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AbbVie Pounces On $63bn Mega-Deal For Allergan

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AbbVie Inc.'s quest to reduce its reliance on Humira (adalimumab) has led the company to Allergan PLC's doorstep. AbbVie announced an agreement to acquire Allergan for approximately $63bn on 25 June in a mega-deal that will move AbbVie into medical aesthetics and establish the merged company as a leading pharmaceutical manufacturer with $48bn in combined revenues, putting it in the top echelon of big pharma with the likes of Pfizer Inc., Novartis AG and Roche.

The stage has been set for a buyer to make a play for Allergan, with the company's stock being out of favor on Wall Street, headwinds from the loss of patent exclusivity for Restasis, growing competition in medical aesthetics and pipeline failures. Activist investors even launched a campaign against CEO Brent Saunders and the Allergan management team, seeking to increase oversight of the company.

AbbVie is facing its own big headwind with Humira, its crown jewel that will begin to fade in 2023, when biosimilars are expected to launch in the US. Finding a patch big enough to fill the Humira void has become the company's pressing dilemma. Humira, the top selling drug in the world, generated $19.94bn in sales last year.

"This will have a profound impact on AbbVie's overall growth story while addressing concerns about the company's reliance on Humira," CEO Richard Gonzalez said in a same-day conference call announcing the deal. The merged company will have leadership positions in immunology, hematological oncology, medical aesthetics, neuroscience, women's health, eye care and virology, he said.

Allergan will be a salve for AbbVie, adding the blockbuster Botox franchise, but a mega-deal won't alleviate all of the problems the companies individually face. The deal follows on the heels of another similar mega-deal, Bristol-Myers Squibb Co.'s planned $74bn acquisition of Celgene Corp., under not entirely dissimilar circumstances. Bristol, looking to reduce its reliance on Opdivo (nivolumab), seized the opportunity to buy the maker of Revlimid (lenalidomide) as Celgene came under mounting pressure from its own setbacks.

RELIEF FOR SOME, SURPRISE FOR OTHERS

AbbVie is buying Allergan in a cash and stock transaction under which Allergan shareholders will receive 0.8660 AbbVie shares and $120.30 in cash for each Allergan share they hold, for a total consideration of $188.24 per Allergan share. The offer represents a 45% premium to the closing price of Allergan's shares on 24 June.

Allergan shareholders will likely be relieved to see an exit door materialize, though a higher offer would be welcomed. Allergan's stock has been depressed, down about 25% compared to where it was trading two years ago. Only three years ago, Pfizer was poised to buy Allergan for a staggering $160bn, but the deal fell apart after the US Treasury changed the tax incentives that were a big driver of the deal.

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from the editor

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Things were getting uncomfortable for AbbVie.

Immunology drug Humira (adalimumab) makes up 57% of the company's revenues. Following the launch in Europe of biosimilar versions of its main growth engine late last year, AbbVie's sales started to slip downwards in the first quarter of 2019.

The company has been able to contain the damage so far thanks to growth in its blood cancer franchise (Imbruvica and Venclexta) and because Humira retains exclusivity in the US, the product's biggest market, where it is still growing. However, Humira will face US biosimilar competition from several rivals from 2023, and despite the recent approval of its IL-23 inhibitor Skyrizi for psoriasis and trial data showing its investigational JAK inhibitor upadacitinib works better than Humira in rheumatoid arthritis, it is unlikely that it will be able to maintain a $20bn slice of the immunology market for much longer.

Clearly, combining with Allergan will reduce AbbVie's exposure to the Humira sales cliff. It also seems to provide a substantial opportunity to make cost savings, particularly in R&D and SG&A. Trimming the early-stage pipeline will help cut spending and pay down debt taken on for the acquisition, for instance.

But integration could be challenging given the dissimilarity between the two firms' areas of focus. And AbbVie is paying a 45% premium for a company operating in completely different market segments whose performance has been in question and whose stock price has been sliding for some years now. This deal may help alleviate the major existing concern about AbbVie, but it does not remove the discomfort.

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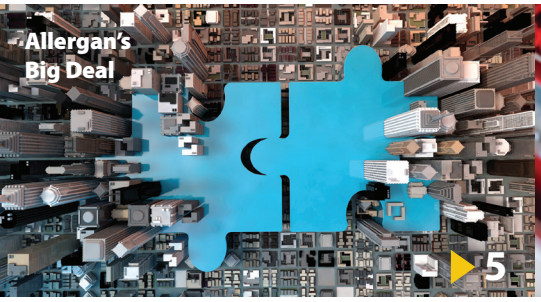

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Sanofi's Ameet Nathwani Brings Life Sciences R&D Expertise To The Digital Space

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Sanofi's Ameet Nathwani readily acknowledges he's not your typical chief digital officer.

Nevertheless, the self-described "technology geek" is excited about being able to meld his life sciences R&D expertise – with its focus on scientific rigor and patient protections – into Sanofi's growing endeavors in the digital space.

A cardiologist by training with more than 20 years' experience in the pharmaceutical industry, Nathwani joined Sanofi in May 2016 as chief medical officer. He added a second title in February, chief digital officer, tasked with scaling up Sanofi's portfolio of digital initiatives by developing broad external partnerships, building out internal infrastructures and exploring new business opportunities.

During the Biotechnology Innovation Organization's recent annual meeting in Philadelphia, Nathwani sat down with Scrip to talk about his unique job title, Sanofi's approach to the digital therapeutic space, and what he sees as the major hurdles to turning the promise of digital technologies into a reality for patients. The conversation took place shortly before Sanofi unveiled its broad partnership with Google and offers insights into the company's digital philosophy.

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

inside:

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What a difference three years can make.

As Gonzalez said in the call, the depressed price for Allergan is one of the reasons AbbVie made its move to buy the company now. "Assets of the quality of Allergan are not always available and certainly not at this value," he said.

Indeed, the deal seems more opportunistic than strategic. Credit Suisse analyst Vamil Divan said in a same-day note that while he had anticipated M&A action from both companies, "the two coming together is the surprise for us as we had expected companies with a consumer-facing presence to be more interested in Allergan, and we expected AbbVie to pursue somewhat smaller deals that are more firmly focused in specialty therapeutic areas."

AbbVie investors appeared perplexed by the merger news, with the company's stock down 16% to $65.20 at the end of the day. While the acquisition presents a near-term sales and earnings fix and substantial savings through synergies, Allergan's portfolio largely falls outside of AbbVie's areas of expertise, its franchises are maturing and the pipeline is lacking.

Whereas Allergan's areas of expertise are medical aesthetics, ophthalmology, women's health and gastrointestinal drugs, AbbVie's portfolio is concentrated in immunology and oncology. The merger of the two and subsequent broadening of AbbVie's focus comes at a time when many innovative drug makers are narrowing their therapeutic areas of expertise.

AbbVie has successfully built out its pipeline with innovative drugs like Imbruvica (ibrutinib) and Venclexta (venetoclax) for blood cancers and Skyrizi (risankizumab) for psoriasis, but those products only make a dent in the vast shadow of Humira.

Wolfe Research analyst Tim Anderson said in a same-day note that "AbbVie investors will understand why AbbVie is doing this. It is in a difficult spot and its own late-stage pipeline is not capable of backfilling enough for Humira, despite AbbVie management's assertions."

"Allergan will help lessen the impact of Humira on AbbVie's financials in 2023+, but it will not likely put AbbVie on a trajectory of sustainable or competitive growth," Anderson added.

AbbVie said it expects the acquisition will result in annual pre-tax synergies and other cost reductions of at least $2bn in year three, with cost savings coming from R&D and SG&A efficiencies, and from eliminating manufacturing and supply chain redundancies.

BUYING THE BLOCKBUSTER BOTOX

What AbbVie will get is a flood of new revenue – $15.8bn based on Allergan's 2018 financials. Sales are driven by Allergan's world-leading medical aesthetics business, including the blockbuster neurotoxin Botox (onabotulinumtoxinA) and dermal filler Juvederm. Botox generated $3.58bn and Juvederm generated $1.16bn in 2018 sales. Allergan has built out its business with other products like Kybella (deoxycholic acid) for double chin, Alloderm regenerative medicine products for plastic surgery and the CoolSculpting body-contouring device.

Allergan has forecast continued strong growth for the dermal aesthetics market, but is also facing more competition from new branded rivals and the potential threat of a biosimilar competitor. Mylan NV and Revance Therapeutics Inc. are working on the development of a biosimilar version of Botox, but have acknowledged the product will take time to develop because of the complexity.

Gonzalez was optimistic about Botox's long-term market exclusivity. "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," he said.

But Allergan's pipeline doesn't have much to excite investors. The company isn't known as a big innovator, and only spent $2.27bn on R&D in 2018. The biggest potential near-term opportunities are the two oral CGRP inhibitors in development for migraine headaches, including ubrogepant for acute migraine treatment, which is pending at the US Food and Drug Administration with action expected in the fourth quarter. Allergan brings experience in the potentially lucrative migraine market with Botox, which has a therapeutic indication for chronic migraine prevention.

AbbVie expects its acquisition of Allergan to close in the first quarter of 2020, depending on regulatory approvals, Allergan shareholder approval and other closing conditions. The fact that there is not a significant amount of portfolio overlap could help the regulatory process and approval by the US Federal Trade Commission, which has delayed some big biopharma acquisitions this year over anti-competitive concerns.

Bristol disclosed a day before the AbbVie/Allergan deal announcement that it would have to divest one of Celgene's big commercial products, Otezla (apremilast), over the FTC's concerns about competition with Bristol's TYK2 inhibitor that's in Phase III for psoriasis, a key Otezla indications.

AbbVie said it is prepared to divest a few small products promptly where there may be portfolio overlap, but that it does not foresee any material concerns.

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It's All About The Revenues

AbbVie's and Allergan's biggest sellers

ABBVIE'S MARKETED DRUGS	2018 REVENUES	ALLERGAN'S MARKETED DRUGS	2018 REVENUES
Humira	$19.94bn	Botox	$3.58bn
Imbruvica	$3.59bn	Restasis	$1.26bn
Mayvret	$3.44bn	Juvederm	$1.16bn
Creon	$928m	Linzess	$785.2m
Lupron	$892m	Lumigan	$684.4m
Synthroid	$776m	Bystolic	$585.8m
Synagis	$726m	Alphagan/Combigan	$551.4m
AndroGel	$429m	Lo Loestrin	$527.7m
Duodopa	$430m	Vraylar	$487.1m
Venclexta	$344m	Eye drops	$482.4m
Orilissa	N/A	Alloderm	$415.3m

Source: Company 2018 financial filings

Allergan's Big Deal: A Buyout, Not A Split, Appeases Wary Investors

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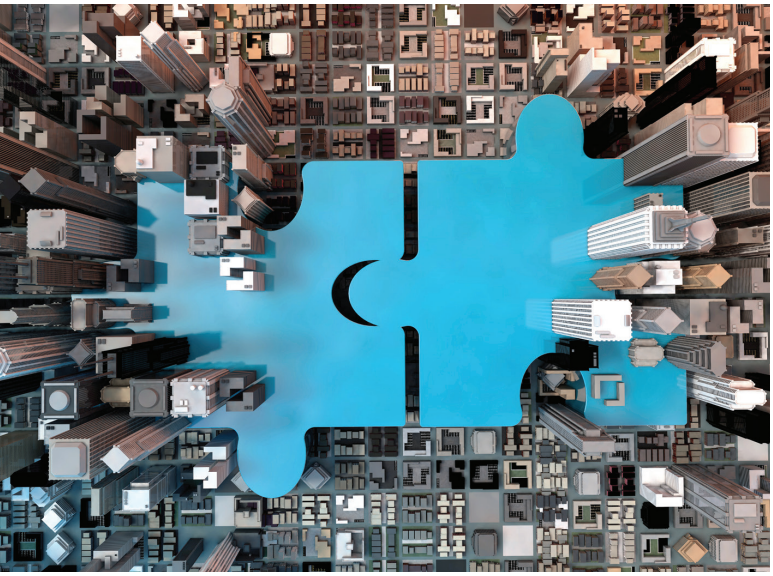
The unexpected announcement on 25 June that Allergan PLC will be acquired by AbbVie Inc. for $63bn far exceeded expectations that Allergan would appease its investors by splitting the company in two after years of watching its stock price sink.



