less effective in extending the patent for its second largest drug, the dry eye treatment Restasis (cyclosporine), despite the company's willingness to take unconventional measures. But like AbbVie, Allergan has faced strong public criticism for putting corporate concerns ahead of lowering prices for patients with its patent extension efforts.

"Two Birds of a Feather: AbbVie to Acquire Fellow Price-Gouger Allergan," the payer-supported Council for Sustainable Rx Pricing trumpeted in a statement on the purchase. "What do AbbVie and Allergan have in common? Both follow the big pharma playbook of price gouging patients and consumers while stamping out competition." Allergan provoked controversy in 2017 with its plan to delay competition for Restasis by transferring the patent to the Saint Regis Mohawk tribe, which then claimed sovereign immunity to withstand any legal challenges.

Under the deal, the tribe received $13.5m up front and was eligible to receive $15m in annual royalties. In exchange, it agreed to claim sovereign status to get an inter partes review proceeding dismissed by the US Patent and Trademark Office's Patent Trial and Appeal Board.

The move put a spotlight on the importance of preserving key assets. Unlike AbbVie's patent estate for Humira, Allergan's approach was unsuccessful, and the resulting decline in Restasis sales was an important reason for Allergan's decision to sell to AbbVie.

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Anxious Investors Relieved At Bayer's Fresh Monsanto Litigation Strategy

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Bayer AG's shares jumped by more than 8% to €60.69 on the Frankfurt stock exchange during 27 June as it announced a new strategy to address US litigation concerning its weedkillers.

The case centers around the seeds firm Monsanto, which Bayer bought in June 2018 for $63bn, the largest acquisition in the German's company's history and which doubled the size of its crop sciences division. However, Monsanto's glyphosate-based weedkillers such as Roundup have been plagued by allegations that they cause cancer.

As of 11 April, lawsuits from approximately 13,400 plaintiffs had been served in the US. Dewayne Johnson was the first to sue Monsanto in 2016 after alleging

that its products gave him cancer and last August a San Francisco jury awarded him $289m although that figure was subsequently reduced.

With each court ruling against Bayer its shares have been sent tumbling. In March they fell by 10%, wiping more than €7bn off its value, when second case was heard before a San Francisco jury which decided that the weedkiller was a significant factor in causing cancer. In May they fell again, this time by 2.3%, when its third court case awarded $2bn to a California couple who claimed its weedkiller caused their cancer.

The stock downward spiral has concerned investors who have expressed a wish to see Bayer settle lawsuits, bringing a clarity to the future of the company.

Bayer is now putting together a team to tackle this issue. The company's supervisory board met for a full day session on 26 June to discuss the legal challenges it is facing "including those articulated by stockholders at the recent Annual Stockholders' Meeting and in the ongoing dialogue with investors," the Leverkusen-based firm said in a statement.

"The supervisory board recognizes the negative effect the litigation uncertainty has had on the stock price and stakeholder perception, and is determined to help the company decisively but prudently advance the matter," it said.

As such, a new supervisory board committee will "intensively monitor" the process, consult with the Board of Management and make recommendations on the litigation strategy. It will be equally composed of shareholder and employee representatives and made up of eight supervisory board members, several of whom have gathered extensive experience with complex litigations.

Bayer has also hired John Beisner, a US trial lawyer that represented Merck & Co. Inc. during the Vioxx litigation process, and Johnson & Johnson on its DePuy hip replacements case, as an adviser. He is expected to attend the new committee meetings and advise on trial tactics and mediation. His appointment is "intended to add fresh and independent perspectives to the advice given to the board of management," said Bayer.

ACTIVIST INVESTORS

Analysts expressed some relief at the development. "We believe the fact that Bayer is taking tangible steps towards bolstering its litigation strategy will provide a degree of solace to investors but, ultimately, success in the courts will be required to trigger a step change in sentiment," said Morgan Stanley in an 27 June note.

Activist investor Elliott Advisors, which holds Bayer shares and financial instruments equivalent to €1.1bn ($1.3bn), said that it welcomed the steps and was confident it marked a step change in the company's approach to the legal challenges. It said: "Elliott believes that the creation of the special committee will provide a new level of oversight and a fresh perspective to a litigation strategy in need of a radical overhaul, and help guide the company towards a rational, fair and swift settlement."

Regarding the appointment of Beisner and the special committee formation, Elliot said that it afforded the company "a valuable platform from which to resolve the uncertainty associated with the glyphosate litigation, offering the opportunity for an accelerated settlement with a limited financial cost."

However, it also said that Bayer could do more to maximize long-term value for all its stakeholders, adding, "Bayer's discounted share price today does not reflect the significant underlying value of its constituent businesses, or the potential value realization opportunity that is in excess of €30bn."

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Doubts Raised Over Regeneron's Anti-IL 33 REGN3500 At Phase II In Asthma

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Sanofi and Regeneron Pharmaceuticals Inc. released positive topline results from a Phase II proof-of-concept trial testing their monotherapy REGN3500 in asthma, showing it met its targets against placebo.

But news that patients treated with Regeneron's first-in-class interleukin-4/IL-13 inhibitor Dupixent – on the market since 2018 – did better than those who received the investigational anti-IL 33 across all endpoints, fanned doubts among analysts about the role the anti-IL 33 class can play in the respiratory condition.

In the trial, REGN3500 (also known as SAR440340) monotherapy "significantly reduced loss of asthma control and improved lung function compared to placebo," the companies said on 21 June.

The greatest improvement was observed in patients with blood eosinophil levels greater than or equal to 300 cells/microliter.

When announcing the trial's topline data the duo also noted that "patients treated with Dupixent (dupilumab) monotherapy did numerically better than REGN3500/SAR440340 across all endpoints, although the trial was not powered to show differences between active treatment arms."

> "The topline IL-33 results raise questions about the role of the class for asthma." - Jefferies

Combining REGN3500/SAR440340 and Regeneron's Dupixent also did not demonstrate higher benefit compared with Dupixent alone. The Phase II proof-of-concept trial was a randomized, double-blind, placebo-controlled, 12-week evaluation that

enrolled 296 adult patients with moderate-to-severe asthma who were not well controlled on LABA and ICS therapy. Patients were randomized into four treatment groups: REGN3500/SAR440340 plus placebo, REGN3500/SAR440340 plus Dupixent, Dupixent plus placebo, and placebo.

The primary endpoint was the proportion of patients who experienced loss of asthma control (LOAC) on REGN3500/SAR440340 with or without Dupixent, compared with placebo.

More detailed results from the trial will be presented at an upcoming, but unidentified medical meeting, the companies said.

Analysts at Jefferies in a reaction note the same day said that "despite monotherapy being superior to placebo, these preliminary results suggest there may be limited benefit to using an IL-33 instead of Dupixent, or from adding REGN3500/SAR440340 to Dupixent."

Therefore "the topline IL-33 results raise questions about the role of the class for asthma," Jefferies said.

REGN3500/SAR440340 is a fully-human monoclonal antibody that inhibits interleukin-33 (IL-33), a protein that is believed to play a key role in type 1 and type 2 inflammation. Preclinical research has shown REGN3500 blocked several markers of both types of inflammation.

IL-33 binds to IL1R1/ST2 receptor expressed on many immune cells. IL-33 inhibition could therefore have broader effects than current biologics, which only target Th2 cytokines.

GlaxoSmithKline PLC and AnaptysBio Inc. also have anti-IL 33s in development for asthma.

Sanofi and Regeneron voiced optimism about the anti-IL 33 monotherapy's prospects.

