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Takeda Sheds Products, Employees To Stada In $660m Move

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Takeda Pharmaceutical Co. Ltd. is continuing the strategic shedding of non-core assets, this time through an agreement to divest a portfolio of selected products in emerging markets to Stada Arzneimittel AG for a total value of $660m.

The move takes the total value of divestments so far closer towards the $7bn mark, out of a stated mid-term target of $10bn, as the Japanese firm focuses on its core therapeutic areas of gastroenterology, rare diseases, plasma-derived therapies, oncology and neuroscience.

It is the fourth major such transaction in the past six months and will further pay down the debt associated with the $62bn acquisition of Shire PLC, completed in early January. In the biggest single deal so far, Takeda completed the divestiture of ex-Shire dry eye drug Xiidra (lifitegrast) to Novartis AG for up to $5.3bn in July.

> "Most of the employees supporting the divested assets will be given the opportunity to transition over to Stada."

The portfolio of around 20 products to be moved over to Stada includes over-the-counter (OTC) and prescription pharmaceutical products in the Japanese firm's Growth & Emerging Markets Business Unit. The group comprises OTC vitamins and food supplements plus selected cardiovascular, diabetes, respiratory and general medicines including Cardiomagnyl (acetylsalicylic acid and magnesium hydroxide).

Markets covered by the new deal comprise Russia, Georgia and a number of countries within the Commonwealth of Independent States (Armenia, Azerbaijan, Belarus, Kazakhstan, and Uzbekistan) and the divestment is expected to close in the fourth quarter of fiscal 2019 (January-March 2020).

Takeda was careful to stress, as in the recent similar deal with Swiss group Acino Holding AG, that it remains committed to the emerging and other markets covered by the transaction, but that it will shift its focus to innovative medicines across this region, helped by an existing access program.

The portfolios being sold to Stada and Acino together generated revenues of approximately $300m in fiscal 2018.

500 EMPLOYEES AFFECTED

Takeda said that "most of the employees supporting the divested assets will be given the opportunity to transition over to Stada once the divestiture is completed."

This is anticipated to affect around 500 people currently working for Takeda, and while the German firm will acquire the rights, title, and interest to the products in the portfolio exclusive to the countries, Takeda will continue to manufacture and supply the products to Stada.

Takeda has a strategic target to reduce its net debt:adjusted EBITDA ratio to 2.0x over the next three to five years; pre-Stada, the figure stood at 3.9x at the end of September.

Published online 5 November 2019

Opioids Haunt Teva
Liability uncertainty hampers turnaround (p7)

TB Takes Center Stage
Pricing remains a concern (p20)

ASH Preview
A first look at what will be hot at the hematology meeting (p14-19)

from the editor

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How long will it take AbbVie to complete and digest its $63bn acquisition of Allergan before it is back on the hunt for new M&A targets? Critics of traditional anti-trust oversight are urging the US Federal Trade Commission to think more carefully about what additional leverage the merged group will have in formulating incentives such as bundling deals for insurers or pharmacy benefit managers. The companies, however, remain confident that they will be able to divest a couple of Allergan pipeline candidates to please the FTC and complete the deal in the first quarter of 2020 (see p4).

Once the deal is completed, rationalization of commercial products should also be expected. Just as Takeda has embarked on a vigorous round of pruning following its acquisition of Shire, leading most recently to the divestment of a portfolio of OTC and primary care medicines for emerging markets (see cover story), there is much that could be classified as "non-core" in the combined AbbVie-Allergan.

But Allergan, with its lack of R&D novelty, looks unlikely to be sufficient to offset the long-term impact on AbbVie of Humira succumbing to biosimilar competition. It will help reduce AbbVie's heavy reliance on Humira revenues for the time being, but further pipeline assets will be needed. AbbVie stepped into the hot area of gene therapy through its development deal with Voyager Therapeutics earlier this year, and last year it started a collaboration with Scripps Research drug discovery arm Calibr on CAR-T therapies. Will further deals in cell and gene therapy ensue?

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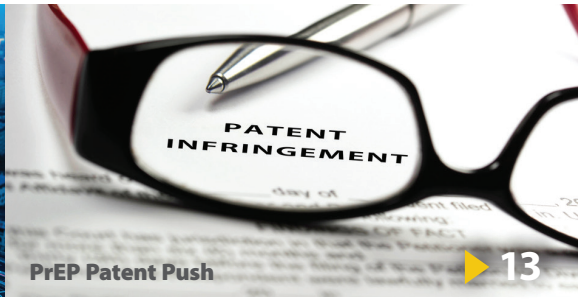

exclusive online content

Mehta Analysis: Who Will Speak Out As Regulators Are Politicized?

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In this new era when politicians seem able to fool some significant number of people all the time, the safety valve of the civil service apparatus is more readily throttled. This came into full view as the autumn colors were fading in late October in Washington.

From the clever and self-serving rotation of three key health officials in the US by the Trump administration, to the regulatory chasm that the trade tiff between the two largest biopharma markets is creating, to the Brexit tragedy, science-based independence of the life science regulators is under serious threat. Public trust in scientific decisions hangs in the balance. Yet biopharma managers lack a united voice, and are keeping silent despite accumulating long-term risks to science-based regulatory processes.

Negative regulatory forces threaten further progress for at least a decade.

To be sure, politicians are never shy, and regularly meddle in health policies to advance ideological if not personal agendas, but the civil service apparatus that is often accused of slowing down innovation comes to our aid in tempering at least the most blatant interference. How long will this safety buffer remain in place?

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To read the rest of this story go to: https://bit.ly/36Y8YW2

inside:

Allergan's Botox Gains Continue, Pipeline Progresses Ahead Of AbbVie Merger

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Allergan PLC's Botox (onabotulinumtoxinA) continued to rise in the face of new competition and Restasis (cyclosporine) held up surprisingly well in third quarter sales reported on 5 November. Also, late-stage research and development programs remained on course ahead of AbbVie Inc.'s pending $63bn acquisition of the company.

There is skepticism that Allergan will add much to AbbVie's bottom line beyond Botox, but key R&D programs are progressing through late-stage trials with the potential to expand the company's commercial portfolio in certain therapeutic areas and extend the life of products nearing the loss of patent exclusivity. Allergan's third quarter total net revenue of $4.05bn was up 3.6% from $3.91bn a year earlier and beat analyst consensus of $3.91bn.

"The Allergan transaction has significant strategic merit and the new AbbVie is poised to deliver top-tier financial performance. Combined, we will generate significant earnings and cash flow to enhance our innovative R&D platform, support a strong and growing dividend and rapidly pay down debt," AbbVie CEO Richard Gonzalez said during the company's 1 November third quarter earnings conference call.

Among Allergan's pipeline updates, US Food and Drug Administration decisions on whether to approve ubrogepant and bimatoprost sustained-release (SR) are on track for December of this year and the first half of 2020, respectively. The products will expand the company's migraine offerings beyond Botox and may boost revenue for the company's glaucoma franchise, which has seen sales decline ahead of the loss of exclusivity for Combigan (brimonidine/timolol) in 2022 and 2023.

Ubrogepant, if approved next month, will be the first oral calcitonin gene-related peptide (CGRP) inhibitor available in the US for migraine headaches. It also will be the first drug in its class indicated for acute (on-demand) treatment of migraine attacks versus the three injectable CGRP inhibitors – Amgen Inc./Novartis AG's Aimovig (erenumab), Eli Lilly & Co.'s Emgality (galcanezumab) and Teva Pharmaceutical Industries Ltd.'s Ajovy (fremanezumab) – which are approved for migraine prevention.

Allergan's Q3 revenue increased 3.6% to $4.05bn, beating expectations.

BOTOX REMAINS TOP ALLERGAN PRODUCT, BEST-SELLING NEUROTOXIN

The launch of anti-CGRP biologics last year raised investor concerns that Botox sales would fall, since the product's biggest therapeutic indication is for the prevention of chronic migraine headaches; the newer therapies are approved to prevent chronic as well as episodic migraine headaches, the latter of which occur less frequently.

However, Botox sales continue to grow with more revenue coming from therapeutic indications than from its well-known aesthetic uses. Allergan reported $928.7m in global Botox sales, which was up 5.6% from $879.7m for the same period in 2018. The most recent quarter included a 5% year-over-year increase to $525.5m for Botox Therapeutic and 6.3% boost to $403.2m for Botox Cosmetic.

Incoming competition in medical aesthetics also has been a concern for Allergan's investors, but Botox remains the best-selling neurotoxin globally by a wide margin versus other established brands – Merz Pharmaceuticals GMBH's Xeomin (incobotulinumtoxinA) and Ipsen's Dysport (abobotulinumtoxinA), the latter of which is marketed by Galderma SA for aesthetic uses.