Allergan's value surged on its reputation of aggressive dealmaking, rising above $300 per share based on rumors of Pfizer Inc.'s interest in buying the company and remaining near that level after a $160bn deal between the two firms was announced in November 2015. *(Also see " Pfizer, Allergan In Third-Biggest Merger Ever " - Scrip, 23 Nov, 2015.)* But Allergan's stock plummeted after the transaction was called off due to political pressure in April 2016 and has continued to drop after several setbacks. *(Also see "Allergan's Back In The (M&A) Saddle Again Post Pfizer Breakup" - Scrip, 7 Apr, 2016.)*

The company has traded below $200 since September 2017, when it made an unpopular bid to protect its Restasis (cyclosporine) revenue with an ill-fated strategy of transferring the blockbuster dry eye drug's patents to a Native American tribe. *(Also see "Allergan Shifts Restasis Patents To Native American Tribe To Invoke Immunity From IPR" - Scrip, 9 Sep, 2017.)* and *(Also see "Allergan's Restasis Defense Falters As PTAB Dismisses Tribal Immunity Ploy" - Scrip, 26 Feb, 2018.)*

Now, the maker of Botox (onabotulinumtoxinA) is selling itself to AbbVie for $188.24 per share, including $120.30 in cash and 0.866 shares of AbbVie stock, which is a 45% premium to Allergan's 24 June closing price of $129.57. The stock closed up 25.4% at $162.43 after the AbbVie deal was announced.

MOUNTING PRESSURE TO SPLIT IN TWO

Given the depreciation of its stock price since 2016, Allergan has been under pressure to split in two with one company focused on the Botox-led aesthetics business and the other focused on maturing brands. While CEO Brent Saunders has resisted that idea, he suggested in May that Allergan would take some kind of urgent action to regain shareholders' trust. *(Also see "Allergan's Saunders Speaks Of Urgency, But Not Of Specifics" - Scrip, 7 May, 2019.)*

This mea culpa came after the company acquiesced – to a degree – to shareholder demands to split the CEO and chairman roles, promising a separation of powers with its next CEO transition. *(Also see "Allergan Acquiesces To Activist Appaloosa With CEO-Chairman Role Split, But Not Yet" - Scrip, 25 Mar, 2019.)*

> "In effect, today's transaction gets Allergan to the valuation of a split (and more) without execution risk." – Jefferies' David Steinberg

The possibility of separating Allergan's market-leading medical aesthetics business from its neuroscience, ophthalmology, gastrointestinal, women's health and other products has gained traction since then, with executives suggesting to analysts that an announcement along those lines could be made soon.

Now, it appears, AbbVie will save Allergan the trouble of splitting itself in two – an effort that would have been particularly challenging since the aesthetic franchise's key product Botox is approved both for aesthetic and therapeutic uses, such as chronic migraine headache prophylaxis.

"For Allergan, this transaction represents a way out for management without having to deliver on an increasingly questionable R&D pipeline and pending competition to core franchises (particularly Botox)," Jefferies analyst David Steinberg said in a 25 June note. "And while there has been much recent discussion of an Allergan split, it wasn't entirely clear if it was feasible given that Botox straddles both aesthetics and therapeutics. In effect, today's transaction gets Allergan to the valuation of a split (and more) without execution risk."

Saunders and Allergan chief commercial officer Bill Meury have insisted that Botox is such an iconic brand in the treatment of both forehead wrinkles and migraine that it wouldn't lose much ground, if any, to newer botulinum toxins in the aesthetics market and CGRP inhibitors approved in 2018 to prevent migraine headaches. *(Also see "Allergan Buys Bonti, Releases New Data In Defense Of 'Iconic' Botox Brand" - Scrip, 14 Sep, 2018.)* and *(Also see "Allergan's Botox Holds Its Own In Migraine, Despite CGRP Competition" - Scrip, 30 Oct, 2018.)*

Indeed, Botox sales rose 12.9% to $3.58bn in 2018 and have continued to increase in 2019, although the rate slowed to 9% year-over-year growth with $868m in global sales for the first quarter.

It remains to be seen if a trio of CGRP inhibitors – one from Amgen Inc. and Novartis AG, the others from Teva Pharmaceutical Industries Ltd. and Eli Lilly & Co. – will grab substantial market share from Botox. *(Also see "Migraine Market Gets Competitive With Second, Third CGRP Inhibitor Launches" - Scrip, 9 Nov, 2018.)*

However, investors also are nervous about Botox's ability to retain its leadership position in aesthetics with an aggressive marketing push promised for Evolus Inc.'s newly approved Jeuveau (prabotulinumtoxinA). *(Also see "With Jeuveau Approval, Evolus Will Focus On The Beauty Business To Gain Market Share" - Scrip, 5 Feb, 2019.)* In addition, Revance Therapeutics Inc. is expected to launch the potentially longer-acting neurotoxin RT002 in 2020; it also is making progress with partner Mylan NV on a Botox biosimilar. *(Also see "Another Botox Competitor: Revance Prepares Longer-Lasting RT002 For BLA Submission" - Scrip, 22 Feb, 2019.)*

WORRISOME SETBACKS ADD TO CONCERNS

With the near-term threat of Restasis generics and the potential for various new Botox competitors, Allergan needs new products to diversify its revenue, but its research and development pipeline has come up short, contributing to the company's falling stock price after years of acquisitions meant to grow its branded drug business. *(Also see "Going Generic: Big Brands Poised To Lose Marketing Exclusivity In The US In 2019 " - Scrip, 15 Mar, 2019.)*

Allergan's origins are in the generics industry, a business that was strengthened when Watson Pharma Inc., acquired Actavis Group for $5.6bn in 2012, eventually choosing to operate under the name Actavis PLC. *(Also see "Watson confirms Actavis acquisition in deal set to take group revenues to $8bn this year " - Scrip, 26 Apr, 2012.)* Actavis then began to build a branded drug business, which got a big boost from the $25bn acquisition of Forest Laboratories Inc. in 2014, bringing Saunders to the company. *(Also see "Actavis in $25bn Forest buy " - Scrip, 18 Feb, 2014.)*

Saunders helmed Actavis when it agreed to buy Allergan Inc. in 2014 for $66bn – $3bn more than AbbVie is paying for the enterprise now. The company rebranded as Allergan PLC when that deal closed in 2015. *(Also see "Actavis will become Allergan to emphasize branded pharma focus" - Scrip, 19 Feb, 2015.)* It became a branded drug-only company with the sale of its generics portfolio to Teva in 2015 for $40.5bn, including $36bn in cash. *(Also see "With $36bn from Teva, what should Allergan buy next?" - Scrip, 28 Jul, 2015.)*

But after all of that consolidation, some of Allergan's acquisitions seeking both commercial products and R&D programs proved less than stellar.

For instance, the company paid $2.1bn for Kythera Biopharmaceuticals Inc. in 2015, but Kythera's double chin-reducing injectable Kybella (deoxycholic acid) has not been a big seller. *(Also see "Allergan buys chin fat firm Kythera for $2.1bn" - Scrip, 17 Jun, 2015.)* Dermatologists have said the product performs well in some people, but the treatment regimen is too burdensome for many patients. *(Also see "Medical Aesthetics: Sales Rise For Popular Products, But Unmet Needs Remain" - Scrip, 12 Sep, 2018.)* Kybella sales actually fell to $38.1m in 2018 from $56.4m in 2017.

In terms of R&D setbacks, Allergan agreed in 2016 to pay up to $1.7bn for Tobira Therapeutics Inc., but the firm's lead drug candidate for non-alcoholic steatohepatitis (NASH) may not be as effective as other later-stage NASH therapies. *(Also see "Allergan's Tab For Tobira's NASH Cocktail With Akarna Chaser Tops $1.7bn" - Scrip, 21 Sep, 2016.)* and *(Also see "Allergan's Two-Year NASH Data Fail To Show Fibrosis Benefit" - Scrip, 22 Sep, 2017.)*

Also, Esmya (ulipristal acetate) for uterine fibroids, which the company licensed from the drug's European marketer Gedeon Richter PLC, was rejected by the US Food and Drug Administration last year due to liver safety concerns. *(Also see "Allergan's Ulipristal, Dogged By Liver Concerns, Gets An FDA Rejection" - Scrip, 22 Aug, 2018.)*

That rejection was followed by an unexpected Phase III failure in depression for rapastinel in March. *(Also see "Allergan Endures Another R&D Setback With Rapastinel Failing Three Pivotal Studies" - Scrip, 7 Mar, 2019.)* The NMDA receptor modulator was purchased in the $560m acquisition of Naurex Inc. in 2015. *(Also see "Allergan paying $560m for Naurex; stays quiet on rumored generics sale to Teva" - Scrip, 27 Jul, 2015.)*

Allergan's abicipar pegol, licensed by Allergan Inc. from Molecular Partners AG, has shown efficacy in Phase III wet age-related macular degeneration (AMD) studies, but the longer-acting VEGF inhibitor may pose safety issues that make it a less attractive treatment option than established AMD injections. Allergan intends to submit abicipar for approval in mid-2019. *(Also see "Allergan Improves Safety Of Abicipar, But Not Enough Compared To Lucentis, Eylea" - Scrip, 2 Apr, 2019.)*

SOME SUCCESSES AMID NOTABLE DISAPPOINTMENTS

It has not been all bad news for Allergan's R&D pipeline, however. The company recently won a long-anticipated new indication in bipolar depression for Vraylar (cariprazine). *(Also see "Pipeline Watch: Phase III Readouts For QMF149, Korsuva And Valoctocogene Roxaparvovec" - Scrip, 3 Jun, 2019.)*

In an earlier pipeline success, Saunders-led Forest paid $1.1bn for Furiex Pharmaceuticals Inc. while its own acquisition by Actavis was pending in 2014 and Allergan now markets the Furiex-developed irritable bowel syndrome drug Viberzi (eluxadoline). *(Also see "Forest gaining 'relevant' GI position with Furiex buy" - Scrip, 29 Apr, 2014.)* Viberzi sales totaled $177.8m in 2018, an increase from $157.1m in 2017.