"This trial suggests that REGN3500 may provide an alternative targeted approach for patients suffering from asthma," said George Yancopoulos, Regeneron's chief scientific officer. "We look forward to working with Sanofi to advance REGN3500 through our asthma clinical trial program, as well as continuing our ongoing trials in atopic dermatitis and chronic obstructive pulmonary disease," he added.

REGN3500/SAR440340 is being studied in different types of asthma (Phase I and Phase II), chronic obstructive pulmonary disease (Phase II) and atopic dermatitis (Phase II).

"We plan to continue studying REGN3500/SAR440340 in these diseases and will provide updates as available," Sanofi said.

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BMS' Bid For Opdivo In First-Line HCC Stymied

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Bristol-Myers Squibb Co. missed in its effort to show PD-1 inhibitor Opdivo could improve upon standard-of-care Nexavar in first-line hepatic cell carcinoma (HCC), leaving the pharma to look for a combination regimen with CTLA-4 inhibitor Yervoy in previously treated patients, as well as monotherapy in adjuvant care.

On a day of dual surprises for investors, BMS revealed that CheckMate-459 did not demonstrate a statistically significant benefit on overall survival (OS) compared to Bayer AG/Amgen Inc.'s Nexavar (sorafenib), long the standard in first-line HCC. Separately, the US pharma announced that its pending merger with Celgene Corp. would be delayed while the companies sell off the latter's psoriasis blockbuster Otezla (apremilast) in order to address concerns of the US Federal Trade Commission. *(Also see "In Merger Plot Twist, BMS Needs A Buyer For Celgene's Otezla, Raising New Questions" - Scrip, 24 Jun, 2019.)*

While BMS did not provide full data from CheckMate-459, it reported on 24 June that Opdivo (nivolumab) showed a positive numerical trend on OS compared to Nexavar but fell short of statistical significance (p=0.0752). Full results from the trial will be presented later at a medical meeting, the firm said. Opdivo obtained accelerated approval for second-line HCC from the US Food and Drug Administration in September 2017. *(Also see "Bristol's Opdivo Diversifies Options In Liver Cancer" - Scrip, 25 Sep, 2017.)*

OPDIVO PROSPECTS

Datamonitor Healthcare senior analyst Zachary McLellan told *Scrip* that these results are "a large blow to [Opdivo's] prospects" in HCC. He added that a recent decision to pull a filing for second-line therapy in Europe with Opdivo seems "well-founded" – the European Medicines Agency expressed concern that the study used for approval in second-line treatment lacked a comparator.

"A path forward in the first-line setting where Nexavar remains the standard is now less clear. Combinations may be an answer, however," McLellan said. At the recent American Society of Clinical Oncology conference, BMS presented data showing that an Opdivo/Yervoy combination regimen yielded better results than Opdivo monotherapy in patients previously treated with Nexavar, the analyst noted.

"A large Phase III may be needed to confirm this benefit, particularly in light of this recent setback, but BMS may forge ahead with another accelerated approval submission in post-Nexavar settings and may test the combination in the front-line setting," McLellan added. "For now, we will have to wait and see."

Nexavar stood as the unchallenged standard of care in the first-line setting for roughly a decade, before last summer's approval of Eisai Co. Ltd./Merck & Co. Inc.'s Lenvima (lenvatinib). *(Also see "First In 10 Years, But Lenvima's First-Line Liver Label Could Be Challenged Soon" - Scrip, 17 Aug, 2018.)* Earlier this year, however, Merck experienced its own setback in HCC when Keytruda (pembrolizumab) failed the Phase III KEYNOTE-240 study in second-line HCC. *(Also see "Merck's Keytruda Loss In Liver Cancer Could Be Gain For Rivals" - Scrip, 19 Feb, 2019.)*

In a statement, BMS said it retains confidence in Opdivo's potential for HCC treatment and will evaluate insights gained from CheckMate-459. More than 1,000 patients were enrolled in the trial, according to Biomedtracker, with treatment continuing until the disease progresses or there is unacceptable toxicity. Beyond

the primary endpoint of OS, secondary endpoints included overall response rate, progression-free survival and relationship between patients' expression of PD-L1 and efficacy – no data for those endpoints were disclosed.

OTHER COMBO REGIMENS PENDING

While HCC is the most common form of liver cancer and fastest-rising cause of cancer-related mortality in the US, Credit Suisse analyst Vamil Divan pointed out in a same-day note that HCC is a relatively small market, with about 11,000 patients in the US and 38,000 worldwide. BMS had seemed well-positioned to gain approval for the first-line setting based on its approval in second-line therapy, he wrote, but its failure to demonstrate an OS benefit with Opdivo monotherapy now opens a door for combination regimens being investigated by competitors including Merck, Roche and AstraZeneca PLC.

William Blair & Co. analyst Matt Phipps wrote on 24 June that the failure of CheckMate-459 places increased importance on other ongoing BMS trials, notably CheckMate-9LA, testing Opdivo with Yervoy and two lines of chemotherapy in first-line lung cancer. That study is expected to report out early in 2020.

Phipps also slashed his revenue estimates for Opdivo in HCC based on the trial miss. Blair now projects $212m in 2020, down from $477m; $179m in 2021, reduced from $666m; and $146m in 2022, rather than the previous estimate of $812m.

BMS noted that it still is testing Opdivo monotherapy in adjuvant HCC (CheckMate-9DX) and in combination with Yervoy (ipilimumab) versus Yervoy monotherapy in previously treated patients as part of the CheckMate-040 trial. Biomedtracker lists nine current Phase III programs in HCC, including AstraZeneca's Phase III HIMALAYA study of anti-PD-L1 agent Imfinzi (durvalumab) and CTLA-4 inhibitor tremelimumab in first-line HCC. Data from that study are expected in 2020.

Meanwhile, Roche expects data before year's end from the Phase III IMBrave150 study combining its anti-PD-L1 Tecentriq (atezolizumab) and chemotherapy agent Avastin (bevacizumab) in first-line HCC."

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Cautious Restart To Venetoclax's CANOVA Trial In Multiple Myeloma

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The lifting of the US FDA's partial clinical hold on only one clinical study – CANOVA – of AbbVie Inc./Roche's bcl-2 inhibitor, Venclexta (venetoclax), in multiple myeloma, after changes to its design and while keeping the hold on other studies in multiple myeloma, suggests a cautious approach is being taken to further evaluation of the drug for the additional indication.

Concerns about a higher proportion of deaths seen in the venetoclax arm than the placebo arm of another clinical study, the Phase III BELLINI trial, led to the partial clinical hold being put in place in March 2019, with analysts at Biomedtracker suggesting the move might dampen venetoclax's future commercial growth.

That said, venetoclax met the primary endpoint of progression-free survival in the BELLINI study, and AbbVie has suggested there may be a potential role for venetoclax in a subset of patients with t(11;14) biomarker-defined myeloma, which accounts for around 20% of patients with the condition.

The first-in-class bcl-2 inhibitor has been of particular interest for its role in becoming a constituent of chemotherapy-free regimens; venetoclax binds and inhibits the B-cell lymphoma-2 protein in cancer cells, which if left unchecked acts to prevent apoptosis of those cells.

This May, AbbVie and Genentech (Roche) gained an additional indication in the US for the use of venetoclax in a chemotherapy-free, fixed duration combination regimen with the CD20-binding Mab, Gazyva (obinutuzumab) for previously untreated chronic lymphocytic leukemia (CLL) in patients with co-existing medical conditions.

RISK MITIGATION METHODS

In the CANOVA (M13-494) study in patients with relapsed/refractory multiple myeloma, venetoclax is being evaluated in combination with dexamethasone and compared with a combination of pomalidomide (Celgene Corp.'s Imnovid) plus dexamethasone in patients with the translocation (11.14) abnormality, said by AbbVie to be among the most common and routinely tested genetic abnormalities in patients with multiple myeloma.