So far, it appears that Evolus Inc.'s Jeuveau (prabotulinumtoxinA) hasn't made a dent in Botox Cosmetic sales, but the potential launch of Revance Therapeutics Inc.'s longer-acting toxin RT002 (daxibotulinumtoxinA) in late 2020 could have an impact. Revance intends to file its biologic license application (BLA) for RT002 with the US FDA this month. *(Also see "Another Botox Competitor: Revance Prepares Longer-Lasting RT002 For BLA Submission" - Scrip, 22 Feb, 2019.)*

While Botox sales grew in the third quarter at a slower rate than in 2018, US sales of Botox Cosmetic maintained double-digit growth with a 10% increase, Jefferies analyst David Steinberg pointed out in a 5 November note. And on the therapeutic side, Steinberg said, Allergan sees little switching from Botox to a CGRP inhibitor in the migraine prevention market.

Bernstein analyst Ronny Gal also noted in a same-day report on third quarter earnings that "the US Botox aesthetic trend is stronger than we expected – a major concern for the name heading into

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CONTINUED FROM PAGE 4

the quarter. However, we would argue that going forward some slowing should be expected in growth given enhanced competition."

Allergan is working to maintain and grow its market-leading position in the medical aesthetics market through the addition of other drugs and devices, including the shorter-acting injectable botulinum neurotoxin serotype E (BoNT/E or EB-001), which recently moved into a Phase IIb trial for the treatment of glabellar frown lines (wrinkles between the eyes). *(Also see "Allergan Buys Bonti, Releases New Data In Defense Of 'Iconic' Botox Brand" - Scrip, 14 Sep, 2018.)*

RESTASIS HOLDING UP DESPITE FUTURE GENERICS

The dry eye drug Restasis also continues to be a major contributor to Allergan's earnings despite the product's loss of exclusivity in the US, because generics have yet to launch. Restasis was a big contributor to the company's higher-than-expected total revenue with $296m in third quarter sales, down just 5% year-over-year from $311.6m.

William Blair analyst Tim Lugo said in a 5 November report that Restasis "significantly beat both our estimate of $121m and consensus at $241m with the key difference being no impact from generic competition, though we see that impact as inevitable and model an impact in the fourth quarter."

Elsewhere in eye care, sales of Combigan and Alphagan (brimonidine) fell 3.4% to $131.3m in the third quarter while Allergan's other major glaucoma asset Lumigan (bimatoprost) fell 9% to $157.2m.

Bimatoprost SR, the glaucoma drug that the company expects to launch soon after US FDA approval in the first half of 2020, is delivered by a biodegradable implant that's designed as an improvement over the standard-of-care eye drops for the reduction of intraocular pressure in glaucoma.

The uniquely delivered glaucoma therapy and abicipar pegol – Allergan's longer-acting every 12-week injection for wet age-related macular degeneration (AMD) – may help grow the company's long-standing ophthalmology franchise. However, based on side effects seen with abicipar in clinical trials, there are some doubts about whether the drug in-licensed from Molecular Partners will be a serious contender in the competitive AMD market. *(Also see "Allergan Improves Safety Of Abicipar, But Not Enough Compared To Lucentis, Eylea" - Scrip, 2 Apr, 2019.)*

The FDA has accepted Allergan's BLA for abicipar and the company anticipates a decision in mid-2020. The European Medicines Agency also is reviewing a marketing authorization application for the biologic and its decision is expected in the second half of 2020.

FEW NOVEL THERAPIES FOR ABBVIE'S PORTFOLIO

Despite the progress in Allergan's R&D pipeline, analysts are quick to point out a lack of new molecular entities (NMEs) in the company's pipeline, which means a lack of truly novel, high-value therapies for AbbVie, whose portfolio is expected to take a big hit in 2023 with the launch of Humira (adalimumab) biosimilars in the US.

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

Nevertheless, AbbVie and Allergan note that the deal is on track to close in the first quarter of 2020 with little delay from anti-competition authorities, which would be a remarkable feat considering the US Federal Trade Commission's scrutiny of other major acquisitions, including the $74bn merger of Bristol-Myers Squibb Co. and Celgene Corp. To date, AbbVie and Allergan have said only that they'll divest Allergan's late-stage interleukin-23 inhibitor brazikumab and Zenpep (pancrelipase) for exocrine pancreatic insufficiency due to cystic fibrosis to prevent regulatory delays for their deal. *(Also see "When It Comes To FTC M&A Review, The Times May Be A Changin' " - Scrip, 8 Jul, 2019.)*

SVB Leerink analyst Geoffrey Porges said in a 4 November note about AbbVie's third quarter earnings call that "management suggested that they are very confident about closing their Allergan acquisition in Q1 2020, and outlined a host of important new indications, approvals and treatment recommendation deadlines for their existing medicines."

"However, none of their commentary offered much in the way of new NME opportunities, nor were these the focus of the company's response to questions about Allergan," Porges continued. "We continue to expect rapid and extensive job and program cuts at Allergan after the merger, and we still anticipate AbbVie returning to the deal-hunt sometime mid-to-late 2020 after the AGN transaction is put to bed and implemented with AbbVie."

Indeed, AbbVie CEO Gonzalez has been frank about the company's interest in Allergan largely because of its Botox revenue, seeing minimal value in the firm's R&D pipeline. He again voiced AbbVie's confidence in Botox during the company's earnings call, citing the product's strong brand recognition in the medical aesthetics market. *(Also see "AbbVie Will Use Allergan Revenue To Fund Combined Firm's Large R&D Pipeline" - Scrip, 27 Jun, 2019.)*

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Teva Turnaround Hung Up By The Uncertain Cost Of Settling Opioid Cases

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Teva Pharmaceutical Industries Ltd.'s revenues declined 6% in the third quarter to $4.26bn, but the decline beat analyst expectations and costs were also lower than expected, signs of stabilization after years of revenue and earnings declines. Uncertainty over how much Teva could have to pay to settle ongoing opioid liability litigation in the US, however, continues to weigh on Teva's recovery.

The company released its third quarter financial results on 7 November and simultaneously announced the appointment of a new chief financial officer and the launch of the first biosimilar version of Roche's Rituxan (rituximab) in the US at the same time.

Management had guided investors at the beginning of the year that 2019 would be a trough year before the generic power player returns to growth. Analysts are gaining confidence in the underlying business trajectory, though the company's low cash flow and high debt remain an issue. Teva had $26.94bn in debt as of 30 September.

"It does appear that management has the business fairly well stabilized (for the moment), which is clearly positive," Cowen analyst Ken Cacciatore said in a same-day research note.

Nonetheless, North American generic revenues declined 1% in the third quarter to $914m, and Copaxone (glatiramer) revenues declined 41% to $271m. Newer specialty brands like the migraine medicine Ajovy (fremanezumab) and tardive dyskinesia therapy Austedo (deutetrabenazine) simply aren't large enough to make up the shortfall. Ajovy generated only $25m in the quarter and Austedo generated $105m.

SHULTZ HOPEFUL ON FINALIZING A NATIONAL SETTLEMENT

The big unknown is opioid litigation and whether or not Teva will be able to hash out a settlement agreement for a national framework that would end the uncertainty.

Under such a proposed settlement framework announced by Teva in October, the company would pay $250m and donate $23bn in supply of opioid addiction treatment Suboxone (buprenorphine naloxone) tablets over 10 years. At the same time Teva announced it had reached a settlement in principle with some attorneys general on that framework, it separately announced an agreement with two plaintiffs in a bellwether trial that was heading to court in Ohio for $20m in cash and a $25m supply of Suboxone. In May, the company paid $85m to settle a case in Oklahoma.

A national framework that would allow Teva to donate product over a 10-year time horizon would be considered a positive outcome for the company. Purdue Pharma LP, the maker of OxyContin, filed for bankruptcy as part of its sweeping settlement proposal, and investors are concerned other manufacturers might end up on a similar path.

It's still unclear, though, if Teva will be able to finalize the agreement it has proposed, or if negotiations with other states attorneys might drag on for years. So far, the company said it has reached a settlement in principle with a number of state's attorneys but is still hashing out the deal.

"This will only work if everybody comes together. I very much hope that everybody will come together," Schultz said, updating investors on the status of the agreement. "It's an interesting and dynamic process, but I have high hopes that we will succeed in the end to the best interest of the American public but also to the best of everybody involved."

In the third quarter, Teva reserved $468m in connection with opioid liability cases, with reserves having accumulated to $1bn.

Cowen's Cacciatore predicted that amount will climb. Cowen has incorporated roughly $3bn of anticipated litigation liability into its cash flow model for Teva.