A coming addition to Allergan's portfolio in gastrointestinal diseases may be relamorelin in diabetic gastroparesis; Phase III results are expected in 2020. *(Also see "Allergan Relying On 'Six Stars' And Other R&D Programs To Blunt Restasis Blow" - Scrip, 19 Jan, 2018.)* The asset was purchased in the acquisition of Motus Therapeutics Inc. in 2016. *(Also see "'Open Science' In Action: Allergan Exercises Option For Motus After Gastroparesis Study" - Scrip, 28 Oct, 2016.)*

The most anticipated R&D programs in Allergan's pipeline, however, are the company's oral CGRP inhibitors for migraine headaches, including ubrogepant, which is under FDA review for the acute treatment of migraines with an approval decision expected in late 2019. (Also see "Keeping Track: Two Goal Date Extensions, Another Herceptin Biosimilar Approval, And A BLA Withdrawal" - Pink Sheet, 15 Mar, 2019.) Its atogepant for migraine prevention is in Phase III. *(Also see "Migraine Drug Atogepant Delivers Good News When Allergan Needs It Most" - Scrip, 11 Jun, 2018.)* Both drugs were licensed from Merck & Co. Inc. *(Also see "Allergan migraine portfolio grows with Merck CGRP antagonists" - Scrip, 8 Jul, 2015.)*

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Sanofi/Google Alliance To Apply Big Data To R&D, Commercial And Marketing Operations

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A few months ahead of incoming CEO Paul Hudson's start at Sanofi, the French pharma is undertaking a big data collaboration with Google that it hopes can help its R&D engine work more efficiently toward personalized medicine while also applying analytics to its commercial operation. The two companies announced their alliance centered around creating a "virtual innovation lab" on 18 June. No financial terms nor the length of the agreement were disclosed.

Details on the partnership are scant at present, but the alliance apparently is not between Sanofi and Google's health care spinout Verily Life Sciences LLC. Those two entities teamed up in 2016 to create a diabetes-focused joint venture called Onduo, with the partners jointly investing $500m in the effort. That deal came roughly a month after Verily announced its Galvani Bioelectronics JV with GlaxoSmithKline PLC, which is focused on bioelectronic medicines for inflammatory, metabolic and endocrine disease.

Sanofi previously has inked big data and artificial intelligence partnerships with IBM Life Sciences, Schrodinger Inc. and Exscientia Ltd. – each focused on drug discovery efforts. *(Also see "What Artificial Intelligence Brings To Drug Discovery – Sanofi Interview" - Scrip, 12 May, 2017.)* At the time of the Exscientia collaboration in May 2017, Sanofi external innovation head Adam Keeney indicated that the pharma was just getting started on employing analytics in its operations. "This is part of an ongoing evolution and evaluation of how to keep on the cutting edge, to aid our efforts in drug discovery," he said of the agreement with Exscientia.

Sanofi said the partnership with Google could allow it to access "the power of emerging data technologies" to transform the delivery of future medicines and health care delivery. Sanofi's chief digital officer and chief medical officer Ameet Nathwani said the alliance will employ artificial intelligence and cloud computing to "accelerate the development of new therapies." *[Editor's note: This article has been revised to correct a misspelling of Ameet Nathwani's name.]*

When Hudson, former head of pharmaceuticals in North America for AstraZeneca PLC and outgoing head of pharmaceuticals at Novartis AG, was tapped to succeed Olivier Brandicourt as the new Sanofi CEO in September, Sanofi chairman Serge Weinberg said his remit would include accelerating growth and leading the group's adaptation to new strategic challenges, particularly in the areas of R&D and digital.

The collaboration with Google will begin with three primary objectives: gain better understanding of patients and their diseases; increase Sanofi's operational efficiency; and improve the experience of Sanofi's patients and other customers. Beginning with Sanofi's proprietary data sets, the effort will use deep analytics to understand "key diseases and extract related patient insights," Sanofi said.

EFFORTS ON PERSONALIZED MEDICINE, OPTIMIZING SALES AND MARKETING

These efforts will seek to bring about more personalized approaches to individual therapy and create accompanying technologies to improve health outcomes – hopefully both optimizing care and creating health care system savings, the pharma added.

Sanofi also will use AI to improve sales forecasts and help direct marketing and supply chain efforts by using real-time information about geographic, logistical and manufacturing factors, it explained. Lastly, Sanofi will look to modernize its infrastructure by migrating some of its business systems to the Google Cloud Platform.

Partnerships between biopharmaceutical companies and big data firms have become more commonplace of late, including at Sanofi. In addition to the diabetes joint venture with Verily, the company's vaccine unit Sanofi Pasteur announced earlier this month that it will team with Kaiser Permanente to evaluate the Flublock vaccine in an observational trial using data collected from roughly 1.6m patients. *(Also see "Real-World Evidence Sought In Sanofi Pasteur Observational Flu Vaccine Trial " - Scrip, 11 Jun, 2019.)*

IBM Watson was an early leader in analytic-focused partnerships with biopharma companies, including Celgene Corp., Pfizer Inc. and Novartis, but its parent company decided earlier this year to end agreements pertaining to drug discovery for that business.

While the interface between biopharma and big data firms is increasing, a panel at the Big Data and Analytics in Healthcare forum in London in February warned that such alliances will only be as effective as they are understood by the various stakeholders participating in them. (*Also see "AI And Big Data In Focus: What Is Preventing Faster Adoption In Health Care Settings?" - In Vivo, 1 Apr, 2019.)* Different functions within a biopharma company might have varying expectations about what a data alliance will offer them, which means a group process toward a shared set of goals is recommended for such partnerships.

One exercise that can help is the "use case" scenario, which can prevent stakeholders from getting caught up in big buzzwords without any understanding of what an end product of the partnership might be, Chris Hutchins of the health care analytics company Northwell Health told the panel. A use case is a sequence of actions, performed by one or more persons or non-human entities in or outside the system, that is expected to produce results of value to the users. The use case, not the technology itself, should drive a partnership, Hutchins said.

Dipak Kalra, president of the European Institute for Innovation through Health Data, stressed the importance of data-sharing in making such an alliance effective. He recommended the concept of FAIR to the audience: the data in an analytics collaboration should be findable, accessible, interoperable and reusable.

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AstraZeneca Plans $630m Korea Investment Amid Favorable Policies

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In the biggest investment plan ever announced by a foreign pharma firm in South Korea, AstraZeneca PLC has agreed to pump a total of $630m into the country over the next five years, in cooperative research projects for new drugs, to foster R&D experts and to improve access to healthcare.

The major UK-based multinational inked a letter of intent on the plan with the Korea Trade-Investment Promotion Agency and Korea Biotechnology Industry Organization at its plant in Sweden during a bilateral business summit between South Korea and Sweden, which took place during South Korean President Jae-in Moon's recent visit to the Scandinavian country.

South Korea's presidential Blue House noted that the agreement also marked the biggest ever investment plan by any foreign investor in the country's biomedical R&D sector, and that it is expected to help step up innovation in the country given the strong focus on R&D. AstraZeneca currently has about 360 employees in the country but expects to hire about 20% more.

AZ commitment signals growing importance of Korean market.

GROWING IMPORTANCE, GOVT SUPPORT

The sizable investment plan would appear to reflect the growing importance of the South Korean market for global pharma firms amid multiple recent measures by the government to nurture the broad bio-health sector. South Korea is ranked the sixth in the world as a clinical research hub, while Seoul is ranked the first in the world by single city as a site for trials.

The government-supported biopharmaceutical industry is considered to have world-class potential, given its modern research infrastructure, excellent workforce and global clinical competitiveness, according to AstraZeneca Korea.

The global pharma said it had positively evaluated the growth potential of the sector in South Korea and the government's industry-nurturing policies. Open innovation projects with AstraZeneca will provide an opportunity to innovate the ecosystem of the domestic bio-health industry, the Ministry of Trade, Industry and Energy said.

In May, South Korea unveiled a new bio-health industry innovation strategy that involves hefty investment in the R&D of innovative new drugs and medical devices along with financial support and tax incentives, as well as steps to shorten drug approval times and ease other regulations to keep pace with global standards. Read the full article here

Mirroring these moves, the AstraZeneca agreement specifically mentions investments to nurture South Korean bioventure start-ups, seeking clinical research to develop new drugs and open innovation with the industry, academia and research institutes, and collaborations in future healthcare technologies such as artificial intelligence.

AstraZeneca also intends to support the South Korean biotech industry's entry into global markets including China, the ministry said. A more detailed memorandum of understanding is expected to be signed later this year.

AZ SUPPORTS BIOMEDICAL INNOVATION

"We regard the Korean government's active engagement in fostering the bio-health industry as positive and believe Korea can be a sustainable partner to AstraZeneca," the company told *Scrip*. "Given President's Moon recently announced commitment to promoting biomedical innovation in Korea, we feel it is important to support this effort and publicly strengthen our commitment to Korea over the next five years."

AstraZeneca has been active in Korea for many years given the country's well-developed healthcare system, world-class R&D environment and excellent human resources. Given its delivery of innovative drugs, particularly in the oncology, cardiovascular and respiratory areas, to Korean patients, the firm says it has unique healthcare domain knowledge on the obstacles that patients face, from the first symptoms to diagnosis, to treatment and follow-up.

"We want to go beyond existing open innovation and new drug development and expand our scope of investment to Korean society and industry in general, and support bioventure start-ups, future healthcare (AI, IoT) technologies, and support Korean bioventures' advancement to China and the global market, employment, etc.," it explained.

The pledged amount of money comprises all forms of tangible and intangible investments in improving access to healthcare, driving collaborative innovation and providing high-quality employment, the company said, noting that it plans to discuss details with its counterparts and relevant ministries.

EXISTING COMMITMENT

AZ has already been consistently expanding its R&D investment in Korea, not only through its local marketing subsidiary but including through global programs. To date, around $105m in total has been invested over the last five years on R&D, the company said.

It was recently awarded Innovative Pharmaceutical Company status by the Ministry of Health & Welfare in recognition of its contributions to biomedical research, and the company has launched more than 130 trials in the country in the past five years. Korea also holds a prominent position in AstraZeneca's Oncology Alliance network, with three out of four sites in the Asia-Pacific located in the country.

As a part of an open innovation effort, AZ has been collaborating with Korean researchers on preclinical and early-stage clinical trials, particularly through the AZ-KHIDI oncology research program that has been supporting four study proposals every year since 2014.

AstraZeneca Korea, established in 1999, had sales of KRW355.7bn ($300m) in 2018, and has been investing 13-15% of revenues in R&D annually.

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Tremfya And Taltz Provide PsA Highlights At EULAR

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Johnson & Johnson's Tremfya has moved closer to joining other interleukin inhibitors in the psoriatic arthritis (PsA) space after promising late-stage data of the drug was presented at the European League Against Rheumatism congress in Madrid.

The healthcare giant unveiled topline data on 14 June from the DISCOVER-1 and DISCOVER-2 Phase III trials of Tremfya (guselkumab) in adults with moderate to severe active PsA. In both studies, the IL-23 inhibitor hit its primary endpoint of American College of Rheumatology 20% improvement (ACR20) at week 24 compared with placebo; multiple secondary endpoints were also assessed that included ACR50 and 70, resolution of soft tissue inflammation, disease activity improvement in physical function, skin clearance and quality of life.