Changes to CANOVA's protocol include new risk mitigation measures, protocol-specified guidelines and updated futility criteria, and recruitment into the study can now continue, AbbVie said. All other studies evaluating venetoclax in multiple myeloma remain on partial clinical hold while next steps continue to be evaluated with the FDA, AbbVie added.

At last week's European Hematology Association meeting in Amsterdam, researchers reported results from the BELLINI study, which included achieving a primary endpoint of improved PFS of 22.4 months in patients treated with venetoclax, bortezomib (Takeda Pharmaceutical Co. Ltd.'s Velcade) and dexamethasone, compared with 11.5 months in patients treated with bortezomib and dexamethasone (hazard ratio = 0.63, p =0.01). The overall response rate was also improved with venetoclax (82% versus 68%, p<0.01).

The study involved 291 patients, of which 194 were in the venetoclax arm and 97 in the placebo arm. Patients had relapsed/refractory multiple myeloma who had received one to three prior lines of therapy and were sensitive or naive to proteasome inhibitors.

However, there were 41 deaths (21%) in the venetoclax arm and 11 (12%) in the placebo arm of BELLINI, with progressive disease the most common cause (45%). The rates of serious adverse events (48% vs 50%) and serious infections (28% vs 27%) were comparable between the two arms of the study.

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Conatus Accepts Defeat For Emricasan In NASH

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Conatus' long struggle with emricasan is at an end

Conatus Pharmaceuticals Inc. hung in and talked up the potential of future results as long as it could but finally conceded on 24 June that its pan-caspase inhibitor emricasan had demonstrated a lack of efficacy in multiple patient types in non-alcoholic steatohepatitis (NASH). The San Diego firm said it will wrap up its obligations related to emricasan with partner Novartis AG and consider its strategic alternatives going forward.

The last gasp for emricasan – which Conatus hoped would offer therapeutic potential from early- to late-stage liver disease – came with the drug's failure in the Phase IIb ENCORE-LF study in 217 NASH patients with decompensated cirrhosis. Emricasan did not show a benefit compared to placebo for event-free survival – an event-driven composite endpoint of all-cause mortality, new decompensation events or four points or greater progression on Model for End-Stage Liver Disease (MELD) score – in a three-arm study testing 48 weeks of treatment with emricasan 5mg or 25mg daily. The primary analysis also showed no clear trends of a treatment effect, the company said.

Conatus said it is discontinuing further treatment of patients enrolled in ENCORE-LF. It also noted that the 24-week extension of the ENCORE-PH study in NASH patients with compensated or early decompensated cirrhosis and severe portal hypertension had shown no statistically significant difference between placebo or three investigational doses of emricasan and no clear trends of a treatment effect. Those two setbacks were only the latest in a series for the NASH therapy candidate.

This past December, Conatus reported that ENCORE-PH failed to meet its primary endpoint – change in hepatic venous pressure gradient (HVPG) from baseline to week 24. *(Also see "In NASH Race, Bad News For Conatus, Good News For Genfit In PBC" - Scrip, 10 Dec, 2018.)* Emricasan had missed the primary endpoint in a Phase II study in liver transplant patients earlier in 2018.

On 21 March, Conatus reported that emricasan also missed its primary endpoint in ENCORE-NF, a 318-patient study of NASH patients with fibrosis, failing to show a one-stage or greater improvement in fibrosis score, compared to placebo, after 72 weeks of treatment. *(Also see "Conatus Endures Another NASH Setback With Failure To Hit Fibrosis Endpoint" - Scrip, 21 Mar, 2019.)*

At the time of the ENCORE-PH failure, Conatus CEO Steven Mento held out hope that emricasan would prove beneficial in sicker NASH patients, those with decompensated cirrhosis. Those hopes went for naught with the ENCORE-LF outcome revealed on 24 June. In a statement, Mento said the ENCORE studies – designed to show emricasan's potential benefit in a broad range of chronic liver disease – "provided a fair evaluation of emricasan's lack of efficacy in these patient populations."

Conatus also announced on 24 June that it is cutting headcount by 40% and suspending development of its other pipeline candidate, preclinical CTS-2090, a caspase inhibitor for inflammasome disease. Mento said the company hoped to end 2019 with a cash balance of between $10m and $15m.

NOVARTIS DEAL TEMPORARILY MOVED CONATUS TO THE FRONT

At the time Novartis took an option to license emricasan in late 2016, the agreement vaulted Conatus near the front of the pack in an indication with no approved drug therapy and projected annual global sales of $20bn or greater in the next decade. The deal brought Conatus $50m up front, a $15m convertible loan and the potential for a $7m option fee and up to $650m in milestones. Conatus also got the right to co-commercialize emricasan with Novartis if the drug reached market in the US.

Novartis already was in Phase II with tropifexor (LJN-452) – a non-bile acid farnesoid X receptor (FXR) agonist – for NASH when the deal was struck. The partners envisioned a combination regimen of emricasan and tropifexor that might offer improvements in both liver function and portal hypertension.

Novartis issued its own release about emricasan's failure in ENCORE-LF on 24 June, saying it remains "fully committed to pursuing the development of multiple compounds [for NASH] in collaborations." The release made no mention of whether the partnership with Conatus would be terminated – Novartis global development unit head-immunology, hepatology and dermatology Eric Hughes told *Scrip* in March that any such decision likely would have to wait until the end of 2019. *(Also see "Novartis's NASH Chief: Our Strategy Is Combos With Tropifexor As 'Backbone'" - Scrip, 12 Apr, 2019.)*

By its actions, however, Novartis appeared to be pivoting away from Conatus and emricasan in its NASH strategy in recent years. In 2017, it partnered with Allergan PLC to test tropifexor with the latter's cenicriviroc – a dual CCR2/5 inhibitor – in NASH. *(Also see "Could High Profile Combo Be Allergan/Novartis Answer To Late-Stage NASH Programs?" - Scrip, 19 Apr, 2017.)* Allergan's drug – acquired in a $1.7bn buyout of Tobira Therapeutics Inc. in 2016 – has faced its own clinical setbacks, however, failing to demonstrate a fibrosis-improvement benefit in a two-year data readout in 2017.

(Also see "Allergan's Two-Year NASH Data Fail To Show Fibrosis Benefit" - Scrip, 22 Sep, 2017.)

Last October, Novartis partnered with big pharma peer Pfizer Inc. to test tropifexor with three different oral NASH drug candidates Pfizer has advanced into clinical development: PF-05221404, a Phase II acetyl CoA-carboxylase (ACC) inhibitor; PF-06865571, a Phase I diacylglycerol O-acyltransferase 2 (DGAT2) inhibitor; and the ketohexokinase (KHK) Inhibitor PF-06835919, now in Phase II studies. *(Also see "Pfizer/Novartis Collaboration Brings Combined Strength To NASH Development" - Scrip, 29 Oct, 2018.)*

TROPIFEXOR MIGHT OFFER SAFETY ADVANTAGES WITHIN FXR CLASS

Novartis has touted tropifexor as offering advantages over other FXR agonists in development – including Intercept Pharmaceuticals Inc.'s obeticholic acid (OCA), widely expected to be the first drug approved to treat NASH in the US – because of its potency and its safety profile. Tropifexor is potent enough to be dosed in micrograms, compared to the 10mg and 25mg strengths Intercept has tested in Phase III, and has not shown the potential to increase LDL cholesterol levels in trial participants or cause pruritus, two issues that have plagued OCA. *(Also see "Intercept's OCA Data Bolster NASH Efficacy, But Pruritus Worries Worsen" - Scrip, 11 Apr, 2019.)*

During an investor presentation on 23 May, Novartis chief medical officer John Tsai said tropifexor's efficacy and safety profile could position it as a backbone agent in combination therapy for NASH, the field's longer-term expectation for treating the disease. Novartis plans to read out Phase II data for tropifexor monotherapy toward the end of 2019, he said, while it has several combination studies that should report data after that.