"Where the liabilities ultimately shake out – and the pressure that puts on refinancing the near-term debt maturities (such as the $4.1bn due in 2021) – remains a critical unknown," he said.

CFO Michael McClellan, who is resigning from the position, responded to the question about the 2021 debt maturity during the call.

"We would like to get out in front of the '21 maturity sometime later in the first half of next year, so we'll continue to monitor the market conditions and look at refinancing when it makes sense," he said. "We have been encouraged by the recent moves both in the broader market interest rates as well as in our own secondary rates."

McClellan also outlined how Teva would financially account for an opioid settlement based substantially on inventory. Teva would book a reserve for the future costs of the settlement, and then as inventory is made and distributed, the cost would be taken against that reserve, along with any other cash settlements as part of future cash flow, he said.

"Over the years, the reserve will then of course be evaluated on an ongoing basis for changes in cost of goods, changes in interest rates or any other thing that may change that liability, but our expectation is that eventually, once there's a final settlement with everyone, that you will see a much more clear number," he explained.

Teva announced the departure of McClellan for personal reasons during the company's second quarter financial update in August. The news only further worried investors, given Teva's challenging financial situation. On 7 November, the company announced the appointment of an industry outsider to fill the role, Eli Kalif, who will take over as CFO on 22 December. He joins the company from a global technology design and manufacturing service provider, Flex Ltd., where he led the finance organization for global operations, components and services.

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Teva/Celltrion's Truxima Is First Biosimilar Rituxan To Reach US Market: **https://bit.ly/2X5JQrV**

GSK Gears Up For Three Cancer Launches In 2020

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GlaxoSmithKline PLC unveiled some promising figures in its Q3 last week, with robust sales of its shingles vaccine Shingrix and its HIV franchise helping to raise its 2019 profit forecast for the second time this year.

The company is also undergoing a momentous transformation, setting up its newly created consumer health joint venture with Pfizer for a spin-out within the next few years. Once complete, this would leave a combined pharmaceuticals and vaccines company, which CEO Emma Walmsley believes will prove to be leaner, more profitable, and more able to focus on innovation.

2020 will represent a turning point in another strand in this transformation, the company's re-emergence as a player in oncology.

Central to this will be the expected approval and launch of two new cancer drugs: myeloma treatment belantamab mafodotin and anti-PD-1 immunotherapy dostarlimab, plus an extension of ovarian cancer drug Zejula (niraparib) into first line use.

The company conspicuously exited the field when it sold all its marketed cancer drugs to Novartis just four years ago, but Walmsley and Hal Barron, R&D chief since January 2018, have focused on reversing this policy.

This has included the rebuilding of internal pipelines and existing partnerships, and the signing of two big deals.

The first of these was the $5.1bn acquisition of Tesaro last year, bringing with it PARP inhibitor Zejula and PD-1 inhibitor dostarlimab (formerly TSR-042).

The second deal was a €3.7bn ($4.09bn) alliance with Merck KGaA for the rights to a novel bispecific immunotherapy, M7824 (bintrafusp alfa).

M7824 is currently in Phase I studies for solid tumors, as well as a randomized Phase II trial to investigate M7824 compared with pembrolizumab as a first-line treatment in patients with PD-L1 expressing advanced NSCLC.

Already in GSK's pipeline is belantamab mafodotin, which has emerged as a lead contender among a crowded field of new multiple myeloma treatments targeting B-cell maturation antigen (BCMA).

The molecule is an immuno-conjugate comprising a humanised anti- monoclonal antibody conjugated to cytotoxic agent auristatin F.

In August, the drug hit its endpoint in the DREAMM-2 study, which looked at its use in patients refractory to a proteasome inhibitor and an immunomodulatory agent, and who had failed treatment with an anti-CD38 antibody.

This early study will be filed with the FDA within the next few weeks, with GSK hoping to steal a march on rivals, including Amgen's bispecific antibody AMG 420 and bluebird bio and Celgene's CAR-T candidate bb2121.

Meanwhile the company has also recently pulled impressive data out of the bag for Zejula (niraparib), which will also be filed before the end of 2019 for a new license in frontline use in ovarian cancer.

The company is also taking special care to build new frontline commercial teams, re-entering an oncology market where companies such as Roche and Novartis dominate after years of sustained investment and success.

GSK's Luke Miels commented last week: "We're making rapid and material progress on building out our oncology commercial capability and the acquisition of Tesaro has catalyzed this process. We've also rebalanced our sales force chargers in the US and have been actively recruiting people with a great track record of success in oncology into key markets." Miels said the company expected to see this new commercial focus pay off in Q4 results, including in Zejula, which currently trails far behind AstraZeneca PLC's rival Lynparza, but is now tipped to gain market share.

NON-CANCER WINNERS?

Despite its new focus on carving out well-defined and unserved therapeutic niches, that still leaves GSK playing catch-up in oncology, the most hotly contested market segment.

A hit in one of its existing specialist areas, where it already has a reputation and commercial advantage would be very valuable.

One such asset could be its vaccine for chronic obstructive pulmonary disease (COPD) patients. This targets infections which are linked to a large proportion of exacerbations seen in these patients.

Proof of concept data are expected in the second half of 2020. It is the only COPD vaccine candidate in development, and could open up a market worth billions if it eventually proves its value in reducing acute exacerbation and disease progression.

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GSK oncology pipeline

Selected products in late-stage development by GSK

MOLECULE	INDICATION	STATUS	ORIGIN/PARTNERS	POTENTIAL US LAUNCH
Zejula	Ovarian cancer (1st line)	Q4 '19 Filing	Tesaro acquisition	H1 2020
belantamab mafodotin	Multiple myeloma monotherapy (4th line)	Q4 '19 Filing	Seattle Genetics, BioWa	H2 2020
dostarlimab	Recurrent MSI-H endometrial cancer	Q4 '19/Q1 '20 Filing	Tesaro acquisition	H2 2020
bintrafusp alfa (M7824)	PD-L1 expressing NSCLC	Phase II	Merck KGaA	2021
Zejula+ dostarlimab	2L+ platinum resistant ovarian cancer	Pivotal results 2H 2020	Tesaro acquisition	2021
GSK3359609	Head and neck cancer	Phase II/III	Merck & Co.	2021/2

GW Still Sees Future For Sativex In US

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While the main focus at GW Pharmaceuticals PLC is on growing its epilepsy seizure drug Epidiolex, the company is looking to kickstart its multiple sclerosis spasticity therapy Sativex, an older cannabis-based drug that has failed to have much impact since its first approval back in 2005.

Sativex (nabiximols) is an oromucosal spray that contains delta-9-tetrahydrocannibinol (THC) and cannabidiol (CBD). Since its first thumbs-up in Canada over 14 years ago, it is now approved in over 25 countries for MS spasticity, following a spate of approvals in Europe from 2010.

GW does not market Sativex but has licensing agreements in Europe, Canada, Israel, Mexico, and South America with Bayer AG and Almirall SA. However it has not exactly proved to be a cash cow and GW's third-quarter 2019 results revealed that net sales of Sativex were just $2.8m.

The company told *Scrip* that the sales figure was based on GW selling Sativex to its commercial partners. There are provisions for milestone and royalties "but these are only listed when receipt of these payments become certain and there's no risk of revenue reversal."

Sativex has struggled to get reimbursed in Europe. As recently as August 2019, NICE, the health technology assessment body for England and Wales, has issued a new draft guideline reiterating previous guidance from 2014 which told doctors not to prescribe Sativex for spasticity in MS because it is not a cost-effective treatment. *(Also see "UK's NICE Not Convinced By Cannabis-Based Medicines " - Pink Sheet, 9 Aug, 2019.)*

The guideline also said that cannabis-based medicinal products should not be used to treat spasticity except as part of a clinical trial. The NICE committee stated in August that "there were reductions in some measures of patient-reported spasticity and no difference in adverse events in the treatment or placebo groups although much of the evidence was assessed as low quality."

NICE agreed that the longer-term benefits of the THC/CBD spray "are likely to outweigh any potential harms, although it was not clear how benefits related to improvements in quality of life."

> "We see a truly exciting opportunity for this product to address market needs in several indications over the coming years." – Volker Knappertz

The prospects for Sativex across the Atlantic also looked grim a couple of years ago. In December 2017, after three Phase III failures looking at expanding the drug into cancer pain, long-time partner Otsuka Pharmaceutical Co. Ltd. decided to hand back the US rights. The companies first linked up in 2007, when Otsuka agreed to pay an $18m upfront fee and up to $273m in potential milestones in exchange for an exclusive license to develop and market Sativex in the US. *(Also see "Interview: GW Pharma Gears Up For Pivotal 2018" - Scrip, 12 Dec, 2017.)*

However, since getting back the rights from Otsuka, GW has been advancing plans for Sativex in the US and on the firm's Q3 call, chief medical officer Volker Knappertz said "we see this product as a major late-stage pipeline opportunity with potential for extended exclusivity."