The full data set will be presented at upcoming medical meetings and will serve as the basis of PsA submissions to the US Food and Drug Administration and the European Medicines Agency later this year. Tremfya, which is partnered with MorphoSys AG, is already approved for psoriasis and is the follow-up to J&J's IL-23/IL-12 inhibitor blockbuster Stelara. *(Also see "ECLIPSE: J&J's Tremfya Beats Novartis' Cosentyx For Long-Term Psoriasis Clearance" - Scrip, 12 Dec, 2018.)*

Tremfya was not the only IL-23 inhibitor to make waves at the Madrid meeting for PsA as Sun Pharmaceutical Industries Ltd. presented promising Phase II data on Ilumya (tildrakizumab). Some 71% of participants in the 450-patient trial who were on the drug, which was given pride of place at one of the EULAR official press conferences, achieved ACR20 response after 24 weeks and lead investigator Philip Mease of the University of Washington told journalists that the results demonstrated a clear separation between tildrakizumab and placebo as early as eight weeks.

Tremfya, Ilumya and - further back - AbbVie Inc.'s IL-23 inhibitor Skyrizi (risankizumab), which has recently been approved on both sides of the Atlantic for psoriasis, have a lot of catching up to do in PsA on the IL-17 inhibitors, principally Novartis AG's Cosentyx (secukinumab). The Swiss major presented new data at EULAR from the MAXIMISE trial evaluating the drug in the management of axial manifestations of PsA and also provided a new analysis from the FUTURE 5 trial showing no radiographic progression in almost 90% of PsA patients, plus significant ACR20, 50 and 70 responses. *(Also see "Novartis MAXIMISEs Cosentyx PsA Position" - Scrip, 13 Jun, 2019.)*

However the IL-17 inhibitor that got the most attention at EULAR was Eli Lilly & Co.'s Taltz (ixekizumab), which is already approved for PsA. What caught the eye was the full data set from the Phase IIIb/IV SPIRIT-H2H head-to-head trial of Taltz and AbbVie's anti-TNF mega-blockbuster Humira (adalimumab).

In the trial, the first head-to-head between two biologics in the treatment of PsA, patients were randomized to receive Taltz (n=234) or Humira (n=231) for 52 weeks, with the primary analysis conducted at 24 weeks. PsA patients who met the study criteria for moderate to severe plaque psoriasis also received Taltz (n=49) or Humira (n=52) for their skin.

At 24 weeks, the proportion of patients achieving both a reduction in disease activity as defined by ACR50 as well as complete skin clearance (PASI 100) was 36% for Taltz and 28% for Humira. Breaking those figures down, Lilly noted that Taltz showed non-inferiority to Humira for the percentage of patients achieving ACR50 (51% vs. 47%) and superiority in terms of PASI 100 (60% vs. 47%).

The results came as no great surprise, given that IL-17 inhibition has been proved in trials across the board to be more effective at clearing the skin than the anti-TNFs, while the benefit in joint symptoms is less marked.

Nevertheless, Lilly will be hoping that the SPIRIT-H2H data are robust enough to persuade more doctors to plump for Taltz instead of Humira in PsA. Mease noted that "head-to-head data like these are significant and help inform treatment decisions. This study underscores that Taltz is an important option." This could prove tricky, not least on the financial front, given that the anti-TNFs, and more significantly their cheaper biosimilars, are now available in Europe, which is impeding take-up of the IL inhibitors as first-line treatment.

While Taltz is the first IL inhibitor to have head-to-head data against Humira in PsA, Cosentyx is following closely behind with the EXCEED study. Novartis began the trial in January last year evaluating Humira versus Cosentyx in over 800 biologic-naïve patients with PsA, with a primary endpoint of statistical superiority for ACR20 response rates at one year, and secondary endpoints including PASI90, ACR50 and resolution of enthesitis. EXCEED is expected to read out before the end of 2019. *(Also see "Novartis' Cosentyx Goes Head-To-Head With Humira" - Scrip, 9 Jan, 2018.)*

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UCB Buoyed By More Positive Bimekizumab Data

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UCB Group may be late to the party when it comes to the interleukin-17 space for immune disorders but with more promising data on bimekizumab for ankylosing spondylitis (AS) and psoriatic arthritis (PsA), the Belgian firm remains confident of getting a foothold in the market.

Bimekizumab is touted by UCB as a "key pipeline molecule" and was showcased during presentations at the European League Against Rheumatism (EULAR) meeting in Madrid last week (12-15 June). The monoclonal antibody inhibits both IL-17A and IL-17F, unlike established rivals - Novartis AG's Cosentyx (secukinumab) and Eli Lilly & Co.'s Taltz (ixekizumab) - which specifically inhibit IL-17A.

First up, UCB presented week 12 results from BE AGILE, its Phase IIb trial in AS, which showed that compared to placebo, up to four times the number of bimekizumab-treated patients achieved at least a 50% improvement in key symptoms, including pain, fatigue, morning stiffness and function. Specifically, Bath Ankylosing Spondylitis Disease Activity (BASDAI) 50 responses were achieved in 23.7% (16mg) and up to 47.5% (320mg) of patients across different doses, compared to 11.9% for placebo, and those on the UCB drug also reported a higher level of improvement in physical function and better quality of life.

UCB head of immunology Emmanuel Caeymaex told *Scrip*, "This is the first time that findings on the direct effect of the potential treatment on patients' lives have been shared and these results show that bimekizumab can deliver benefits that can make a real difference to AS patients' daily lives."

Emmanuel Caeymaex

The company also presented results from BE ACTIVE, a Phase IIb trial in PsA which, Caeymaex noted, "saw the achievement of stringent endpoints," including American College of Rheumatology 50% improvement (ACR50), complete skin clearance (PASI 100), minimal disease activity (MDA) and resolution of enthesitis at week 12. Responses increased to week 24 and were sustained to week 48 and the safety profile was consistent with previous studies of bimekizumab.

The drug, which is already in late-stage trials for psoriasis that could read out early next year, has recently gone into Phase III for AS and PsA. Even if all goes well, UCB will have a lot of catching up to do with Cosentyx and Taltz but Caeymaex noted another presentation at EULAR on the biology of IL-17A and IL-17F which supported the value of dual neutralization of those cytokines. In preclinical research, bimekizumab reduces skin and joint inflammation, as well as pathological bone formation to an extent greater than inhibition of IL-17A alone, UCB claimed. *(Also see "Taltz Results In Spondyloarthritis Add To Lilly Franchise Hopes" - Scrip, 23 Apr, 2019.)*

Caeymaex concluded by saying that "based on the Phase IIb results we've seen in AS and PsA, as well as in psoriasis, we believe bimekizumab shows potential to bring significant, differentiated value to these patient populations where there are still substantial unmet needs."

CIMZIA ON THE RISE

While bimekizumab is expected to be a future growth driver, EULAR also saw data presented on UCB's well-established anti-TNF agent Cimzia (certolizumab pegol), notably in non-radiographic axial spondyloarthritis (nr-axSpA) for which UCB received FDA approval at the end of March.

Post-hoc results from the 52-week C-AXSPAND study showed the benefit of

early intervention for rapid and durable symptom control in patients with nr-axSpA with Cimzia. Further data being presented include an interim analysis from C-OPTIMISE that demonstrated sustained remission during 48 weeks of Cimzia treatment in patients with AS and nr-axSpA.

UCB also unveiled a new analysis at the Madrid congress from the RAPID-axSpA study confirming that Cimzia, when given to axSpA patients rapidly reduced active inflammation in the spine, which was sustained over four years and was associated with no erosions or sclerosis, and only negligible increase in fatty lesions in the vertebral edges.

Caeymaex concluded by saying that these new data "are further validation of the important role this treatment can play in sustaining remission. As Cimzia is the only FDA and European Medicines Agency-approved treatment for nr-axSpA, UCB is poised to be a leader" in the treatment of the latter and axSpA.

That view is shared by analysts at Deutsche Bank who recently issued an investor note saying that the FDA approval for nr-axSpA "should help improve investor confidence in the outlook for the franchise, which faces increasing competitive and pricing risks." They added that "the realistic commercial opportunity in nr-axSpA is likely to be modest (around $300m). However, combined with the drug's preferential label in women of childbearing age and last year's approval in psoriasis, we believe it will enable UCB to continue to modestly grow, then defend sales in the medium term."

The broker went on to say that its forecasts "remain modestly below management's peak sales target for Cimzia of €1.7bn, leaving upside potential." It rates UCB as a buy, "given our belief that its pipeline can ultimately offset expected medium-term pressures and return the company to growth."

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Japanese OK In COPD Gives AstraZeneca's Breztri Aerosphere First Regulatory Approval

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AstraZeneca PLC's Breztri Aerosphere has been approved in Japan as therapy for chronic obstructive pulmonary disease (COPD), marking the product's first regulatory approval.

The approval means AZ will join GlaxoSmithKline and Chiesi in marketing a triple-combination therapy for COPD.

Breztri Aerosphere, formerly known as PT010, consists of the long-acting beta-2 agonist (LABA) formoterol, the long-acting muscarinic antagonist (LAMA) glycopyrronium and the inhaled corticosteroid (ICS) budesonide. The product is to be taken twice daily via a pressurized metered-dose inhaler.

> "We think two thirds of COPD patients are biologically eligible for triple therapy and that as a class we'll see an immediate impact in patients with more frequent exacerbations." – Tom Keith-Roach

The Japanese regulatory approval, announced 19 June, was based on the Phase III KRONOS trial which showed that the triple combo, delivered using the Aerosphere pressurized metered-dose inhaler, demonstrated a significant improvement in eight out of nine lung function primary endpoints in patients with moderate to very severe COPD.

Japan's Ministry of Health, Labour and Welfare the same day also gave regulatory approval to AstraZeneca's fixed-dose, long-acting dual bronchodilator Bevespi Aerosphere, combining glycopyrronium and formoterol fumarate as a treatment to relieve symptoms in patients with COPD.

Bevespi Aerosphere is already approved in the US, EU, Canada, Australia and other countries as a dual bronchodilator for the maintenance treatment of moderate to very severe COPD.

"These two approvals in Japan represent an important milestone for AstraZeneca because both of these medicines are on the Aerosphere delivery platform and, in the future, we expect to be able to offer all of the major inhaled combinations on a single device," said Tom Keith-Roach, who heads up the UK pharma's respiratory, inflammation and autoimmune business.

AstraZeneca's head of respiratory said there is a growing urgency for efficient COPD treatments. "There are 384 million people suffering from COPD globally, and the number is growing," Keith-Roach said in an interview.

"COPD is the third leading cause of death and typically diagnosed pretty late and characterized by progressive loss of lung function. The median survival of patients following their first severe exacerbation is less than four years, which is worse than many cancers."

He predicted triple-combination therapy would become increasingly important treatment option for COPD patients and will play a central role in helping them manage their disease going forward. "The current guidelines for triple-combination therapies recommend that you should wait and only treat patients who have had exacerbations in the last year or two with triple therapy," he said.

"At this stage, therefore, about one in four patients with COPD are eligible and recommended for a fixed dose triple-combination therapy, because in general today patients

will have started on a dual therapy and they therefore will wait until they've had two or more exacerbations before they would step up to a triple."

In the longer term, he said, the company sees the opportunity for triple therapy to be used earlier and significantly more broadly than they are today. "We think two thirds of COPD patients are biologically eligible for triple therapy and that as a class we'll see an immediate impact in patients with more frequent exacerbations."