At the same event, Novartis' Pharma CEO at the time, Paul Hudson, called NASH one of the few opportunities where the pharma might extend itself outside of its focus therapeutic areas. "We can be bold," he told the audience. "And if our FXR [agonist] reads out where it needs to and the combinations [also perform well], that's worth considering a different model." Hudson has since left Novartis to become the CEO of Sanofi.

Besides tropifexor, Novartis has two other candidates in Phase II in NASH – LIK066, a dual SGLT1/2 inhibitor and LMB763, also an FXR agonist. *(Also see "NASH Pipeline: Racing To The Finish" - Scrip, 21 Mar, 2019.)* The pharma also has pointed to its recent acquisition of inflammasome specialist IFM Tre as offering the possibility of an immunomodulatory approach to NASH. *(Also see "Novartis Dives Into Inflammasome Pool With IFM Tre Purchase" - Scrip, 1 Apr, 2019.)*

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Genfit Assesses Optimal Elafibranor NASH Combo Therapy Opportunity

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Genfit SA is ready to begin combination therapy studies of its Phase III non-alcoholic steatohepatitis (NASH) candidate elafibranor with two classes of already marketed diabetes drugs, but that does not mean it has found a partner for a potential combo regimen. The Lille, France-based company wants to get proof-of-concept data first so that it then can choose the partner associated with the greatest opportunity.

Genfit research and development head Dean Hum explained that moving into combination trials is part of the launch strategy for elafibranor, an agonist of peroxisome proliferator-activated receptors (PPAR) alpha and delta for which Phase III data are expected before the end of 2019. The company believes getting combination data for elafibranor with a validated diabetes drug can improve uptake as the launch progresses.

Genfit will be the third company to report Phase III data in NASH, following Gilead Sciences Inc.'s unsuccessful trial with ASK1 inhibitor selonsertib in February and Intercept Pharmaceuticals Inc.'s success with FXR agonist obeticholic acid (OCA) a week later.

In May, Genfit announced that it will initiate Phase II proof-of-concept (POC) studies this summer to assess the potential of combination therapy in NASH for elafibranor plus well-known diabetes drug mechanisms. The dual PPAR agonist will be tested with a GLP-1 analog, such as Eli Lilly & Co.'s Trulicity (dulaglutide), AstraZeneca PLC's Byetta (exenatide) or Novo Nordisk AS' Victoza (liraglutide). It also will be combined with an SGLT2 inhibitor, such as AstraZeneca/Bristol-Myers Squibb Co.'s Farxiga (dapagliflozin), Lilly/Boehringer Ingelheim GmbH's Jardiance (empagliflozin) or Janssen Biotech Inc.'s Invokana (canagliflozin).

However, Genfit is initiating the POC studies without a partnership, which led Bryan Garnier & Co. analyst Jean-Jacques Le Fur to speculate that the company might want to wait for Victoza's patent to expire to create a relatively inexpensive combo regimen for NASH.

Separately, Genfit announced on 24 June that it is licensing development and commercial rights in greater China for elafibranor in NASH and primary biliary cholangitis to Terns Pharmaceuticals Inc., a liver disease- and cancer-focused company based in both the San Francisco area and Beijing. Genfit gets $35m up front and can earn up to $193m in clinical, regulatory and commercial milestones under an agreement that gives Terns rights to the drug in mainland China, Hong Kong, Macau and Taiwan.

If elafibranor is launched commercially for NASH in greater China, Genfit also would be eligible for sales royalties in the mid-teens in Terns' territories. The companies also will jointly conduct liver disease R&D projects, including development of elafibranor in tandem with Terns' proprietary drug candidates. These include FXR agonist TERN-101, in-licensed from Lilly in April 2018. Terns initiated a Phase I study of the compound on 13 June.

Speaking with *Scrip* on 20 June, Hum conceded that Intercept's OCA will reach market first, but asserted that elafibranor's efficacy

and safety profile will position it as both first-line monotherapy and the backbone of combination therapy in NASH. Intercept will seek approval in the US and Europe based on the ability of OCA to reduce fibrosis without worsening of NASH, while Genfit hopes its Phase III data will confirm earlier trials showing elafibranor can resolve NASH by eliminating ballooning of hepatocytes and eliminating or reducing inflammation.

"It's important for us to get ahead of [the competition] and consider what kind of combinations make sense," Hum explained. "If you consider some of the drugs and who NASH patients are, our understanding is … different combinations will be tried by different doctors. We think GLP-1 will be a good candidate for combination therapy. We have preclinical data in disease models, *in vivo* animal models, showing that that combination does provide synergy. And then, the other class of drugs which makes a lot of sense is SGLT2 inhibitors, and we also have results looking at *in vivo* animal models."

Genfit will launch studies of two doublets – elafibranor with a GLP-1 analog and an SGLT2. It has not said yet whether it also plans to investigate triple combination therapy, Hum said. The goal is to demonstrate safety and tolerability with those combinations, while looking for signs of efficacy in both imaging data and circulating markers of liver health.

"This is all a part of our strategy to ensure a successful launch with elafibranor and make sure it has good market uptake," the exec said. "And this, of course, is all for the benefit of the patients, to make sure that they will be optimally managed by the different physicians."

Genfit's expectation is that in the early days after NASH drugs hit the market, patients will be seen more often by general practitioners and endocrinologists than by hepatologists, making the availability of data for combination therapy extra important, Hum added.

Genfit already is building a commercial team, led by recent hire Pascal Prigent, most recently VP of marketing for GlaxoSmithKline PLC vaccines and before that a commercial executive with Lilly. The commercial team will be split between Genfit headquarters in Lille and its US offices in Boston, Hum said.

Doing its combination work independently leaves Genfit with ideal optionality, he asserted. "The objective for us is not to be tied down to any one drug at this point," Hum said. "What's important for us is that when the time comes, we can have a drop-in strategy for combination … with another drug which has the biggest market share. That is the long-term view."

NO READ-THROUGH FROM CYMABAY PPAR AGONIST DATA

But before Genfit obtains combo therapy data, SVB Leerink analyst Pasha Sarraf said in a 19 June note that the company's upcoming Phase III RESOLVE-IT data for elafibranor monotherapy is the most significant near-term catalyst in the NASH drug development space.

However, Genfit's shares have been trending down slightly since a competitor reported disappointing interim Phase II data for a similar drug on 11 June. That's when CymaBay Therapeutics Inc. said its PPAR delta agonist did no better than placebo in reducing hepatic fat in NASH patients. CymaBay has contended that its candidate is more potent than Genfit's elafibranor and offers advantages by only targeting the PPAR delta receptor.

CymaBay's shares finished trading on 20 June down 3.6% to $6.77, as the company struggles to recover from the loss of more than half of its valuation following the Phase II data report. CymaBay closed at $11.09 a share on 10 June but was down to $5.80 in heavy trading on 11 June.

Meanwhile, although analysts including Leerink's Sarraf and Garnier's Le Fur cautioned that there should be no read-through from CymaBay's poor data to elafibranor, Genfit's stock has declined from $23.87 on 10 June to $20.14 on 20 June.