He claimed, "We have spent the last several months evaluating the development strategy and commercial potential for Sativex across a range of neurological and psychiatric indications." First up, and "based on an ongoing dialogue with the US Food and Drug Administration," GW's plan is to perform one additional Phase III trial of approximately 450 patients starting in the first quarter to supplement positive data from the three European Phase III trials it has already carried out.

Knappertz said the new trial was "intended to address the FDA's preference for a primary endpoint that focuses directly on the physical manifestations of spasticity. To complement this trial, GW is also initiating two mechanistic studies of about 35 patients each, so "we have a comprehensive data package in place together with over 80,000 patient-years of safety data," he added.

Over 35% of MS patients have moderate to severe spasticity and represent candidates for this treatment, Knappertz said. Discussions with MS experts in the US have revealed an appetite for Sativex, he added, "in a space where there continues to be a substantial need for new therapies as there have been no new oral anti-spasticity treatments introduced for over 20 years."

Knappertz said that during 2020 and 2021, GW hopes to initiate clinical programs in additional follow-on indications for Sativex. "We see a truly exciting opportunity for this product to address market needs in several indications over the coming years."

His enthusiasm was shared by analysts at SVB Leerink. In an investor note on 6 November, they said the spray "receives minimal attention, but we believe it could become a $380m drug in 2029 in terms of global sales."

Published online 7 November 2019

GW Pharma Bets On Europe For Epidiolex Growth: **https://bit.ly/32zSpg1**

Embracing China 2.0: AZ, Merck KGaA Set Up Funds, J&J Steps Up Digital Push

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The rise of local innovation, artificial intelligence (AI) and mobile technology are fast changing the health industry in China, compelling large pharma multinationals to jump on board with these trends.

AstraZeneca to set up global R&D and AI Center in Shanghai.

The latest company to do so, AstraZeneca PLC, has just announced several initiatives in a new show of commitment to China. They include a Healthcare Industrial Fund with a target size of $1bn to support local innovation, a global R&D Center and an AI Innovation Center, both in Shanghai.

Announced during the second China International Import Expo (CIIE), AstraZeneca said the global R&D center with a headcount of roughly 1,000 will be focused on locally prevalent conditions such as cancer, respiratory and other chronic diseases and has a goal to forge closer partnerships with local companies.

The investment fund, set up jointly with China International Capital Corp (CICC), one of China's leading investment banks and majority-owned by state-owned Central Huijin Investment Co., aims to tap into CICC's investment and capital management capabilities and use AstraZeneca's healthcare expertise to support both local and international health start-up companies, said Leon Wang, the UK firm's head of International.

"The new fund will inject vitality into small and medium-sized healthcare innovation enterprises with promising development prospects, so that they can achieve substantial growth in China," he said.

Separately, the UK drug maker has also licensed India company Sun Pharmaceutical Industries Ltd.'s novel oncology drugs to commercialize in China.

MERCK: GREATER BAY AREA CALLING

Meanwhile, Merck KGaA has committed CNY100m ($143,000) in seed funding for start-ups in China, the German company said on 18 October. It has also opened an Innovation Hub in Shanghai and will soon inaugurate another in Guangzhou in November.

The seed fund is aimed at nurturing local innovative ventures across three Merck business areas – healthcare, life science and performance materials – as well as new businesses such as AI-based healthcare solutions.

The new Guangzhou center will tap into the potential of the emerging "Greater Bay Area" which includes Guangzhou, Zhuhai, Hong Kong and Macau.

The fund and innovation hubs will allow the German firm to work closely with local partners to accelerate innovation in China and beyond, commented CEO Stefan Oschmann.

The seed fund, along with Merck's existing M Ventures capital fund, intends to invest in Chinese seed-stage companies with individual investments of between €500,000 to €1m ($552,000-1.1m) to help them to reach the next stage of development within 18-24 months.

Like others including Johnson & Johnson, Merck is looking to work closely with local start-ups in China and so far six ventures from China and other Asian countries have taken part in the first phase of the Merck Accelerator program in China.

J&J: AI, ROBOTICS PUSH

Embracing for a digital health future in China, J&J itself in late October announced the set-up of its J&J China Data Empowerment Center.

As China continues to shift wholesale to digital technology, the healthcare sector's digital transformation is being driven by social e-commerce, big data and "internet-plus" initiatives. J&J needs to embrace the trend to build data-driven precision medicine and open-innovation platforms, noted the company, which was among the few foreign firms to embrace China's Open and Reform policy started in 1978 by setting up a joint venture in Xi'an, Shaaxin Province.

The new Data Empowerment Center will be tasked to analyze data to gain insights on consumer needs and market demand, and build digital detailing and data-driven branding efforts.

As part of this strategy, J&J Medical China has signed a joint marketing, distribution and R&D agreement with Beijing Tianzhihang (Tinavi) Medical Technology Co., Ltd., a Chinese orthopedic robotics marker. The partnership will focus on spinal and trauma surgery and is intended to improve patient care through digital solutions, supporting local orthopedic surgeons to become more efficient and precise.

The US drug and medical device conglomerate reported double-digit growth for its pharma, devices and consumer health business in China in 2018.

Published online 8 November 2019

Sun Allies With AZ To Drive China Oncology Push:
https://bit.ly/2qNwHYp

Gene Therapy 'Vant' Unveiled As Dainippon, Roivant Finalize $3bn Deal

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Following their early September surprise announcement of a broad alliance, Sumitomo Dainippon Pharma Co. Ltd. (SDP) and Roivant Sciences Inc. have now finalized and fleshed out their $3bn deal under which the Japanese firm will acquire stakes in up to 11 "vant" companies.

On a strategic level, the transaction will provide SDP with much-needed late-stage candidates to tide it over its immediate post-Latuda (lurasidone) period, following the expected loss of US exclusivity for the atypical antipsychotic in early 2023.

The alliance will also bring "an early stage pipeline, health technology platforms and talent for sustained growth and transformation," SDP president and CEO Hiroshi Nomura told a 1 November investors' briefing.

The first positive impact on SDP revenues is expected to come from the start of fiscal 2022 (in April that year). While no figures were given, there may potentially be a large hole to fill; Latuda booked North American sales of $1.66bn last fiscal year.

Myovant Sciences Ltd.'s relugolix (licensed from Takeda Pharmaceutical Co. Ltd.) and Urovant Sciences Ltd.'s vibegron (Merck Sharp & Dohme Ltd.) are seen as near-term "potential blockbusters" by SDP, both of which are at the US pre-NDA stage, the former for uterine fibroids and the latter for overactive bladder. Both are also in late development for a range of other indications.

For Roivant founder and CEO Vivek Ramaswamy, the deal represents a "validation of Roivant's model," he told the meeting. "The large capital injection will drive value creation at Roivant with strengthened ability to build new vants."

One of these has newly emerged as part of the transaction with SDP, Spirovant being disclosed as the fifth of the vants to be included in the initial scope of the deal. The Philadelphia-based venture, headed by Joan Lau, has a preclinical portfolio of gene therapies for cystic fibrosis.

UP TO 11 VANTS

In the now finalized alliance, expected to close in SDP's current fiscal year ending next 31 March, the Japanese firm will initially acquire Roivant's ownership in five US-based subsidiaries: Myovant (NYSE-listed, 46% held by Roivant), Urovant (Nasdaq-listed, 75%), Enzyvant Sciences Ltd. (100%), Altavant Sciences Inc. (100%) and Spirovant (100%).

SDP also has an option – exercisable until 2024 and requiring additional payments – to acquire Roivant's holdings in another six subsidiaries (Dermavant Sciences Ltd., Genevant Sciences Ltd., Sinovant Sciences Ltd., Cytovant Sciences, Metavant Sciences Ltd. and Lysovant Sciences Ltd.), plus a right of first refusal to Roivant's interest in Axovant Gene Therapies Ltd.

Also included are contract technology access deals relating to Roivant's Datavant and Alyvant technologies and at least a 10% holding in the Roivant parent itself.

To effect the transaction, Roivant will first set up an as yet unnamed new 100% owned company, to which it will transfer its interests in the first five subsidiaries. This new entity will then be fully acquired by SDP.