OTHER MARKETS

AstraZeneca's triple combination therapy for COPD is under regulatory review in the US and EU with anticipated regulatory decisions in 2020.

The Chinese National Medical Products Administration has granted a priority review to Breztri Aerosphere, with an expected regulatory decision in the second half of 2019.

GlaxoSmithKline PLC is clearly ahead in the three-in-one COPD market, having received US and EU approval for its product Trelegy Ellipta in 2017 and a Japanese launch in March 2019.

Trelegy, which was co-developed with Innoviva Inc., comprises the ICS fluticasone, the LAMA umeclidinium and the LABA vilanterol, dosed once daily using GSK's Ellipta dry powder inhaler.

Chiesi Farmaceutici SPA's triple therapy Trimbow (beclomethasone/formoterol/glycopyrrolate), which is approved in Europe in mid-2017, is dosed twice-daily.

Keith-Roach voiced confidence that AstraZeneca's triple combo Breztri Aerosphere would nonetheless fare well against the competition. "Their product has different molecules and a different anti-inflammatory and is on a different device platform. Breztri Aerosphere has a highly competitive clinical profile beyond those characteristics."

He added, "What we saw in the KRONOS study which was the basis of this submission and approval was that Breztri provided really rapid and sustained improvements in lung function which is really critical for patients with COPD."

"Also, in a critical secondary endpoint showed a 52% reduction in the rate of moderate or severe exacerbations versus a versus a LAMA / LABA." Keith-Roach said the fact GSK's Trelegy Ellipta is taken once daily would not put twice-daily Breztri at a competitive disadvantage.

"Market research suggests that some patients prefer once-daily administration while others prefer to get that feeling of rapid lung function improvement twice daily, so it is very hard to generalize.

"It's the clinical efficacy and clinical profile that will be far more important in driving things like competitive share positioning and patient choice," he concluded.

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Roche Beats Rivals To Japan Tumor-Agnostic Market With World-First Rozlytrek Nod

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Roche's Rozlytrek (entrectinib) has been approved in Japan for the treatment of adult and pediatric patients with *NTRK* (neurotrophic tyrosine receptor kinase) fusion gene-positive advanced or recurrent solid tumors, regardless of cancer type.

The nod from the country's Ministry of Health, Labour and Welfare for 100mg and 200mg capsule formulations marks the first such regulatory clearance worldwide for the oral ROS1/TRK inhibitor, which is now set to become both the first tumor-agnostic and NTRK-targeting therapy in Japan.

It also gives the product a lead in this market over its rivals, notably Bayer AG/Loxo Oncology Inc.'s Vitrakvi (larotrectinib), which beat Roche to the tissue-agnostic market in the US last year.

Rozlytrek will be marketed locally by the Swiss firm's affiliate and licensee Chugai Pharmaceutical Co. Ltd. following reimbursement price-listing under Japan's national health insurance scheme, which usually happens within 60 days and enables nationwide launch.

'SAKIGAKE' STATUS

The approval follows an expedited priority review granted under Japan's orphan drug and "sakigake" schemes, the latter status being awarded to pioneering therapies that are developed in the country ahead of, or in parallel with, other markets and confer significant therapeutic or safety advantages.

Chugai made the marketing authorization filing only in mid-December, for what was its first sakigake product, and the approval timing is in line with the target six-month review period for the scheme. Sakigake status is usually accompanied by a requirement

for comprehensive post-marketing surveillance for a certain period to ensure proper use and safety and efficacy in actual use, while orphan drugs in Japan are eligible for extended periods of exclusivity.

Rozlytrek use is accompanied by a dedicated companion diagnostic (developed by Roche's acquired subsidiary Foundation Medicine Inc. on its F1CDx platform) to identify the very rare NTRK gene fusion, which occurs when the *NTRK1/2/3* genes fuse with other genes. This results in alterations in the genes' related TRK proteins (TRKA/TRKB/TRKC) that in turn can activate signaling pathways involved in the proliferation of certain types of cancer.

Chugai told *Scrip* that the diagnostic is still awaiting approval after a submission this January, but that this is expected before the price-listing of Rozlytrek. The diagnostic will have a separate reimbursement price.

LOWER JAPAN *NTRK* INCIDENCE?

While the fusion has been identified across a broad range of solid tumor types, including pancreatic, thyroid, salivary gland, breast, colorectal and non-small cell lung cancer, and neuroendocrine tumors and cholangiocarcinoma, it occurs in only 1% or 2% of all solid tumor patients carrying any mutation. Entrectinib acts by selectively targeting the kinase activity of the altered TRK A/B/C proteins, as well as ROS1 proteins.

However, some research has suggested that the incidence of the *NTRK* gene fusion in Japanese patients may be even lower than in the west - occurring in only 0.04% of surveyed lung cancer patients, according to one study.

Despite the limited market, both Chugai and Roche hailed entrectinib's first global approval as a milestone in personalized healthcare, in terms of the targeting of a common molecular driver of a tumor rather than individual cancer types.

Roche acquired the molecule only in February 2018 when it completed its $1.7bn purchase of US rare cancer venture Ignyta Inc.

SUPPORTING CLINICAL DATA

The Japanese approval was supported mainly by the international, 51-patient open-label STARTRK-2 Phase II "basket" study. The pivotal trial showed an objective response rate (ORR; the primary endpoint) of 56.9% (95%CI: 42.3-70.7%) per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1), estimated by the independent review committee, across 10 *NTRK* fusion-positive cancer types, including in people with and without CNS metastases at baseline. Median duration of response was 10.4 months.

Entrectinib shrank tumors that had spread to the brain in more than half of people (intracranial response ORR = 50.0%).

The Japanese regulatory submission also included findings from the Phase I STARTRK-1 and Phase I ALKA-372-001 dose escalation trials, plus data from the Phase I/II STARTRK-NG study in paediatric patients (see side box).

US APPROVAL IN AUGUST?

Two entrectinib NDAs are also under priority review in the US, with user fee dates set for 18 August. One is for the treatment of NTRK fusion-positive, locally advanced or metastatic solid tumors in adult and pediatric patients who have either progressed following prior therapies or as an initial therapy when there are no acceptable standard therapies, a setting for which breakthrough therapy designation has been granted.

Roche acquired the molecule only in February 2018 when it completed its $1.7bn purchase of US rare cancer venture Ignyta Inc.

The other is for the treatment of people with metastatic, ROS1 fusion-positive non-small cell lung cancer (NSCLC), which accounts for 1-2% of all cases of the disease. Entrectinib has also been granted Priority Medicines (PRIME) designation in the EU, although Roche has failed in its bid to secure an accelerated assessment in this market. *(Also see "Roche's EU Accelerated Assessment Bid For Tumor Agnostic Entrectinib Backfires" - Scrip, 4 Mar, 2019.)*

The ROS1 US NDA was notable for the use of Roche's Flatiron Health Inc. subsidiary to generate an external control arm of cancer patients with ROS1 mutations to provide a comparator for the pivotal single-arm trial. *(Also see "Roche Outlines Use Of Real-World Evidence In Entrectinib NDA" - Pink Sheet, 11 Jun, 2019.)*

LIMITED SALES?

In Japan, entrectinib is also already undergoing regulatory review for the treatment of ROS1 gene fusion-positive locally advanced or metastatic NSCLC, a setting in which the drug's promising activity in patients with brain metastases is seen as potentially setting it apart from its rivals.

But given its highly targeted patient population, global sales of entrectinib could be limited. Datamonitor Healthcare is forecasting these will reach a modest $110m per year by 2026, with the US accounting for $80m of this figure and Japan just $15.6m.

Broker Jefferies is more bullish, estimating peak annual sales of around $750m, but dependent on the actual impact of close competitor Vitrakvi, for which Bayer has also pointed to peak sales in the $700m range.

Vitrakvi had its first launch, in the US, late last year in the first-line setting for NTRK-positive cancers. The molecule was recently granted orphan status in Japan, where it has yet to be approved.

Japan is now routinely issuing global-first approvals for novel products, helped by the sakigake scheme and other expedited review systems. Other such products have recently included Pfizer Inc.'s Lorbrena (lorlatinib) for ALK-positive NSCLC and AbbVie Inc.'s Skyrizi (risankizumab) for various forms of psoriasis. *(Also see "Japan Approvals Include World-First For Skyrizi, Kymriah As Asia's First CAR-T" - Pink Sheet, 28 Mar, 2019.)*

(Modified on 20 June 2019 to include comments from Chugai on the status of the companion diagnostic.)

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US FDA Approval Of Novo Nordisk's Victoza For Young T2D Patients A Treatment Milestone

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Young patients aged 10-17 years in the US suffering from type 2 diabetes have a new treatment option after the US Food and Drug Administration approved Novo Nordisk AS's injectable therapy Victoza (liraglutide) as a means to lower their blood sugar, along with diet and exercise.

The expanded indication for Victoza, announced on 17 June, provides younger type 2 diabetics with a new medicine option beyond metformin and insulin for the first time in 19 years.

The human glucagon-like peptide-1 (GLP-1) receptor agonist was first approved in the US in 2010 to help improve glycemic control in adults with type 2 diabetes.

Its new approval was based on the ELLIPSE trial involving 135 patients aged 10 to 17 years. The study, completed last August and unveiled in April, was the first completed Phase III trial in children and adolescents with type 2 diabetes for more than a decade.

In it, Victoza, when added to metformin with or without basal insulin, was shown to significantly reduce average blood sugar levels at 26 weeks and 52 weeks compared with placebo, with the percentage of children and adolescents achieving HbA1C levels of less than 7% at week 26 being significantly higher in those treated with Victoza compared to those treated with placebo (63.7% versus 36.5% respectively). Victoza's expanded indication provides an additional treatment option at a time when an increasing number of children are being diagnosed with type 2 diabetes.

The expanded indication for Victoza, announced on 17 June, provides younger type 2 diabetics with a new medicine option beyond metformin and insulin for the first time in 19 years.

The growing number of children and adolescents with type 2 diabetes is being driven by rising rates of childhood obesity. But treatment options have, until now, been limited to metformin and insulin in contrast with the wide range of oral and injectable treatments that are currently approved for adults.

The new indication will give a boost the sales of Victoza, which have been declining in recent quarters as new therapies come to market.

Revenue generated from Victoza fell 4% in the first quarter of the current financial year compared to the same period last year to DKK 5.7bn ($856m).

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AML Contender Quizartinib Gains First Approval, In Japan

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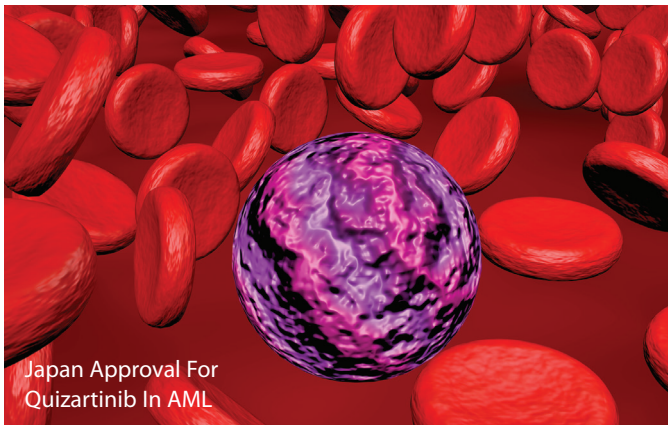
As part of a group of global-first approvals for a handful of novel therapies, Japan has granted marketing authorization to Daiichi Sankyo Co. Ltd.'s Vanflyta (quizartinib) for a specific form of acute myeloid leukemia (AML) with a particularly poor prognosis.