"It's important for us to get ahead of [the competition] and consider what kind of combinations make sense. If you consider some of the drugs and who NASH patients are, our understanding is … different combinations will be tried by different doctors." – Dean Hum

Hum also said there should be no read-through from CymaBay to Genfit, even though both drugs are in the same class, because Genfit's drug offers different benefits as a dual PPAR agonist and because its thesis for Phase III is showing that elafibranor can resolve NASH by reducing or eliminating liver inflammation and eliminating ballooning hepatocytes, not by reducing liver fat.

CUTTING FAT VS. REDUCING INFLAMMATION

While quantity of liver fat – CymaBay's focus – is an upstream characteristic of NASH, it can be benign in pre-NASH patients, Hum noted, pointing out that the thesis that reducing hepatic fat can resolve NASH is not proven. Regardless, the liver-fat-reduction hypothesis is being pursued by several companies, including Madrigal Pharmaceuticals Inc., which recently entered Phase III with thyroid hormone receptor (THR) beta agonist MGL-3196.

Elafibranor addresses inflammation through two separate and independent but complementary pathways, Hum explained, with agonism of the PPAR alpha receptor targeting inflammation in hepatocytes, while PPAR delta agonism targets Kupffer cells, which clear bacteria and help break down red blood cells in the liver.

He added that CymaBay's interim Phase II data was derived from magnetic resonance imaging – proton density fat fraction (MRI-PDFF) scans – while elafibranor's benefits have been demonstrated with histological data from liver biopsies.

"Elafibranor has shown benefit on resolution of NASH without worsening of fibrosis independent of whatever happens on [hepatic] fat," Hum noted. "It's going to be the histology that is most important."

Genfit also has Phase II data indicating that elafibranor can offer patients additional therapeutic benefit by increasing insulin sensitivity in the liver and peripheral tissue, the exec said.

Published online 24 June 2019

Dupixent Gets Room To Grow With New Indication In Chronic Rhinosinusitis

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Sanofi and Regeneron Pharmaceuticals Inc. are successfully executing on their pipeline-in-a-molecule strategy for Dupixent (dupilumab), announcing the US Food and Drug Administration's approval of a third indication for the IL-4/IL-13 blocker on 26 June. The new indication is for chronic rhinosinusitis patients with nasal polyposis (CRSwNP) whose disease is not controlled, adding to Dupixent's existing approvals in atopic dermatitis and moderate to severe asthma.

The two partners have expressed big ambitions for Dupixent as a treatment for a range of conditions characterized by type 2 inflammation. Inhibiting IL-4 and IL-13 regulates the type 2 inflammatory response. The companies are continuing to explore Dupixent in a range of diseases including eosinophilic esophagitis, chronic obstructive pulmonary disease, and food and environmental allergies.

The approval in CRSwNP expands Dupixent's reach to a new set of patients, although there is some overlap in patients who also experience asthma. In the US, Sanofi estimates there are approximately 55,000 to 90,000 adult patients in the US whose disease is uncontrolled despite surgery or oral corticosteroid treatment.

Dupixent is the first biologic medicine approved by the FDA to treat CRSwNP, which results in obstructed sinus and nasal passages and can lead to difficulty breathing, congestion and reduced sense of smell or taste. Some patients also have severe asthma and can be more difficult to treat. The current standard of care is intranasal or systemic steroids or nasal surgery.

Dupixent generated $374m in the first quarter and is well on its way to becoming an important blockbuster franchise. The first-in-class drug was approved by the FDA in March 2017 as the first biologic for moderate-to-severe atopic dermatitis. *(Also see "Sanofi/Regeneron Choose Access Over Price With Dupixent Launch" - Scrip, 28 Mar, 2017.)* The second indication for moderate to severe asthma followed in October 2018, with Dupixent receiving a slightly broader label compared to IL-5 biologic rivals. *(Also see "Dupixent Approved For Severe Asthma With Broader Label Than Other Biologics" - Scrip, 21 Oct, 2018.)*

The FDA approved the newest indication under a priority review, based on the results of two Phase III trials. These evaluated Dupixent 300mg every two weeks with standard of care, mometasone furoate nasal spray, compared to placebo plus MFNS. Dupixent improved key disease measures and met all primary and secondary endpoints, resulting in improved nasal polyp size, nasal congestion severity, chronic sinus disease and improvements in smell. *(Also see "Triple Threat: Full Rhinosinusitis Data Place Dupixent Top Of The IL Heap" - Scrip, 26 Feb, 2019.)*

Treatment also resulted in a reduction in systemic corticosteroid use. In a prespecified pooled analysis of the two trials up to 52 weeks, the proportion of patients who required systemic corticosteroids was reduced by 74% with Dupixent versus placebo. Dupixent is priced the same for all three indications at a current wholesale acquisition cost of $3,019 per month.

Novartis AG and Roche also are developing the asthma biologic Xolair (omalizumab), an immunoglobin E (IgE) blocker, for CRSwNP, and recently announced positive top-line data from two Phase III trials in the condition.

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Pfizer's Talzenna To Compete With AZ's Lynparza In Breast Cancer After EU Okay

KEVIN GROGAN kevin.grogan@informa.com

Having received the green light in Europe for its PARP inhibitor Talzenna, Pfizer Inc. is now gearing up to take on AstraZeneca PLC's class-leading Lynparza in the *BRCA*-mutated breast cancer market.

After getting a positive opinion from the European Medicines Agency's Committee for Medicinal Products for Human Use at the end of April, Pfizer has got the official thumbs-up to market Talzenna (talazoparib) for germline (inherited) *BRCA* 1 and 2-positive, HER2-negative locally advanced or metastatic breast cancer. The approval, which was based on the EMBRACA Phase III study that showed a 46% reduction in the risk of disease progression and a more-than-doubled overall response rate compared with chemotherapy (63% versus 27%), comes eight months after the US Food and Drug Administration approved the therapy in this indication.

> "Lynparza's built-in physician familiarity remains a strong intra-class revenue driver."

The nod comes just two months after AstraZeneca and partner Merck & Co. Inc. secured European approval for Lynparza

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CONTINUED FROM PAGE 16

(olaparib) for germline *BRCA*-mutated HER2-negative advanced breast cancer. The latter drug is fast becoming a blockbuster, with first-quarter sales of $237m due mostly to its ovarian cancer revenues.

Talzenna is only approved for breast cancer and Pfizer and partner Merck KGaA suffered a setback in March when they discontinued the Phase III JAVELIN Ovarian PARP 100 study of their PD-L1 inhibitor Bavencio (avelumab) plus Talzenna (talazoparib) in previously untreated advanced ovarian cancer.

The trial was pulled in part because of the changing treatment landscape in ovarian cancer, and especially following the approval of Lynparza in the front-line maintenance setting but Pfizer seems confident it can take on the biggest-selling PARP in the breast cancer indication. The US giant pointed out that Talzenna, which was acquired by Pfizer through its $14bn purchase of Medivation Inc. in 2016, is the only once-daily PARP inhibitor approved in Europe for hereditary breast cancer - Lynparza is dosed twice daily.

However, Datamonitor Healthcare analyst Zachary McLellan told *Scrip* that while the approval "broadens Talzenna's geographic availability to the EU breast cancer market, it will likely remain in Lynparza's shadow in the near term. As such, Talzenna is expected to received moderate uptake in this indication due to need and the established efficacy of this class in heavily pre-treated gBRCAm+ patients, but sales will likely still lag behind Lynparza."

He went on to say that "there seems to be a general consensus of PARP-parity within this class and Talzenna is no exception. Any differences between medications are relatively minor and may impact prescribing decisions on a per-patient basis, but likely won't impact overall revenues to a significant degree. McLellan claimed that "Talzenna's reduced pill burden is negligible and although it may have slightly improved gastrointestinal side effects compared to Lynparza, other adverse events like alopecia and higher anemia rates balance that out," adding that "Lynparza's built-in physician familiarity remains a strong intra-class revenue driver."