> "The large capital injection will drive value creation at Roivant with strengthened ability to build new vants." – Vivek Ramaswamy

FINANCING

The $3bn price tag comprises $2bn for the acquisition of this new company and $1bn for the purchase of shares in NYSE-listed Roivant. SDP's Nomura said financing would come from a mix of cash, bridge loans and a loan-supported refinancing "through a hybrid financing instrument to raise equity-like capital."

The financial aspects of the deal also include loan facilities to be extended by SDP to the two vants with late-stage assets. A $350m low interest, five-year loan facility will support general operations at Myovant, while Urovant will have a similar $200m loan, with both to become available on the close of the wider deal.

The new operation housing the five vants will be headed by CEO Myrtle Potter, a former president and chief operating officer at Genentech Inc. and the current vant operating chair at Roivant. Other executives have been named as Sam Azoulay (chief medical officer), Adele Gulfo (chief business and commercial development officer) and Dan Rothman (chief information officer).

IMPORTANCE OF TECH PLATFORMS

In addition to acquiring the pipeline assets, Nomura highlighted the benefits of Roivant's DrugOme analytics platform, which he said would help "accelerate clinical development and pipeline acquisition" at the expanded SDP.

The system gathers and synthesizes a broad range of data to analyze trends and support discovery and clinical development, trial enrollment and the identification and valuation of promising assets for in-licensing.

Digital innovation forms a pillar of Dainippon Sumitomo's current mid-term business plan and the strategic aim is to raise operational efficiency, the CEO said.

Rothman will also act as chief digital officer for the broader SDP group, which will establish a new dedicated office to promote the adoption and use of DrugOme and other digital technology.

NEAR-TERM DRUGS

As for the main near-term vant assets, Ramaswamy pointed to relugolix's potential best-in-class profile as a once-daily GnRH receptor antagonist combination therapy (with estradiol and progestin) for uterine fibroids.

"There is no need to titrate and the therapy maintains bone density and mitigates hot flushes, potentially enabling long-term use" by optimizing estrogen levels, he noted.

As for vibegron, the beta-3 agonist reduced urge urinary incontinence micturition in the Phase III EMPOWUR trial, and the Roivant head pointed to differentiation in terms of dementia and drug-drug interaction risks.

The potential US market opportunity is sizable, with over 18 million prescription annually for overactive bladder symptoms.

SPIROVANT GENE THERAPIES

Of the two gene therapies for cystic fibrosis under development at Spirovant, SPIRO-2101 uses a proprietary adeno-associated virus vector to deliver a functional CFTR gene to airway epithelial cells.

SPIRO-2012 uses a proprietary engineered, tropic lentiviral vector to transduce airway epithelial cells and deliver the CFTR gene. Both therapies use technology developed at the University of Iowa Center for Gene Therapy and the Carver College of Medicine in the US. Spirovant has also developed aerosolization technology to maximize lung uptake.

Others working on the gene therapy approach to the disease include Boehringer Ingelheim International GmbH, which last year teamed up with Oxford BioMedica PLC and the UK Cystic Fibrosis Gene Therapy Consortium.

SDP has just reported revenues of JPY230.6bn ($2.11bn; +2%) and core operating profit of JPY44.8bn (+21%) for its fiscal first half ended 30 September.

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US Pharma Firms Not In Post-Brexit Trade Talks

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Following claims that UK trade officials have held secret discussions with US pharmaceutical majors about drug pricing after the country leaves the European Union, some of the major players in the sector have told *Scrip* that they have had no such talks about a trade deal post-Brexit.

As the UK prepares for a general election on 12 December, the future of the National Health Service and the possibility of drug prices being hiked has become a hot topic. That debate has been stoked by *Dispatches*, a television program aired on Channel 4 on 28 October which claimed that drug pricing has been discussed in six initial meetings between trade officials from the UK and the US ahead of a possible free trade agreement after the former leaves the EU; the latest deadline for Brexit is now 31 January 2020.

The *Dispatches* team also claimed that secret meetings have taken place between US drug makers and British civil servants where medicine price caps have been talked about. However, the American Pharmaceutical Group (APG), a key stakeholder which represents 11 research-based companies with a presence in the UK, told *Scrip* that "there have been no meetings between the APG and government officials on the topic of a future US/UK trade deal."

The APG's members are AbbVie Inc., Amgen Inc., Amicus Therapeutics Inc., Biogen Inc., Bristol-Myers Squibb Co., Celgene Corp., Eli Lilly & Co., Gilead Sciences Inc., Johnson & Johnson, Merck & Co. Inc. and Pfizer Inc.. The group, which was established in 1985, told *Scrip* that "like all industry bodies, and as representatives of significant inward investors to the UK, the APG meets regularly with government departments and the NHS to discuss matters such as the continued supply of medicines post-Brexit and the implementation of the government's Life Sciences Industrial Strategy."

Health secretary Matt Hancock spent much of last week insisting that neither the NHS nor higher UK drug prices will be on the agenda of negotiations on a post-Brexit free trade deal with the US. Claiming he had no knowledge of any such meetings cited by *Dispatches*, he said, "The full talks haven't started yet, we haven't yet signed off the mandate for how these trade talks happen, and in that mandate it will be absolutely clear that the NHS is off the table and that pharmaceutical pricing is off the table."

The opposition Labour Party is not convinced by Hancock's assurances which were repeated by prime minister Boris Johnson in an exchange in parliament with Labour leader Jeremy Corbyn on 30 October. Johnson also paid tribute to NHS England officials "who have just done a brilliant job in reducing the cost of Orkambi – made in America, by the way – so that cystic fibrosis sufferers in this country get the treatment they need at a cost that is reasonable to the taxpayers."

He was referring to the deal inked last month which brought to an end the protracted and controversial wrangling between Vertex Pharmaceuticals Inc. and the NHS that began in 2016 when the National Institute for Health and Care Excellence declined to recommend Orkambi (lumacaftor/ivacaftor). The agreement will see patients get access to Orkambi and Symkevi (tezacaftor/ivacaftor) and extended access to another Vertex CF therapy Kalydeco (ivacaftor).

Johnson went on the attack, saying of Corbyn, "Is he seriously suggesting that the NHS should not engage in negotiations to ensure that British patients get the drugs they deserve? Is he so phobic of American companies that he would forbid the NHS from having those discussions?"

He added a dig at the Scottish Nationalist Party, saying it negotiated "a much higher price for Orkambi in Scotland. They got the price totally wrong. The leader of the opposition should have a word with them."

Corbyn responded by saying that "the US has called for 'full market access' to our NHS, which would mean prices of some of our most important medicines increasing by up to

sevenfold. Of course we need to import medicines from various places; I just want it to be done in an open and transparent way. I do not want secret talks between government officials, on behalf of ministers, and big pharma corporations in the US."

The *Dispatches* program included an interview with Andrew Hill from Liverpool University who cited calculations which show that adopting the US system of drug pricing could cost the NHS £2.9bn alone for AbbVie's autoimmune blockbuster Humira (adalimumab). He said that for the NHS, the drug is the single most expensive drug, historically costing £450m a year, although the service noted in September that by switching to biosimilars and using "the best-value adalimumab product available," it expects to save more than £300m in its current financial year. *(Also see "NHS England Backs Biosimilar-To-Biosimilar Switching As It Counts Adalimumab Savings" - Generics Bulletin, 6 Sep, 2019.)*

Hill also calculated that if the US pharma lobbyists got their way in any future trade negotiations, the total extra cost to the UK could be £27bn. "We're talking about billions of pounds...we've got to go in with our eyes open, understanding just the crazy amounts of money that are involved," he said.

Notwithstanding the statement from the APG, it is no secret that the US negotiators have the NHS and UK drug pricing and reimbursement in their sights. In its final negotiating objectives released earlier this year, the US Trade Representative said it planned to "seek standards to ensure that government regulatory reimbursement regimes are transparent, provide procedural fairness, are non-discriminatory, and provide full market access for US products."

In its submission to the USTR, the US pharmaceutical industry body PhRMA criticized UK market access policies, saying they were characterized by "rigid health technology assessments, government price controls, insufficient health care budgets, and increasingly punitive and proactive national procurement initiatives and local barriers to uptake." It said the UK system "significantly undervalues innovative medicines and restricts patient access to those medicines" and that drugs should be priced "either through a market-based system… or some type of equivalent system."

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HIV PrEP Patent Dispute Escalates As HHS Files Suit Against Gilead

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The dispute between Gilead Sciences Inc. and the US government over its pre-exposure prophylaxis (PrEP) products has escalated, offering the Trump Administration a drug pricing talking point and creating a worrisome precedent for firms contemplating involvement with government-funded research.