AstraZeneca PLC and Merck & Co. Inc.'s Lynparza (olaparib) is also set to become the first PARP inhibitor to be commercialized in the country for first-line maintenance use in *BRCA*m ovarian cancer following a regulatory nod.

The Vanflyta clearance, following a filing last October, marks a commercial breakthrough for the Japanese firm's lead product for AML, following a rougher regulatory ride in the US. A Complete Response Letter is expected there after an FDA advisory committee voted 8-3 against an approval in mid-May, after questions over persuasive evidence of efficacy. *(Also see "Quizartinib Looks Like A Good Drug, ODAC Says, But Needs Another Efficacy Trial Before Approval" - Pink Sheet, 14 May, 2019.)*



Japan Approval For Quizartinib In AML

The same global Phase III QuANTUM-R study looking at single-agent use was used to support the new approval in the orphan indication of FLT3-ITD-positive AML in Japan, where reviewers

at the Pharmaceutical and Medical Devices Agency appeared to have fewer reservations over the data.

QuANTUM-R showed a statistically significant overall survival benefit for the oral FLT3 inhibitor versus salvage chemotherapy in adult patients with relapsed/refractory (R/R) FLT3-ITD AML. This showed a median overall survival of 6.2 months versus 4.7 months.

The Japanese nod was also supported by a Phase II open-label local trial that was stopped early on meeting its primary endpoint (composite complete remission rate) at interim analysis.

STRATEGIC IMPORTANCE

Quizartinib was the major attraction behind Daiichi's $410m purchase of originator Ambit Biosciences Inc. in 2014, and the approval and upcoming first launch mark a significant commercial build-out of the Japanese company's oncology franchise, as it pivots away from genericizing sales of its former blockbuster antihypertensive olmesartan.

Strategically, Daiichi is aiming for JPY500bn ($4.51bn) in global oncology revenues and the launch of seven new molecular entities by fiscal 2025, an ambition that received a major boost in March through the $6.9bn deal with AstraZeneca for lead antibody-drug conjugate trastuzumab deruxtecan. *(Also see "Boost For Daiichi's Oncology Ambitions As AZ Agrees Huge $6.9bn Deal For Lead ADC Asset" - Scrip, 28 Mar, 2019.)*

Datamonitor Healthcare is forecasting Japanese sales of a modest $8.6m in 2025, out of a predicted global total of $85.8m.

Identification of patients suitable for Vanflyta will be determined by an already approved companion diagnostic. Daiichi noted that there are around 5,500 new cases of AML annually in Japan, with the FLT3-ITD mutation occurring in around a quarter of patients.

The presence of the mutation is associated with a particularly poor prognosis in AML, including higher risk of relapse and death with or without hematopoietic stem cell transplantation.

GLOBAL DEVELOPMENT STATUS

Quizartinib has Breakthrough Therapy and Fast Track designations in the US for adult R/R FLT3-ITD AML and orphan status for R/R AML (also in the EU). In November 2018, the US and EU filings were accepted for review, and granted Priority Review and Accelerated Assessment respectively.

Quizartinib is also in the international Phase III QuANTUM-First trial in combination with chemotherapy for first-line use in FLT3-ITD AML, Phase I/II for pediatric and young adult R/R FLT3-ITD AML in North America and Europe, and a Phase I US trial in combination with the MDM2 inhibitor miladematan for R/R FLT3-ITD AML and the newly diagnosed same form of the disease unfit for intensive chemotherapy.

LYNPARZA IN OVARIAN MAINTENANCE

Also approved at the same time was Lynparza as a maintenance treatment after first-line chemotherapy in patients with ovarian cancer with the *BRCA* mutation (*BRCA*m).

The drug becomes the first PARP inhibitor to be approved in the country for this setting, which follows on from a January 2018 approval as a maintenance therapy in women with platinum-sensitive relapsed ovarian cancer, regardless of *BRCA* mutation status. *(Also see "First-Line Ovarian Cancer Approval Solidifies Lead For AstraZeneca's Lynparza " - Scrip, 19 Dec, 2018.)*

In a parallel development, Myriad Genetics Inc.' BRACAnalysis was also approved as the companion diagnostic system for Lynparza in ovarian cancer.

The approval was supported by the placebo-controlled Phase III SOLO-1 study, which looked at monotherapy use after platinum-based first-line chemotherapy. The drug reduced the risk of disease progression or death by 70% versus placebo in patients responding to chemotherapy, and extended progression-free survival by three years. *(Also see "Stellar Survival Data For AZ's Lynparza Hailed At ESMO" - Scrip, 22 Oct, 2018.)*

The companies noted that there were around 10,600 estimated new diagnoses of ovarian cancer in Japan in 2018, and around 5,200 deaths. Some 10-15% of the ovarian cancer has the *BRCA*m type.

AZ reported Lynparza sales of $647m in 2018 (+118%), driven by expanded use in ovarian cancer and new approvals for breast cancer; the drug was recently approved as a first-line treatment for *BRCA*m ovarian cancer in the US.

Datamonitor sees sales of $39.2m in Japan in 2025 in the ovarian cancer setting under its patient-based forecast.

Lynparza was also approved in Japan around a year ago for unresectable or recurrent *BRCA*-mutated HER2-negative breast cancer after prior therapy.

The first approvals worldwide have also just been granted in Japan for Roche/Chugai Pharmaceutical Co. Ltd. 's tissue-agnostic drug Rozlytrek (entrectinib) *(Also see "Roche Beats Rivals To Japan Tumor-Agnostic Market With World-First Rozlytrek Nod" - Scrip, 19 Jun, 2019.)* and AstraZeneca's Breztri Aerosphere (formoterol, glycopyrronium and budesonide) and Bevespi (glycopyrronium and formoterol fumarate) for chronic obstructive pulmonary disease. *(Also see "Japanese OK In COPD Gives AstraZeneca's Breztri Aerosphere First Regulatory Approval" - Scrip, 19 Jun, 2019.)*

All the new products are now awaiting price listing under Japan's national health insurance scheme, which usually occurs within 60 days of the approval and will allow nationwide commercial launch.

Published online 20 June 2019

No-Deal Brexit 'Very Bad' For Business And Patients

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Dutch pharma group Norgine BV, which has significant operations in the UK, continues to spend money preparing for a Brexit outcome that it believes would have a negative impact on the industry, and management is concerned about the lack of political will to avoid such a scenario. "A no-deal Brexit would be very unpredictable and very bad for our business, but more importantly it would be very bad for patients," the firm's chief operating officer, Peter Martin, told *Scrip*.

But with the ruling Conservative party concentrating on the contest to replace outgoing leader and Prime Minister Theresa May, "the focus of government and the governing party is elsewhere at the moment: they're not particularly focused on the impact to patients of a no-deal Brexit," he warned. "The mood music is not encouraging for companies like mine that want to have as close an arrangement with the EU and its establishments post-Brexit as we had before Brexit."

Front-running candidate Boris Johnson has declared that he will ensure the UK leaves the EU on 31 October 2019 whether or not an exit deal has been secured.

Norgine, which generated the majority of its 2018 annual turnover of €429m in the EU including 14.5% in the UK, has now spent €12m on preparing for the UK leaving the European Union without a deal, "and that's irritating and unfortunate because it's money we could have directed towards serving our patients rather than dealing with something that may or may not happen," Martin commented.

The firm began planning for a no-deal eventuality in 2017, making commitments in late 2018 for warehousing facilities, which it then secured in early 2019. By late March, when Brexit was originally scheduled to take place, it had spent around €11m on these preparations. With Brexit now postponed until the end of October 2019, the costs continue to mount. Longer-term stockpiling entails additional complexity, since it is not simply a question of setting aside raw materials, APIs, finished goods and packaging materials

"People understand now that there is actually a real risk of no deal, which means that every company is taking it seriously." – Peter Martin

for a fixed period. "You need to take out older stock and put new stock in, on a first-in, first-out basis as time goes on. So you not only have warehousing costs, you also have all the costs of transport – which is pretty expensive – and shifting things around the warehouse," explained Martin.

"For the time being we don't know how long that will last. In theory it could be that we'll have to start using some of those inventories if there's a no-deal Brexit, but we also hear that the date may shift, and if it shifts we'll just have to maintain those warehouses. So the prudent thing to do is to view them as potentially a long-term commitment, in effect being part of business as usual," he added.

SITUATION NOT CLARIFYING FOR PHARMA

Scrip previously spoke to Martin in mid-March when the original Brexit deadline was looming and clarity about the future relationship between the UK and the EU was in short supply. "If things are clearer now I must have missed it," he told *Scrip* in a second interview on 18 June.

In March the executive had flagged up the risks of drug shortages should parallel traders buy up stockpiled medicines to sell in other countries. He said that the government had taken no subsequent action to avert such a risk. "We've challenged members of the civil service on this directly but there doesn't seem to be a will. I think they understand the risk but for some reason they're not able to put a policy in place that would alleviate that risk. So that remains a real possibility."

Another potential disruption to supplies could be represented by hold-ups at docks if border checks come into force. "If pharmaceuticals end up being held at docks or somewhere else for a couple of weeks, then that might give issues with the security of the supply chain and potentially also the storage conditions."

The UK head of Sanofi Pasteur recently told *Scrip* the company was preparing for the necessity of airlifting essential medicines in the event of a no-deal Brexit. *(Also see "Disorderly Brexit May Necessitate Drug Airlifts, Sanofi UK Head Warns" - Scrip, 4 Jun, 2019.)* Martin said Norgine would do the same.

"We have a product called Dantrium [dantrolene, used to treat malignant hyperthermia, a rare complication of anesthesia], which has to be available in every operating theater, and it's not produced in the UK. If the supply chain by land or sea were to be interrupted and that were to be in short supply we'd have to airlift it because if it weren't available then operating theaters across the UK would grind to a halt. And there are other medicines where we might well do the same thing."

Other members of the pharma manufacturing and distribution industry outlined

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CONTINUED FROM PAGE 16

the risks of a no-deal Brexit in October to the UK parliament's Exiting the EU Committee in a hearing on 19 June, warning that the sector would not have time to prepare and that critical shortages would occur. *(Also see "'Impossible' To Prepare UK Supply Chain For October No-Deal Brexit" - Pink Sheet, 19 Jun, 2019.)* A confidential Cabinet note leaked the previous week had said the government would need six to eight months of engagement with the pharmaceutical industry to ensure adequate stockpiling arrangements had been made. *(Also see "UK Pharma Sector 'Not Ready' For No-Deal Brexit" - Pink Sheet, 13 Jun, 2019.)*

One positive that Martin identified was that the delay to Brexit had given companies more time to prepare. "People understand now that there is actually a real risk of no deal, which means that every company is taking it seriously," something that should reduce the risks he had previously identified of discontinuities in the supply chain, particularly in cases where smaller firms had been unable to make contingency plans. The delay has also given more breathing space for companies to implement the safety features regulation of the Falsified Medicines Directive that came into force in February, something he described as "quite a complex logistical exercise."