As is always the case in Europe, price will be an issue. Pfizer has not disclosed any details about the latter or specific launch plans but in the US when approval was obtained, it set a $14,580 per month price tag for Talzenna; Lynparza cost around $16,200 per month.

There are two other approved PARP inhibitors for ovarian cancer – GlaxoSmithKline PLC's Zejula (niraparib) - which came with its $5.1bn acquisition of Tesaro Inc. - and Clovis Oncology Inc.'s Rubraca (rucaparib). While those PARPs are also being evaluated for breast cancer, the primary focus seems to be in other indications [on 24 June, GSK announced that its supplemental new drug application for Zejula for late-stage ovarian cancer has been granted a priority review by the FDA and has an action date of 24 October].

Pfizer is no stranger to breast cancer, notably with its market-leading CDK4/6 inhibitor Ibrance (palbociclib) which is approved for hormone receptor-positive, HER2-negative advanced or metastatic breast cancer. The drug was approved in 2015 and has been the cornerstone of the company's oncology growth plans which will soon be expanded following last week's announcement of Pfizer's proposed $11.4bn acquisition of Array BioPharma Inc.. *(Also see "Array's Three Value Drivers Align With Pfizer's Three Oncology Pillars In $11.4bn Deal" - Scrip, 17 Jun, 2019.)*

In announcing that deal, Pfizer noted that one of the main drivers of that deal was to get hold of the BRAF/MEK inhibitor combination Braftovi (encorafenib) and Mektovi (binimetinib) which is approved for melanoma and colorectal cancer. Interestingly, a Phase II trial is underway looking at a combination of Talzenna, Bavencio and Mektovi is underway in adult patients with locally advanced or metastatic *KRAS*- or *NRAS*-mutant non-small cell lung cancer and pancreatic ductal adenocarcinoma.

Talzenna is also being evaluated in several ongoing clinical trials, including early triple-negative breast cancer and prostate cancer; the drug is in Phase III for the latter in combination with Pfizer's own Xtandi (enzalutamide).

The Talzenna green light is also good news for BioMarin Pharmaceutical Inc. which will pocket a $15m milestone payment from Pfizer that has been triggered by the European approval. The cash is part of an agreement inked with Medivation in August 2015 which involved a $410m upfront to Biomarin, and up to an additional $160m in regulatory and sales-based milestones, of which $50m has been earned to date, plus mid-single digit royalties.

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AMAG Must Build Market For Approved Female Libido Drug To Avoid Addyi's Fate

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The US Food and Drug Administration has approved AMAG Pharmaceuticals Inc.'s Vyleesi (bremelanotide injection), a melanocortin receptor agonist, to treat hypoactive sexual desire disorder (HSDD) in premenopausal women.

The Vyleesi autoinjector is the first treatment for this patient population that can be self-administered as needed in anticipation of sexual activity.

The product will be commercially available in September through select specialty pharmacies, said the company, although analysts still retain some skeptism over market potential of the drug. Analysts at Leerink said that "commercial potential of Vylessi remains an outstanding debate given its route of administration via injection and risks around market creation," in a 23 June company update note.

Leerink analysts highlight the 6 million premenopausal women in the US (one in 10) with HSDD, of which the clear major-

ity are not on therapy. AMAG's strategy is to destigmatize the conversation, create an online community and focus on digital channels, much like it did for its vaginal atrophy drug Intrarosa (prasterone). But Leerink analysts believe AMAG "will have its work cut out to build this market", as research suggests that 95% of women who have HSDD do not know they have a specific medical condition.

AMAG will work to improve on the fortunes of its only competitor in the market,Sprout Pharmaceuticals Inc.'s Addyi (flibanserin), which was approved in 2015 but has been unable to make in-roads in the market, so far peaking at around $13m sales in 2016.

Addyi has not been the commercial success its originators had hoped. Immediately following its approval, Valeant Pharmaceuticals International Inc., as was, acquired Sprout for $1bn. However, two years later, Valeant sold the subsidiary and Addyi back to its original owners in exchange for a 6% royalty on global sales of the drug. Payers had been questioning a price tag in the region of $800 for 30 tablets; the product needs to be taken every day. *(Also see "Valeant Returns $1bn Female Libido Drug For Free" - Scrip, 7 Nov, 2017.)*

Analysts at Jefferies has said in a 22 May note, based on AMAG's analyst day, that "given the commercial failure of the same target market drug Addyi… commercial challenges remain although one could argue for difference in products' profiles."

Addyi has a Black Box warning, is contraindicated with alcohol, and only available through a REMS program, while Vyleesi has none of these drawbacks. Its method of administration, however, has left some doubts in the minds of industry observers. *(Also see "US FDA Squashes Sprout's Attempt To Remove Boxed Warning From Addyi Label" - Pink Sheet, 14 Apr, 2019.)*

Leerink conceded that, while they had been concerned about the subcutaneous method of administration, they were surprised that physicians at AMAG's Analyst Day acknowledged how insignificant this issue was in the clinical trials. They also noted that nearly 80% of patients who completed the Phase III trials elected to remain in the open-label portion of the study.

Stephanie Yip, senior analyst at Datamonitor Healthcare, told *Scrip*, "The fact that Vyleesi is intended to be taken as needed is a key differentiating selling point for the brand over its once-daily competitor, Addyi. Although injections may not be the preferred route of administration for patients compared to oral pills, Vyleesi's longer dosing schedule offers the benefit of convenience, which should drive its uptake."

Leerink forecasts that Vyleesi can make around $90m per year by 2025, and sees the potential that Vyleesi can make in-roads in this market where Addyi has not, and "be a much-needed growth driver for AMAG in the medium-to-longer term."

RECONNECT STUDY

Bremelanotide is the first of a new class of drugs developed to treat sexual dysfunction, melanocortin agonists. It acts on the MC1 and MC4 receptors, the latter of which are associated with the regulation of metabolism, sexual behavior and male erectile function.

Vyleesi's approval is based on two Phase III studies, named RECONNECT. The trials lasted for 24-weeks and enrolled 550 patients in each, in which they injected bremelanotide under the skin of the abdomen or thigh at least 45 minutes before sexual activity. Twenty five percent of patients had improved sexual desire scores compared with placebo patients (17%).

The FDA notes that patients shouldn't use more than one dose a day, or eight doses a month. Patients should stop treatment at eight weeks if they don't notice any improvement in sexual desire and distress.

The most common adverse events found in the trials were nausea, flushing, injection site reactions, and headache. In clinical trials, Vyleesi caused small, transient increases in blood pressure, and is contraindicated in women with uncontrolled high blood pressure or known cardiovascular risk.

AMAG in-licensed Vyleesi from Palatin Technologies Inc. in February 2017. Under the terms of the agreement, the approval of Vyleesi by the FDA triggers a $60m payment obligation to Palatin.

In addition, AMAG will pay Palatin tiered royalties on annual net sales of Vyleesi ranging from the high-single digits to the low double-digits. AMAG will also pay Palatin sales milestones based on escalating annual net sales thresholds, the first of which is $25m, triggered at annual net sales of $250m.

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Bring Them On: China Releases Generics List To Encourage Competition

BRIAN YANG & ANJU GHANGURDE

In a bid to encourage generic drug development, China's National Health Commission has listed 34 drugs whose domestic patents have expired or are expiring but for which there have been no abbreviated new drug applications, leading to what it views as insufficient competition.

The list is part of a coordinated effort to encourage generic drug development, a priority outlined in a plan by China's State Council to support the manufacturing, stable supply and expand the use of such products.