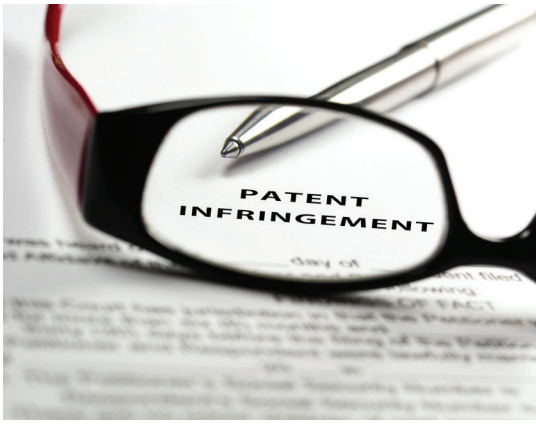
In a lawsuit filed on 6 November, the Department of Health and Human Services is seeking to compel Gilead to license the government's four patents issued in 2015 related to for HIV prevention. The company's drug Truvada has been approved for PrEP since 2012 and the Food and Drug Administration cleared its follow-on antiretroviral regimen Descovy for this indication in October.

HHS argues that Gilead is willfully infringing the HHS patents by not licensing the intellectual property created through taxpayer-funded PrEP research conducted by the Centers for Disease Control (CDC), according to the lawsuit, filed in the US District Court for the District of Delaware.

Gilead disputes the allegations in a statement about the lawsuit, reiterating claims it made in August when it asked the US Patent and Trademark Office (USPTO) Patent Trial and Appeal Board (PTAB) to conduct an inter partes review of the HHS patents.

"We strongly believe that the patents granted to HHS since 2015 for PrEP and [post-exposure prophylaxis (PEP)] are not valid and reject any notion of willful infringement," Gilead said on 7 November. "HHS improperly filed for patents without alerting Gilead, despite its obligation to do so, and we have openly explained the defects in the patents since becoming aware of them."

The company, which said it will ask the district court in Delaware to stay the HHS lawsuit until after the inter partes review, argued that there is "compelling evidence" showing that others considered the idea of using antiretroviral therapy for PrEP and PEP long before the CDC claims to have invented the prophylaxis strategy in 2006.



This prior art was not disclosed in the patent applications for the four HHS patents, Gilead noted.

The company pointed to its invention of Truvada [emtricitabine/tenofovir disoproxil fumarate (TDF)] and the $1.1bn it spent on research and development of the antiretroviral drug combination with a similar investment in Descovy [emtricitabine/tenofovir alafenamide (TAF)].

HHS DISPUTES GILEAD'S PREP INVESTMENT

The HHS lawsuit disputes Gilead's investment in Truvada for prophylaxis, citing PrEP studies sponsored and funded by the CDC and National Institutes of Health with substantial funding from the Bill and Melinda Gates Foundation.

Gilead used the results of the studies, known as iPrEX and Partners PrEP, to support its application to the US FDA for approval of Truvada for PrEP, but the company's funding for those studies was limited to free supplies of the drug and placebo, the government's complaint says.

The HHS lawsuit notes that Gilead agreed in a material transfer agreement for CDC PrEP studies in 2004 that it would license patents related to the studies' findings. And contrary to the company's claims, the HHS complaint says, Gilead was informed in of the CDC's intent to seek patents for its research findings – that combinations of emtricitabine and tenofovir or prodrugs of tenofovir, such as

TDF in Truvada, are effective in preventing HIV in primates and at-risk humans.

The lawsuit details the timelines for the CDC studies and findings as well as the publication and presentation of the studies' results. Those publications and presentations noted in as early as 2006 that researchers involved in the studies intended to patent their findings.

HHS Secretary Alex Azar acknowledged Gilead's efforts to sell Truvada and Descovy, which has reduced the spread of HIV and saved lives in the US, in the department's statement about its lawsuit. However, Azar said Gilead must respect US patent laws and the CDC researchers' "groundbreaking work."

The HHS lawsuit is seeking damages, reimbursement of legal fees and ongoing reasonable royalties on sales of Truvada and Descovy.

HIGH DRUG COSTS CITED FOLLOWING MAY HEARING

The government's complaint notes that private sector investment in PrEP studies increased after the CDC studies' findings were widely published and presented – all of which was backed by "hundreds of millions of dollars" in US taxpayer funding.

The lawsuit also notes the high cost of Gilead's PrEP regimens, which for Truvada has increased from $1,250 per month in 2012 to nearly $1,800 monthly in 2019 as the number of people using the combination pill for PrEP has grown from 8,768 to 200,000-plus in the US – a fraction of the 1.1m at-risk individuals eligible for treatment.

Gilead was grilled by members of the US House of Representatives during a House oversight hearing in May about the pricing of its PrEP drug Truvada despite the government-funded research that supported the drug's approval in that indication.

The company simultaneously announced that it would donate 2.4m bottles of Truvada to the US government annually to distribute to uninsured PrEP users for up to 11 years. It also announced that through a settlement with Teva Pharmaceutical Industries Ltd. a generic version of Truvada would become available in September 2020 – a year before the 2021 expiration of Gilead's patents.

CHILLING RESEARCH COLLABORATIONS?

The hearing and Gilead's donation illustrate the difficult, dual roles that biopharma firms often have to play in Washington: punching bag and public health partner. The Trump administration has continued this frequently dysfunctional relationship – desperate for what drug firms have to offer, but loathe to give them what they say they need.

But the HHS lawsuit, like Trump's pricing blueprint, puts the rhetoric into action in ways that previous administrations have not. The Obama administration, for example, was fond of criticizing pharma, but opted not to exercise "march-in" rights on government inventions when presented with the opportunity.

So far, the Trump administration has, if anything, been even more hesitant about using march-in rights. *(Also see "End Of The 'March-In' Pricing Petitions? " - Pink Sheet, 24 Apr, 2019.)*

And even if HHS won the suit against Gilead, that victory wouldn't seem to directly impact the price of the products.

However, the PrEP patent suit, while not directly related to the government's march-in powers, suggests that the Trump administration may now feel that drug pricing concerns are worth the risks of upsetting the long-standing government-industry research paradigm.

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ASH First Look: CAR-T Therapies Against BCMA, CD19 And More

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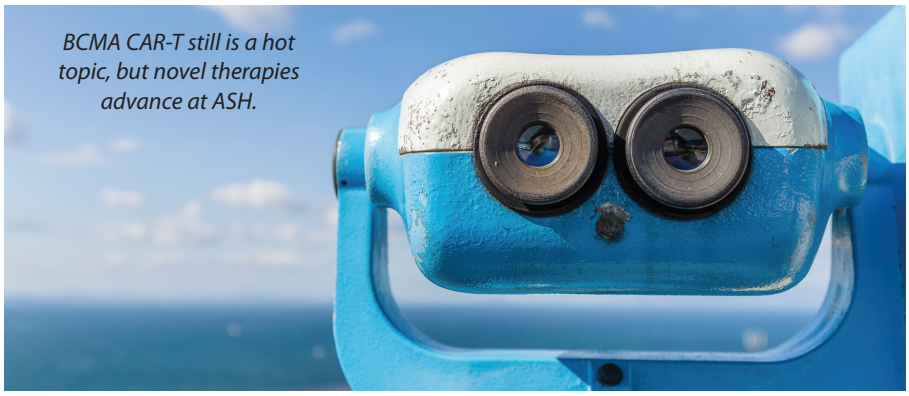
T-cell therapies once again will be a hot topic at this year's American Society of Hematology annual meeting 7-10 December in Orlando, FL, ranging from the latest round of BCMA-targeting chimeric antigen receptor T-cell therapy results in multiple myeloma to very early first-in-human results for the first CRISPR/Cas9 gene-edited T-cell therapy.



BCMA CAR-T still is a hot topic, but novel therapies advance at ASH.

BCMA CANDIDATES: J&J AND CELGENE CAR-TS, REGENERON BISPECIFIC

Data for CAR-T therapies, bispecific antibodies and other candidates targeting B-cell maturation antigen (BCMA) for the treatment of multiple myeloma were a highlight of last year's ASH meeting, including results from the most advanced program – Celgene Corp. and bluebird bio Inc.'s bb2121, which was challenged by JNJ-4528 (LCAR-B38M) from Legend Biotech Corp. and Johnson & Johnson's Janssen Pharmaceutical Cos.

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Scrip Awards
Finalists 2019

Scrip Awards
Informa Pharma Intelligence

Worldwide Clinical Trials' Licensing Deal of the Year Award

This Award recognizes licensing deals that are vital both in helping to keep pharma's pipelines replenished and in generating income for smaller firms.