KEEP NHS OUT OF US TRADE DEAL

Meanwhile, US President Donald Trump caused a stir on his recent visit to the UK when he said the country's National Health Service would be "on the table" in future trade talks between the two nations. This would not be supported by Norgine.

"We hope that the NHS does not become part of a negotiation of a UK-US trade deal: we think that we would be destructive to the business," said Martin. "We're a Dutch company but we like the fact that there is a certain degree of predictability in the UK environment because of the VPAS [Voluntary Pricing and Access Scheme], the new pricing scheme which guarantees prices for the next five years, essentially. And if the NHS and medicines were to become part of a UK-US trade deal, all that predictability would be thrown out of the window, and it might make it more difficult for patients to access the medicines they need."

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Gilead Dives Into Protein Degradation With Nurix Pact

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Gilead Sciences Inc. is jumping into the increasingly busy pool of protein degradation R&D by tapping into Nurix Inc.'s technology platform in a deal that could be worth more than $2bn for the San Francisco-based firm.

Gilead's aim is to create a pipeline that applies this type of scientific development specifically to cancer and other "challenging diseases," according to the companies when they announced the partnership on 19 June.

Nurix will receive an upfront of $45m and will be eligible to receive up to approximately $2.3bn in total additional payments based on the successful completion of certain research, pre-clinical, clinical, regulatory and commercialization milestones, as well as up to low double-digit tiered royalties on net sales.

For those programs that Nurix opts in to co-develop, the parties will split development costs as well as profits and losses 50/50 for the US. Nurix will be eligible to receive royalties on ex-US sales and reduced milestone payments.

Nurix's technology platform manipulates the ubiquitin protease system (UPS) and its component E3 ligases, the key enzymes responsible for controlling protein levels in human cells.

With this collaboration, Nurix will use its proprietary drug discovery platform to identify novel agents that utilize E3 ligases to induce degradation of specified drug targets and Gilead will have an option to license drug candidates directed to up to five targets resulting from the work. Nurix will retain the option to co-develop and co-detail up to two programs in the US.

"There are many molecular targets involved in disease pathways that have traditionally been challenging to manipulate using conventional approaches," said John McHutchison, Gilead's chief scientific officer and head of R&D. "Nurix's innovative protein degradation discovery technology provides Gilead with a new strategy to interrogate these drug targets, as we continue to build a pipeline of small molecule therapeutics for patients with cancers and other diseases."

COMPANY BUZZ

Protein degradation is a drug strategy becoming more popular with R&D heads at big firms. It centers around the cell's natural ability to discard unwanted or damaged proteins, rather than just inhibiting them. Researchers are excited by the fact that previously undruggable targets can be affected and conditions such as Alzheimer's disease could reap the benefits from this new approach.

Only last month Vertex Pharmaceuticals Inc. signed a $1bn deal with Kymera Therapeutics Inc. to discover small-molecule protein degraders for use against multiple diseases. *(Also see "Vertex Targeting Protein Degradation In $1bn Kymera Deal" - Scrip, 16 May, 2019.)* Others that have joined the fray include GlaxoSmithKline PLC, which also signed a deal with Kymera in April 2018,AbbVie Inc., Genentech Inc., and Bayer AG *(Also see "AbbVie Explores Uncharted Territory With DUB Inhibitor Neuroscience Deal" - Scrip, 15 Nov, 2018.)(Also see "Bayer Pays Arvinas $50m To Form Protein Degrader R&D Pact" - Scrip, 5 Jun, 2019.)*

Biogen Inc. signed a deal worth $415m with C4 Therapeutics Inc. in January, to use the latter's platform technology to find new therapies for neurological conditions.

Celgene Corp. was one of the earliest big names to team up with Nurix when, in 2015, it signed a $150m collaboration to discover, develop and commercialize novel small molecule therapeutics in oncology, immuno-oncology, inflammation and immunology.

Nurix was started in 2012 by Third Rock Ventures and The Column Group with $6.2m in seed capital. It currently has two preclinical candidates, one of its own and a CDL-B program partnered with Celgene that will move to Bristol-Myers Squibb Co. when those firms complete their proposed $74bn merger.

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Dainippon Partnership Rejig Helps Healios Focus Resources

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Japanese regenerative medicine venture Healios KK and big pharma partner Sumitomo Dainippon Pharma Co. Ltd. (SDP) have reallocated roles and costs under an agreement for a novel cell therapy for age-related macular degeneration (AMD).

The two partners say the move is designed to speed up development and streamline sales and manufacturing activities, while allowing Healios to allocate more near-term attention and resources to its current clinical pipeline.

Following joint discussions, the revisions modify the original 2013 joint development agreement between the firms, under which they are progressing a regenerative therapy for wet/dry AMD and other refractory retinal disorders based on retinal pigment epithelial cells (RPEs) derived from induced pluripotent stem cells (iPSCs).

SDP will now take over from Healios the main responsibility for conducting clinical trials with the therapy, HLRC011, and unlike before is now able to jointly submit (with Healios) related manufacturing and marketing approvals in Japan.

A previous cap of JPY5.2bn ($48m) on SDP's contribution to development costs has been lifted, and the larger company will now bear a proportion of costs under a "flexible framework," details of which are remaining confidential due to their strategic nature.

Reflecting these changes, SDP's total development milestone payments have now been capped at a maximum of JPY1.0bn (of which JPY0.7bn has already been received), rather than JPY1.6bn; SDP additionally gets non-exclusive global rights to the therapy on top of its earlier Japan-only exclusive rights.

MANUFACTURING JV CHANGES

On the manufacturing side, the two companies set up an equally owned Japanese joint venture, Sighregen, in 2014 to manufacture and also conduct sales promotion of the AMD therapy.

The promotional function has now been transferred to SDP, with Sighregen – which now has around 20 staff – to focus solely on manufacturing. The facility is located within an SDP regenerative medicine site in Osaka.

SDP also made an equity investment in Tokyo-based Healios in 2013 as part of the original deal, and this arrangement continues unchanged.

MOVING INTO TRIALS

HLRC011 is now moving into its first clinical trial program, in Japan, and involves the transfer of RPE cells into the eye, via either a single suspension injection or cell sheet. Functional decline of these cells is thought to be linked to both the "wet" and "dry" forms of AMD.

The wet form of the disease involves photoreceptor impairment through abnormal neovascularization caused by RPE cell damage, while the dry form stems from age-related inflammation and death of RPE cells.

> "The two partners say the move is designed to speed up development and streamline sales and manufacturing activities, while allowing Healios to allocate more near-term attention and resources to its current clinical pipeline.

Healios originally acquired an exclusive worldwide licence to a patent to commercialize this technique from Japan's national research institute, Riken. It has also licensed basic iPSC creation technology from iPS Academia Japan, the technology licensing arm of Kyoto University, the home of Japanese iPSC pioneer and Nobel Prize winner Shinya Yamanaka.

FOCUS ON SOMATIC THERAPIES

Healios, which was formed as Retina Institute Japan in 2011 and floated on the Mothers bourse in Tokyo in 2015, raising around $76m, is already conducting two early-stage trials in Japan. But both these are regenerative therapies based on somatic (as opposed to iPSC), bone marrow-derived adult somatic stem cells.

These are being developed for ischemic stroke and acute respiratory distress syndrome, and trials with HLCM051 in the latter setting started recruitment recently.

The venture is also continuing to evaluate partners and technology, and is "making progress in creating next generation iPS cells which will require the use of minimal or no immunosupressants via gene editing technologies," chairman and CEO Hardy Kagimoto noted.

The bioventure reported a widened net loss equivalent to around $46m on zero revenues in calendar 2018, while R&D expenses (including licensing costs) more than doubled to nearly $39m.

For its part, SDP has positioned regenerative medicine as a core R&D focus, and a Phase I/II, investigator-initiated trial is already underway in Japan with an allogeneic, iPSC-derived dopamine neural progenitor cell therapy for Parkinson's disease.

In late 2014, Japan enacted revised and new regulations governing the development and approval of cell and regenerative therapies, in a move seen as highly supportive for the sector.

Strategically, the country is aiming to build on its pioneering research into iPSCs to become a global leader, and several cell therapies are already available and covered by the national health insurance scheme. *(Also see "Japan Regenerative Medicine Laws Take Effect, Encourage Industry" - Scrip, 4 Dec, 2014.)*

NEW HEALIOS-SUPPORTED FUND

In another financing-related development, Healios said it will be one of a number of limited partners in a new JPY10bn Japanese fund that will invest in the bioscience industry.

Majority Healios-owned Apollo Capital Partners plans to invest in a limited liability partnership that will be the general partner in the fund, to be set up in the second half. Under a service agreement with the fund, ACP will become a consolidated Healios subsidiary once the fund is set up, and will receive fees for managing the fund. These will be booked as consolidated sales by Healios.

The new fund will invest around JPY1bn on average in bioventures both inside and outside of Japan over a planned 10-year period, and Helios said it aims to gain access to technology, information and possible partners along with investment returns.

The fund may also invest in early stage technologies at Healios, again allowing the company to focus available resources on its clinical stage pipeline.

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Bayer's Stivarga First Drug To Enter Brain Cancer Platform Trial

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Following years of failures in glioblastoma (GBM), Bayer AG is participating in an innovative platform clinical trial designed to find new treatments for the deadliest form of brain cancer, with the company's multi-kinase inhibitor Stivarga to be the first drug to be evaluated.

The German major has announced that the Stivarga (regorafenib) arm of the GBM AGILE platform trial, sponsored by the non-profit Global Coalition for Adaptive Research, has opened for enrolment in the US for patients with newly diagnosed and recurrent glioblastoma, the most aggressive and common form of primary brain cancer. The study, which Bayer said has a "seamless Phase II/III design set up to rapidly identify effective therapies for patients with GBM," will go on to test several drugs, both as monotherapy and in combinations, simultaneously.

The theory is that with GBM AGILE's nimble model, the drugs that show initial evidence of benefit will transition to a confirmatory stage while those that are underperforming will be dropped. The intent is to lower the cost, time, and number of patients required to evaluate potential new, effective GBM therapies.

Stivarga has been selected based on promising results from the Phase II REGOMA trial, published in *The Lancet* in December 2018. They showed that the Bayer drug, which was developed with Onyx Pharmaceuticals Inc., (now part of Amgen Inc.), showed preliminary efficacy compared with standard of care, the chemotherapy drug lomustine.

Stivarga is already approved for metastatic colorectal cancer, metastatic gastrointestinal stromal tumors and hepatocellular carcinoma. Bayer said it would supply the drug and grants for the study and head of oncology development Scott Fields added, "We are excited that the regorafenib arm of the GBM AGILE trial is the first to enrol patients and are looking forward to seeing how regorafenib can potentially help these patients in need of treatment options." He went on to say that Bayer is actively supporting trials of Stivarga "in a range of different tumor types to explore the potential of this drug."

GBM AGILE will be initiated at the Henry Ford Cancer Institute in Michigan and by the end of 2019, it will open in over 40 academic medical centers and community-based institutions across the US. There are plans to expand it across Europe, China, Canada, and Australia through 2020.

Janet Woodcock, director of the Center for Drug Evaluation and Research at the US FDA, claimed that "understanding of GBM biology over the past decade has led to few improvements in survival for patients with the disease. One clear barrier to progress is the inefficient clinical trial system for testing and developing new therapies and biomarkers in the clinic [and] developing new therapies for patients with GBM will require more engagement from industry and enhanced learning from clinical trials."