Of the 34 products, oncology, anti-infective and orphan drugs dominate the list, signaling the government's strong desire to promote access to cancer and HIV therapies, as well as medicines for rare diseases.

Major cancer drugs on the list include ixabepilone and fulvestrant for breast cancer and mercaptopurine for leukemia. The seven orphan disease products include nitisinone for type 1 hereditary tyrosinemia (HT-1) and glatirameracetate, a first-line treatment for multiple sclerosis. Developed by Teva Pharmaceutical Industries Ltd., this was ranked 17th in the global list of top-

selling drugs in 2014, with sales of more than $4bn.

Also listed are two treatments for pulmonary arterial hypertension, treprostinil and bosentan. The other rare disease drugs for which insufficient generic versions have been developed in China include icatibant, a treatment for hereditary vascular edema, and deferasirox, the first oral iron chelator approved by the US FDA, for patients over six years of age with thalassemia iron overload.

The National Health and Family Planning Commission is now gathering public comments on the list until 25 June 25, via email to yzsmlc@nhfpc.gov.cn.

INDIA-CHINA MEETING

Interestingly, almost alongside the new China initiative to increase generics, the Indian government machinery is continuing to make concerted efforts to engage with the country to push for improved market access for Indian drugs, as its Asian neighbor takes definitive steps to open up its market to generic suppliers. India, which prides itself as the pharmacy to the world, saw its global exports exceed $17bn in 2017-18 (expected to touch $20bn by 2020), though formulation exports to China have been minuscule at just $30m.

Markets like the US are important contributors to India's pharma growth - one in every three pills consumed there is estimated to be made by an Indian generics manufacturer – but China has generally been a tough market to crack.

India has been pressing for fast track registration and exports of its medicines to China, and sought a clear road map for upping its share of supplies in China at the India-China Drug Regulations Meeting on June 21 in Shanghai, the first such initiative between the two nations. India's top ask at the meeting, as indicated by joint secretary of commerce Shyamal Misra, continues to be easing of regulatory hurdles faced by Indian firms in China. Indian officials also sought a "more coordinated role" by the regulators on both sides.

The meeting covered, in six sessions, a range of areas including the registration of imported drugs and the procurement system in China, overseas inspections by China's regulator, compliance and the active pharmaceutical ingredient registration process in China.

S Eswara Reddy, India's drugs controller general, underscored the role of the regulator in facilitating improved affordability and accessibility of quality medicines, while Xu Jinghe, deputy commissioner of China's National Medical Products Administration, elaborated on the reforms undertaken by China over the past two years and "hoped for more engagement on this issue," a statement from the the Embassy of India in Beijing noted.

Close to 70 pharma firms - 35 Indian and 30 Chinese - attended the session, in addition to government delegates from both sides.

Published online 24 June 2019

NO	GENERIC NAME	FORMULATION	DOSAGE
1	Nitisinone	capsule	20mg
2	Fumatero	inhalation	0.02mg/2mL
3	Posaconazole	injection, tablet	300mg/16.7mL (18mg/mL); 100mg
4	Ammonia benzene	tablet	50mg,100mg
5	Valganciclovir	tablet	50mg/mL
6	Rilpivirin	tablet	450mg
7	Abacavir	injection	25mg
8	Ertapenem	suspension liquid	1.0g
9	Atovaquone	injection	750mg/5mL
10	Ixabepilone	injection	15mg, 45mg
11	Fulvestrant	injection	5ml: 0.25g
12	Mercaptopurine	tablet	25mg, 50mg
13	Methotrexate	tablet	2.5mg
14	Cyclophosphamide	tablet	50mg
15	Vitamin A acid	injection	10mg
16	Fesoterodine	injection	4mg, 8mg
17	Glatiramer acetate	tablet	20mg/ml, 40mg/mL
18	Azathioprine	tablet	50mg, 100mg
19	Raloxifene	tablet	60mg
20	Levothyroxine	tablet	50µg
21	Eletriptan	tablet	20mg, 40mg
22	Pyridostigmine Bromide	tablet; suspension release	0.25g (0.2g:0.05g)
23	Levodopa	tablet	20mg, 40mg
24	Brivaracetam	injection	10mg, 25mg, 50mg, 75mg, 100mg
25	Fosaprepitant dimeglumine	injection	150mg
26	Treprostinil	tablet	1mg/mL, 2.5mg/mL, 5mg/mL, 10mg/mL
27	Bosentan	tablet	62.5mg, 125mg
28	Colesevelam	capsule	625mg
29	Dofetilide	injection	0.125mg, 0.25mg, 0.5mg
30	Icatibant	tablet	30mg/3ml (10mg/ml)
31	Deferasirox	eye drops	0.125g, 0.25g, 0.5g
32	Alcaftadine	eye drops	0.25%
33	Tafluprost	tablet	0.00%
34	Vigabatrin	tablet	500mg

Clovis CEO's Rough Guide To European Launches

KEVIN GROGAN kevin.grogan@informa.com

With Clovis Oncology Inc. having just launched its PARP inhibitor Rubraca in Germany, the company's CEO Patrick Mahaffy has been giving some guidance to fellow US companies who may be looking at setting up operations in Europe themselves.

In an interview with *Scrip*, Mahaffy quipped that his first piece of advice to small-to-medium enterprises looking to make inroads into Europe is that "they shouldn't try to do it all on their own and they may want to use us as a commercial partner." On a more serious note, he said it was vital to assemble an experienced leadership team early on, "and you have to be considered local in each of those territories to be competitive to enable a good dialogue with the key opinion leader (KOL) community."

Mahaffy added, "It is kind of obvious but you don't just send a bunch of Americans over to tell people how to do things. In Germany, we hired highly experienced people who know the European Medicines Agency and can also manage the reimbursement process there," including staff the Clovis chief knew from his spell as CEO at Pharmion Corp., the company Mahaffy founded in 2000 and sold to Celgene Corp. in 2008.

He stressed, "You've got to be doing clinical trials in Europe and think about it as a means of building experience and a dataset associated with your drug. Don't try to come into Europe with US-only and somehow think that's going to be enough in Europe."

However, he also cautioned that "it is easy to get ahead of yourself in terms of the timing of hiring" when it comes to commercialization. In January this year, the European Commission expanded the label on Rubraca (rucaparib) beyond its initial marketing authorization in Europe for advanced ovarian cancer in selected patients – granted in May 2018 – to include maintenance treatment for eligible patients regardless of their *BRCA*-mutation status.

Rubraca being the first PARP inhibitor to be approved for both treatment and maintenance treatment was the catalyst that led to Clovis launching in Germany and Mahaffy noted that "we only brought on board our German teams at the end of the year and the first part of this year, because we knew we were going to be launching in March." He added that "we didn't bring in a field based organization in the other European territories with the exception of a relatively small number of medical science liaison (MSL) staff to coordinate and work with KOLs and investigators."

The German launch has started well, Mahaffy said, and Clovis has about 25 staff there in varying roles. "We are building good relationships with the KOLs," he said, pointing out that those relationships had begun earlier through an expanded access program that made the drug available to eligible patients before launch and allowed physicians who had limited experience with Rubraca to get more knowledge about the product.

As for the rest of the continent, Mahaffy said a launch in the UK was possible later this year, depending on the outcome of negotiations with the National Institute for Health and Care Excellence,

"You've got to be doing clinical trials in Europe and think about it as a means of building experience and a dataset associated with your drug. Don't try to come into Europe with US-only and somehow think that's going to be enough in Europe." – Patrick Mahaffy

with access through the Cancer Drugs Fund being an option. Rubraca is already available for UK patients on the private pay market.