AGENUS AND GILEAD SCIENCES FOR GS-1423 IN IMMUNO-ONCOLOGY

Gilead licensed worldwide exclusive rights to Agenus's GS-1423, a bispecific antibody designed to block two powerful resistance mechanisms in the tumor micro-environment, and obtained the exclusive option to license two other products, AGEN1223 and AGEN2373, for $150m upfront and around $1.7bn in potential future fees and milestones, and royalties. The partnership combines Agenus' IO expertise with Gilead's commitment to delivering disruptive therapies.

ASTRAZENECA AND DAIICHI SANKYO FOR TRASTUZUMAB DERUXTECAN IN MULTIPLE TUMOR TYPES

AstraZeneca and Daiichi Sankyo entered into a worldwide (excluding Japan) co-development and co-commercialisation partnership for Daiichi's late-stage HER2 targeting antibody drug conjugate (ADC) trastuzumab deruxtecan for $1.35bn upfront and up to a further $5.55bn in approval and sales milestones. This collaboration enables the parties to leverage each other's capabilities, share costs and risks, and accelerate product development in an area of unmet medical need.

INNATE PHARMA AND ASTRAZENECA'S FIVE-PART DEAL INCLUDING MONALIZUMAB IN IMMUNO-ONCOLOGY

This novel, complex and strategically important five-part licensing and investment deal strengthened one of the leading immuno-oncology collaborations in the industry and accelerated the corporate strategies of both companies. AstraZeneca secured a constant stream of innovation with Innate's anti-NK2Ga mAb, monalizumab, and CD39 mAb program, while Innate acquired a launch-ready asset Lumoxiti, which will transform it into a commercial company.

MERCK KGAA AND GLAXOSMITHKLINE FOR M7824 (BINTRAFUSP ALFA) IN DIFFICULT-TO-TREAT CANCERS

GSK and Merck KGaA agreed a potential €3.7bn strategic alliance to position them as leaders in the field of TGF-β biology. Bintrafusp alfa is the first and only bispecific IO molecule in clinical development addressing both TGF-β and PDx tumor immune evasion strategies. For GSK, which paid €300m upfront, this alliance is a further step to re-establish its leadership role in oncology with bintrafusp alfa as a key IO asset.

OXFORD BIOMEDICA AND AXOVANT SCIENCES FOR OXB-102 IN PARKINSON'S DISEASE

In June 2018, Oxford Biomedica and Axovant Sciences entered into an exclusive and worldwide license agreement worth up to $842m for OXB-102 for the treatment of Parkinson's Disease. OXB-102, now AXO-Lenti-PD, was a gene therapy originally developed by Oxford Biomedica for Parkinson's disease, using its LentiVector platform.

PELLEPHARM AND LEO PHARMA FOR PATIDEGIB TOPICAL GEL IN GORLIN SYNDROME

This deal between San Francisco-based PellePharm and LEO Pharma centers around the Phase III topical hedgehog inhibitor patidegib as the first potential treatment for Gorlin syndrome. Valued at up to $760m, the deal could lead to the elimination of the need multiple debilitating surgeries in a condition where patients develop basal cell carcinomas at repeatedly high rates of occurrence.

To find out more about attending the Scrip Awards, visit www.scripawards.com

Best Partnership Alliance

Scrip's Best Partnership Alliance Award recognizes the importance of pharmaceutical and/or biotech companies working together to develop new medicines.

ALLOGENE THERAPEUTICS AND PFIZER FOR CAR-T ASSETS

Allogene entered into an asset contribution agreement with Pfizer, under which Allogene received the rights to 16 preclinical CAR T assets as well as clinical candidates ALLO-501 and UCART19 to further its goal of catalyzing the next revolution in cancer treatment through the development of "off-the-shelf" allogeneic CAR T-cell therapies for hematologic and solid tumors. Pfizer also took a 20% equity stake in Allogene.

BENEVOLENTAI AND ASTRAZENECA'S ARTIFICIAL INTELLIGENCE PARTNERSHIP IN CHRONIC KIDNEY DISEASE AND IDIOPATHIC PULMONARY FIBROSIS

AstraZeneca and BenevolentAI's long-term partnership will harness the power of artificial intelligence (AI) and machine learning (ML) for the discovery and development of new treatments for chronic kidney disease and idiopathic pulmonary fibrosis. By combining AstraZeneca's disease area expertise and large, diverse datasets with BenevolentAI's leading AI and ML capabilities, the partnership aims to improve the understanding of complex disease biology and identify new targets.

CRUK, LIFEARC AND ONO CANCER IMMUNOTHERAPY ALLIANCE

This multimillion pound strategic partnership brings together Cancer Research UK, the medical charity LifeArc and Ono Pharmaceutical Co in a unique alliance that relies on the complementary expertise of each partner to progress research into new immuno-oncology drug targets. It provides a clear path for the development of drug targets identified by the research community supported by investment from Ono and LifeArc.

MICROBIOTA AND GENENTECH (ROCHE) IN INFLAMMATORY BOWEL DISEASE

Microbiotica, a leading microbiome player, secured a multi-year strategic collaboration with Genentech to discover and commercialise bacterial biomarkers, targets and medicines derived from patients in clinical trials for inflammatory bowel disease. The deal, worth up to $534m, was the largest ever in the sector, catapulting both Microbiotica and Genentech into the forefront alongside some well-established companies in the field.

MISSION THERAPEUTICS WITH ABBVIE FOR DUB INHIBITORS FOR ALZHEIMER'S AND PARKINSON'S DISEASES

Mission Therapeutics, a company focused on selectively targeting deubiquitylating enzymes (DUBs), teamed up with AbbVie to collaborate on the research and preclinical development of DUB inhibitors for the treatment of Alzheimer's and Parkinson's diseases. By modulating specific DUBs within the brain, AbbVie and Mission are aiming to develop potential therapeutics that enable the degradation of toxic proteins and prevent their accumulation.

23ANDME AND GLAXOSMITHKLINE FOR THE USE OF GENETICS TO IMPROVE R&D SUCCESS RATES

23andMe and GSK signed an exclusive four-year collaboration to focus on R&D of innovative new medicines and potential cures using human genetics as the basis for discovery to overcome the industry's historically low success rate of one in 10 molecules. This collaboration represents an exciting new model, joining a direct-to-consumer personal genetics company with a world-class pharma leader.

CONTINUED FROM PAGE 14

This year, Celgene and bluebird aren't presenting updated results for bb2121, which they expect to submit for US Food and Drug Administration review in the first half of 2020, but they will have updated results for the follow-on BCMA-targeting CAR-T, bb21217. Approval of bb2121 by 31 March 2021 is one of the three drug approvals needed for Celgene investors to earn a $9 per share contingent value right from Bristol-Myers Squibb Co., which is buying the company for $74bn up front plus the CVR. *(Also see "Bristol Values Celgene's Hematology, Immunology Portfolio At $74bn, But Does It Price In Risk?" - Scrip, 3 Jan, 2019.)*

However, Janssen will present the first results from its Phase Ib/II CARTITUDE-1 study of JNJ-4528 in relapsed or refractory multiple myeloma after data from Legend's Phase I/II LEGEND-2 trial were presented at last year's meeting.

According to the CARTITUDE-1 ASH abstract, a reduction in tumor burden was observed among all 21 patients treated with JNJ-4528 and evaluated as of the 24 June data cutoff. With a median follow-up of three months, the overall response rate was 91%, including four stringent complete responses (sCRs), two complete responses, seven very good partial responses (VGPRs) and six partial responses (PRs). Among 15 of the evaluable patients, 10 were minimal residual disease-negative – MRD negativity generally is associated with a good prognosis.

The rate of cytokine release syndrome, which can be severe for CAR-T-treated patients, was 88% among the 25 patients who received JNJ-4528 as of the data cut-off date. Most cases of CRS were grade 1 and 2 (80%), with one grade 3 and one grade 5 event. Three patients experienced neurotoxicity, another potentially severe side effect often associated with CAR-T therapies, including two grade 1 neurotoxicity cases and one grade 3 event, but all cases resolved within one or two days.

Updated results from 57 patients treated in LEGEND-2 show that the CRS rate was 90%, but most cases were grade 1 (45%) or grade 2 (37%) with four grade 3 events (7%) and no grade 4 or 5 CRS. There was one case of grade 1 neurotoxicity.

The median duration of follow-up as of 31 December in Legend's study was 19 months and median overall survival had not been reached, but the OS rate at 18 months was 68% and the median duration of response was 22 months. Median progression-free survival (PFS) was 20 months and 26 patients (46%) were progression-free at the data cut-off date. The study has had 17 deaths, including 11 attributed to progressive disease.

Last year's early results for Celgene and bluebird's bb21217 showed an 83% ORR with 10 of 12 evaluable patients responding to treatment. Rates of CRS and neurotoxicity were 67% and 25%, respectively.