She concluded, "Platform trials can accelerate the time from discovery in the laboratory to implementation in the clinic. GBM AGILE will raise the bar for all clinical trials."

The platform approach is becoming more common and recently the Multiple Myeloma Research Foundation initiated the MyDRUG study to test drugs that are approved or in late-stage development for other cancers but have not been tested in myeloma. These types of studies follow the example of the pioneering I-SPY2 trial in breast cancer which graduated 12 of 17 drugs studied into pivotal studies.

Bayer noted that glioblastoma treatment options were limited. "Patient outcomes have remained largely unchanged over several decades and 95% of patients die within five years of diagnosis, with more than half dying within the first 15 months after diagnosis."

THE GBM space is littered with failures, one of the most recent ones being another failure reported last month for Bristol-Myers Squibb Co.'s Opdivo (nivolumab). The last medicine to improve survival for patients with newly-diagnosed GBM, carmustine, was approved by the FDA in 2005.

Published online 21 June 2019

Galapagos Pipeline In Good Shape

KEVIN GROGAN kevin.grogan@informa.com

Galapagos NV is pushing ahead with one of the largest pipelines in the biotech sector and while there is much attention on the JAK1 inhibitor filgotinib, the Belgian firm believes it also has game-changing therapies in other areas, notably osteoarthritis.

Speaking to *Scrip* at the European League Against Rheumatism congress in Madrid, chief medical officer Walid Abi-Saab talked initially about filgotinib, the Gilead-partnered therapy that has caused a stir within the rheumatoid arthritis community. More data were presented at EULAR from the Phase III FINCH 1 and 3 data confirming the oral selective JAK1 inhibitor's efficacy.

In FINCH 3 for example, significantly more patients receiving filgotinib 200mg and 100mg plus methotrexate (81.0% and 80.2% respectively) saw a 20% improvement in symptoms (ACR20) than those on methotrexate monotherapy (71.4%). Those on the filgotinib 200mg and 100mg combo with methotrexate were also significantly more likely to achieve ACR50 (61.5% and 57.0%) and ACR70 (43.8% and 40.1%) than those on methotrexate alone (ACR50 45.7% and ACR70, 26.0%).

Abi-Saab noted that not so long ago in the field of psoriasis, "people talked about a 50% reduction in the psoriasis area and severity index (PASI 50) and now with the advent of new therapies, nobody talks about PASI 50, you talk about PASI 90, PASI100. In rheumatoid arthritis, we still talk about ACR20, so we still have a quantum leap to make."

He added that filgotinib and AbbVie Inc.'s rival JAK1 inhibitor upadacitinib are starting to register "some respectable numbers" but "the future is to start talking about 80% on ACR70." That could be reached through combination therapy but such treatments are some way down the road, Abi-Saab noted. *(Also see "AbbVie Ups The Ante For Upadacitinib At EULAR" - Scrip, 17 Jun, 2019.)*

If approved, and no details on filing have yet been disclosed, filgotinib will probably be the fourth JAK inhibitor for rheumatoid arthritis after Pfizer Inc.'s blockbuster Xeljanz (tofacitinib), Eli Lilly & Co.'s Olumiant (baricitinib) and upadacitinib which has been submitted for US approval, with a decision expected in the third quarter. However, Abi-Saab (and a number of analysts) believe filgotinib's superior safety profile versus other JAKs would make it potentially best-in-class and allow it to compete with the established but off-patent anti-TNF agents such as AbbVie's Humira (adalimumab), Amgen Inc./Pfizer Inc.'s Enbrel (etanercept) and Johnson & Johnson/Merck Sharp & Dohme Ltd.'s Remicade (infliximab) in rheumatoid arthritis.

Many strings to Galapagos R&D bow

However, the greatest potential for filgotinib could like in other indications. Abi-Saab noted that there were Phase III studies running in ulcerative colitis and Crohn's disease, each with about 1,600 patients, while a late-stage trial in psoriatic arthritis is set to start before the end of 2019 followed by a Phase III study in ankylosing spondylitis beginning early next year.

Walid Abi-Saab

He acknowledged that in rheumatoid arthritis, "people think we are late but if you combine UC, Crohn's, PsA and AS, these four indications actually combined are a bit more than in value. Also for those indications, we are either first in the case of Crohn's and AS or second in UC and PsA."

Beyond that, Abi-Saab said that in the next few months, Galapagos would also have Phase II data for filgotinib in cutaneous lupus and Sjögren's syndrome. "If they look good, the natural step is to start the Phase III, so there's a lot going on."

There is also a lot going on with GLPG1972, an investigational drug partnered with Servier SA for knee osteoarthritis (KOA). Abi-Saab said that the firms has just completed recruitment of nearly 900 patients for their ROCCELLA Phase II trial way ahead of schedule, adding that "I was teasing the team, saying 'you're going to be done by September' because initially they thought it going to be done in November. We were done in June."

He claimed that the speedy recruitment "speaks to the unmet medical need and a

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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, 14–21 JUNE 2019

Event Stage	Lead Company/Partner	Drug Name	Indication	Comments	Change To LOA (%)	LOA (%)
Phase III Published Results	Global Blood Therapeutics, Inc.	voxelotor	Sickle Cell Anemia	HOPE; NEJM, 14 June, 2019	0	63
Phase III Updated Results	bluebird bio	Zynteglo gene therapy	Thalassemia	Northstar-3 (HGB-212), -2 (HGB-207); Promising Results	0	65
Phase III Updated Results	Gilead Sciences/Galapagos	filgotinib	Rheumatoid Arthritis	FINCH 3; Improved Symptoms	0	72
Phase III Updated Results	Johnson & Johnson/Genmab	daratumumab subcutaneous	Multiple Myeloma	COLUMBA (vs. IV); Endpoints Met	0	41
Phase III Updated Results	AbbVie/Roche	Venclexta (venetoclax)	Multiple Myeloma	BELLINI; Mixed Results	0	34
Phase III Updated Results	AstraZeneca PLC	Calquence (acalabrutinib)	Chronic Lymphocytic Leukemia	ASCEND (vs. Investigator); Encouraging Results	0	43
Phase III Updated Results	GenSight Biologics S.A.	GS010	Leber's Hereditary Optic Neuropathy	REVERSE; Symptom Improvement	0	47
Phase III Updated Results	Cancer Prevention Pharmaceuticals	CPP-1X/sulindac	Familial Adenomatous Polyposis	CPP FAP-310; Encouraging Results	35	35
Phase II/III Updated Results	Geron Corporation	imetelstat	Myelodysplastic Syndrome	IMerge (Transfusion-Dependent Subjects); Encouraging Results	0	37
Phase III Top-Line Results	Johnson & Johnson/Morphosys	Tremfya (guselkumab)	Psoriatic Arthritis	DISCOVER-1, -2; Primary Endpoints Met	3	67
Phase III Top-Line Results	BeiGene, Ltd.	zanubrutinib	Waldenstrom Macroglobulinemia	ASPEN (vs. ibrutinib); Encouraging Data	0	39
Phase III Top-Line Results	Hutchison MediPharma Limited	surufatinib	Neuroendocrine Tumors	SANET-ep; Met Primary Endpoint	0	10
Phase III Top-Line Results	Kyowa Hakko Kirin	Siliq (brodalumab)	Axial Spondyloarthritis	Study 006; Positive Results	0	0
Phase III Top-Line Results	Johnson & Johnson/Genmab	daratumumab subcutaneous	Amyloid Light-Chain Amyloidosis	ANDROMEDA (w/CyBorD); Clinical Responses Seen	0	62

Source: Biomedtracker | Informa, 2019

CONTINUED FROM PAGE 21

great desire in the community, both academically and with patients, to have an oral disease-modifying drug for KOA." However, Abi-Saab stressed, "Let's not get kid ourselves, this is still a very difficult path because demonstrating changes in imaging and cartilage thickness – anatomical changes – hasn't yet been shown to translate to pain and function and the US Food and Drug Administration is very focused on those endpoints."

He went on, "It is like where non-alcoholic steatohepatitis (NASH) was about five years ago, you are going to be pioneering and trying to break that wall. I think you have a much better chance to convince the agency if you have a drug that starts to move the needle, because then they may say 'okay, I can now see it where it's going. If you can show me this in a bigger trial, perhaps I can give you provisional approval and then you continue the trial and confirm the benefit.'"

Abi-Saab cited the example of Intercept Pharmaceuticals Inc.'s Ocaliva (obeticholic acid), a farnesoid X receptor (FXR) agonist which secured accelerated approval from the FDA in May 2016 for the rare liver disease primary biliary cholangitis on the proviso of committing to longer term studies that could pave the way for a label expansion into NASH. "So maybe there is a path that way," he argued, noting that "this is a moving field but if we hit that space with GLPG1972, then the value for patients and financially for the company will be massive."

> "We believe in our science and we're not going to be hitting it out of the park every time but you can't win if you don't play." – Walid Abi- Saab

In a recent note, Bryan Garnier analyst Hugo Solvet wrote that "the fast recruitment translates the high interest from patients in GLPG1972," and highlights the fact that there are currently no disease modifying drugs on the market with preferred options being NSAIDs and intra-articular steroid injections. He is forecasting peak sales of €3bn.

Abi-Saab also spoke glowingly about GLPG1690, an oral, once daily autotaxin inhibitor that is currently in Phase III studies based on feedback from the FDA and the European medicines Agency and which many observers believe has the potential to become the standard of care for idiopathic pulmonary fibrosis. Two identically designed trials, ISABELA 1 and ISABELA 2, are enrolling 1,500 patients diagnosed with IPF on top of their local standard of care, whether or not they were previously or currently are treated with Roche's Esbriet (pirfenidone) and Boehringer Ingelheim GmbH's Ofev (nintedanib). Readout is expected in 2021. *(Also see "Galapagos Targets Liver Fibrosis With Evotec Deal" - Scrip, 7 Feb, 2019.)*

He concluded by telling *Scrip* that "we believe in our science and we're not going to be hitting it out of the park every time but you can't win if you don't play."

Published online 18 June 2019

APPOINTMENTS

Executive	To Company	New Role	From Company	Previous Role	Effective Date
Joseph Farmer	Akrevia Inc	Chief Operating Officer	Tesaro Inc	Senior Vice President, General Counsel, and Corporate Secretary	12-Jun-19
Simon Jordan	Amicus Therapeutics Inc	Senior Vice President, International	Biogen	Vice President	13-Jun-19
William H. Collier	Arbutus Biopharma Corp	Chief Executive Officer, President and Director	ViiV Healthcare	President and General Manager, North America	24-Jun-19
Brian C. DeSchuytner	Mersana Therapeutics	Senior Vice President, Finance and Product Strategy	Tesaro Inc	Vice President	12-Jun-19
Marie-France Tschudin	Novartis AG	President, Novartis Pharmaceuticals	Advanced Accelerator Applications	President	7-Jun-19
Deepika Jalota	PMV Pharmaceuticals Inc	Senior Vice President and Head, Regulatory Affairs	Bayer	Vice President, Global Regulatory Strategy Head, Oncology	13-Jun-19
Laxman Narasimhan	Reckitt Benckiser plc	Chief Executive Officer	PepsiCo	Chief Executive Officer	1-Sep-19

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