After that, Clovis is hoping to be in a position to launch in Spain, France and Italy around the first quarter of 2020, while some smaller territories such as the Netherlands which have "a more accelerated reimbursement negotiation process" may back Rubraca later this year.

The PARP market is a fiercely competitive one, headed by AstraZeneca PLC and Merck & Co. Inc.'s Lynparza (olaparib), while GlaxoSmithKline PLC's Zejula (niraparib) – which came with its $5.1bn acquisition of Tesaro Inc. is also a rival for Rubraca on the ovarian cancer space. However, Mahaffy is confident that Rubraca can gain market share in Europe, saying that "we have found a little more willingness to differentiate based on the clinical profile that's been established and published for our drug than we see in the US where unfortunately, some say the PARP inhibitors are all the same with the exception of toxic differences."

Mahaffy pointed to a recent symposium in Germany where attendees were encouraged to review the differences between the various PARPs and "not just asserting that they really are all the same when the data don't fully support that view. There are differences."

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

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

PIPELINE WATCH, 21–27 JUNE 2019

Event Stage	Lead Company/Partner	Drug Name	Indication	Comments	Change To LOA (%)	LOA (%)
Phase III Published Results	Tricida, Inc.	veverimer (TRC101)	Metabolic Acidosis in CKD	The Lancet online, 25 June, 2019	0	69
Phase III Updated Results	Motif Bio plc	iclaprim (IV)	Skin and Skin-Structure Infections	ASSIST-1,2, REVIVE-1,2; Additional Data	0	64
Phase III Updated Results	Actinium Pharmaceuticals, Inc.	Iomab-B	Bone Marrow Transplant In AML	SIERRA; Engraftment Facilitated	0	37
Phase III Top-Line Results	Poxel, Sumitomo Dainippon	imeglimin	Diabetes Type 2	TIMES 3 (Japan); Met Primary Endpoint	0	22
Phase III Top-Line Results	LSK BioPartners, Inc.	rivoceranib (apatinib)	Gastric Cancer	ANGEL; Missed OS Endpoint, Improved PFS	-5	30
Phase III Top-Line Results	AstraZeneca PLC	Imfinzi (durvalumab)	Small Cell Lung Cancer, First-Line	CASPIAN; Improved Overall Survival	0	35
Phase III Trial Initiation	Axsome Therapeutics, Inc.	AXS-05	Major Depressive Disorder	GEMINI; A Multimodal NMDA Antagonist	0	57
Phase III Trial Initiation	X4 Pharmaceuticals, Inc.	mavorixafor (X4P-001)	WHIM Syndrome	4WHIM; A 52-Week Study	39	59
Phase III Trial Initiation	Regeneron/Bayer	Eylea (aflibercept)	Retinopathy Of Prematurity	Multi-Country Study		51
Phase II/III Trial Initiation	WAVE Life Sciences Ltd.	suvodirsen (WVE-210201)	Duchenne Muscular Dystrophy	DYSTANCE 51; A Global Study	8	24
Phase III Trial Announcement	Laboratoris Sanifit S.L.	SNF472	Calciphylaxis In Dialysis Patients	In The US And Europe	0	13
Phase III Trial Announcement	Ovid Therapeutics, Inc.	OV101 (gaboxadol)	Angelman Syndrome	NEPTUNE; In The US	0	18
Phase III Trial Announcement	Catabasis Pharmaceuticals	edasalonexent	Duchenne Muscular Dystrophy	GalaxyDMD; Open Label Extension	0	57

Source: Biomedtracker | Informa, 2019

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The GSK purchase of Tesaro once again put Clovis into the spotlight as a potential takeover target but Mahaffy, who has plenty of experience in M&A, played a straight bat. He told *Scrip,* "At the moment, my strong belief is the company needs to keep its head down, grind out our clinical development and drive sales growth both in the US and Europe. Good things will happen if you grind it out, it keeps you focused and could potentially lead to interest on the part of somebody else. We don't think about it all that much, we just keep pushing the ball forward with Rubraca."

One of the ways the ball is being pushed forward is in the Phase III ATHENA trial which is evaluating a combination of Rubraca and Bristol-Myers Squibb Co.'s checkpoint inhibitor Opdivo (nivolumab) in patients with newly diagnosed advanced ovarian cancer. Mahaffy said the partners were very pleased with the pace of enrollment, "which is ahead of our predictions and I think that speaks to the enthusiasm for the combination of a PD-1 with a PARP inhibitor."

He spoke about the hope that physicians have for a combo that "could potentially change the shape of the curve sufficient to deliver far more long term progression free survivors and potentially even increase the number of women who are effectively cured in the frontline setting, who never recur have to go on a second or third round of chemo."

The trial is set to be fully enrolled in the middle of next year for the 1,000-patient study and "we're optimistic but it's always fingers crossed when you're when you're engaging in a trial of this size." A study this big does not come cheap but Clovis signed an innovative financing pact with TPG Sixth Street Partners last month whereby the latter is providing a loan up to $175m to cover the ATHENA trial costs up to the end of the first half of 2022.

Mahaffy explained that "necessity is the mother of invention and we found a path that was not dilutive and allowed us to bring cash in as we needed it to fund this trial on a quarterly basis. It extends our cash runway pretty significantly and there's no payback expected from this financing until after not only the completion of the trial, but also approval of the expanded label," ie, first-line ovarian cancer maintenance.

The next indication that Clovis will hope to get a Rubraca approval for is prostate cancer. A filing is planned with the FDA by the end of 2019 based primarily on data presented at ESMO 2018 from the Phase II TRITON2 trial of Rubraca which showed a 44% confirmed objective response rate (ORR) in 25 patients with a *BRCA* 1/2mutation; in April Clovis provided an update to FDA on 52 patients that showed a similar positive trend.

Mahaffy also noted that Clovis was about to initiate a basket study that looks at a handful of different mutations across tumor types, with the dominant ones being *BRCA* 1 and 2 mutations, including patients with pancreatic cancer. "The goal is to ultimately get a tumor-agnostic indication not unlike Loxo Oncology Inc.'s Vitrakvi (larotrectinib) and we've had a good dialog already with FDA about that trial and we're really enthusiastic about it."

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APPOINTMENTS

Executive	To Company	New Role	From Company	Previous Role	Effective Date
Eric Hoefer	Arcus Biosciences	Chief Commercial Officer	AstraZeneca	Head, Immuno-Oncology Global Marketing	24-Jun-19
David Caponera	Dicerna Pharmaceuticals Inc	Head, Patient Advocacy and Patient Services	Catalyst Pharmaceuticals	Vice President, Patient Engagement and Access Support	13-Jun-19
Steven Kates	Dicerna Pharmaceuticals Inc	Vice President, Regulatory Affairs	Takeda Pharmaceuticals	Director, Regulatory Affairs	13-Jun-19
Purnanand Sarma	Immunome Inc	Chief Executive Officer, President and Director	Taris Biomedical	Chief Executive Officer, President and Director	24-Jun-19
Jean-Paul Kress	MorphoSys AG	Chief Executive Officer and President	Syntimmune	Chief Executive Officer and President	1-Sep-19
John N. Bonfiglio	Qrons Inc	Chief Operating Officer	Bonfiglio Consulting Group	Principal	27-Jun-19
Matthew Osborne	Unum Therapeutics Inc	Chief Financial Officer	Voyager Therapeutics	Vice President, Corporate Affairs, Communications and Investor Relations	24-Jun-19
Mert Aktar	Unum Therapeutics Inc	Head, Business and Corporate Development	Shire plc	Global Head, Hematology and Immunology Business Development	13-Jun-19

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

Source: Medtrack | Informa, 2019

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