Now, according to the ASH 2019 abstract, ORR still is 83% based on responses in 15 of 18 evaluable patients assessed after at least two months after treatment, but only nine continued to respond as of a 20 April cut-off. Thirteen of the full 22 patients treated through the cut-off date experienced CRS and five developed neurotoxicity, including one grade 3 and one grade 4 event.

All of the BCMA-targeting CAR-T therapies presented at ASH in 2018 and in 2019 are autologous therapies, which require extraction of patients' own T-cells, which are reengineered to target a specific antigen then infused back into the same patients. Many off-the-shelf allogeneic, or donor-derived, CAR-T therapies still are largely preclinical programs.

Outside of CAR-T therapies, Regeneron Pharmaceuticals Inc. also will report results at this year's ASH from the Phase I portion of its Phase I/II study in relapsed or refractory multiple myeloma for REGN5458, which is a bispecific antibody targeting BCMA and CD3. The ASH abstract has data for just three patients treated with REGN5458 as of the 12 July cut-off, including one man with a PR that improved to a VGPR, a woman whose disease progressed and another woman who achieved stable disease.

Jefferies analyst Biren Amin said in a 6 November note that the JNJ-4528 data from the LEGEND-2 study improve upon Legend's previously presented data, while the bb21217 data are consistent in terms of ORR with previously disclosed results, but data showing durable responses are eagerly awaited. Amin also noted that Regeneron's updated REGN5458 data, while early, are not as robust as those reported last year for Amgen Inc.'s bispecific T-cell engager AMG 420. *(Also see "ASH Preview: BCMA-Targeting CAR-Ts And Bispecifics Hog The Spotlight" - Scrip, 28 Nov, 2018.)*

GlaxoSmithKline PLC is far ahead of most companies with a BCMA-targeting therapy for multiple myeloma. It intends to seek approval for its antibody-drug conjugate (ADC) belantamab mafodotin (GSK2857916) before the end of this year. *(Also see "DREAMM-2 Put GSK's BCMA Drug In Pole Position In Multiple Myeloma " - Scrip, 23 Aug, 2019.)*

CD19 CAR-T THERAPY: BEYOND YESCARTA AND KYMRIAH

Arguably Celgene's most important CAR-T candidate with data at ASH this year is the CD19-targeting therapy JCAR017 (liso-cabtagene maraleucel, or liso-cel) with final results from the TRANSCEND NHL 001 study in relapsed or refractory non-Hodgkin lymphoma. Celgene, which acquired JCAR017 with its $9bn purchase of Juno Therapeutics Inc. in January 2018, hopes to deliver a CAR-T therapy against CD19 that's safer than its predecessors. *(Also see "Celgene Seeks CAR-T Leadership, Hematology Diversification With Juno Buy" - Scrip, 22 Jan, 2018.)*

Celgene plans to submit JCAR017 to the US FDA in the fourth quarter of this year; approval by the end of 2020 is required as one of the three components for the CVR payout under Bristol's acquisition of the company.

The first two CD19-targeting CAR-T therapies approved in the US are the diffuse large B-cell lymphoma treatment Yescarta (axicabtagene ciloleucel) from the Gilead Sciences Inc. subsidiary Kite Pharma Inc. and Novartis AG's Kymriah (tisagenlecleucel) for adults with DLBCL and pediatric acute lymphoblastic leukemia. Both have struggled to achieve significant sales due to the cost and complexity of the autologous therapies and various reimbursement challenges.

The ASH abstract for the pivotal study of JCAR017 in large B-cell lymphomas, including NHL, showed a 73% ORR among 255 evaluable patients with a 53% CR rate. The median duration of response was 13.3 months, median PFS was 6.8 months and median OS was 19.9 months. The abstract notes that "overall, PFS after liso-cel infusion was substantially longer than PFS from the immediate prior therapy."

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Grade 3 or higher treatment-related adverse events (TEAEs) were observed in 79% of patients, primarily neutropenia, anemia and thrombocytopenia. CRS was experienced by 42% of patients (2% of cases were grade 3 or higher) and 30% had neurotoxicity (10% of cases were grade 3 or higher).

"The abstract calls out four deaths (i.e., grade 5 TEAEs related to liso-cel). The most important thing to remember is that Yescarta and Kymriah had deaths too, and still got approved," Mizuho Securiteis analyst Salim Syed said in a 6 November report.

He noted that the Yescarta label describes four deaths for patients who experienced CRS. Meanwhile, the Kymriah label points out that five deaths occurred within 30 days of Kymriah infusion due to CRS or disease progression in ALL, while three adults with DLBCL who developed CRS died.

Syed said JCAR017 looks comparable to its rivals on efficacy with lower rates of grade 3 and 4 CRS and neurotoxicity.

Kite will have updated results for Yescarta and for a next-generation CD19-targeting CAR-T therapy known as KTE-X19 in mantle cell lymphoma (MCL).

Autolus Ltd. will present early results at ASH for its CD19-targeting CAR-T therapy AUTO1 in pediatric and adult ALL as well as for AUTO3, a programmed T-cell therapy that targets CD19 and CD22, in DLBCL and pediatric ALL. Data for a third candidate, AUTO2 targeting BCMA and TACI, but the company has discontinued development of that multiple myeloma candidate.

"Overall, we believe AUTO1 continues to show a strong efficacy and safety profile in adult ALL patients, with no patients reporting grade 3 or higher CRS," William Blair analyst Matt Phipps wrote on 6 November, noting that there is not enough data yet to determine whether AUTO3 is a competitive candidate.

EARLY-STAGE T-CELL, NK CELL THERAPIES

There will be an abundance of earlier-stage data at ASH for novel T-cell and natural killer (NK) cell therapies, including:

- Results from the first three patients infused with T-cells gene-edited with CRISPR/Cas9 technology show the therapy is safe, so far. Researchers at the Abramson Cancer Center of the University of Pennsylvania (UPenn) used CRISPR/Cas9 editing to remove a T-cell's natural receptors and remove the checkpoint PD-1 before using a lentivirus to insert a T-cell receptor (TCR) targeting the antigen NY-ESO-1. The private biopharma firm Tmunity Therapeutics Inc. and the Parker Institute for Cancer Immunotherapy are partnered with the UPenn researchers.
- Celyad SA will present Phase I results for its autologous NKG2D-based CAR-T candidates CYAD-01 and CYAD-02, including Phase I does-escalation data from THINK study and interim results from the DEPLETHINK trial, both for CYAD-01 in relapsed/refractory acute myeloid leukemia (AML) and myelodysplastic syndromes (MDS), and preclinical results for CYAD-02.
- Celularity Inc.'s presentations for its allogeneic cell therapies derived from donated placental cells will include Phase I data for the NK cell therapy PNK-007 in multiple myeloma.
- Gamida Cell Ltd. also has an allogeneic NK cell-based therapy, GDA-201, for which it will present Phase I results in NHL and multiple myeloma. The therapy comes from its nicotinamide-based cell-expansion technology platform.
- Initial Phase I/IIa results in NHL, MCL and DLBCL will be presented for Precision BioSciences Inc.'s lead allogeneic CAR-T candidate PBCAR0191, which targets CD19 and is being developed with partner Servier SA.

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ASH Preview: J&J And Legend's CAR-T Takes Center Stage

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As 2019 nears its end, there are several major congresses remaining, not least the year's biggest blood disorders meeting, the American Society of Hematology (ASH).

The congress takes place in Orlando, Florida 7-10 December, and abstracts released on 6 November will highlight a huge breadth of data across malignant and non-malignant hematology.

Among the most anticipated trial readouts will be Johnson & Johnson's Janssen and Legend Bio's ongoing CARTITUDE study of their CAR-T candidate JNJ-4528 (previously known as LCAR-B38M).

The drug is one of a field of contenders vying for future dominance in targeting the B-cell maturation antigen (BCMA) present on the surface of multiple myeloma cells.

It will take center stage at this year's congress as the two frontrunners, GlaxoSmithKline PLC's and bluebird bio and Celgene's bb2121 will not be presenting any major updates *(Also see "DREAMM-2 Put GSK's BCMA Drug In Pole Position In Multiple Myeloma" - Scrip, 23 Aug, 2019.)*

NEW DATA

J&J jumped into the collaboration with China's Legend less than two years ago, and are progressing their candidate rapidly.

Data from the LEGEND-2 study were presented at ASH last year, and the data proved impressive, producing an 88% response rate in objective response rate in treatment-resistant and a complete response in 68% of the relapsed myeloma patients after eight months.

This compared favorably with an initial readout from the field's pacesetter, bluebird bio Inc. and Celgene's bb2121.

However the LEGEND trial was conducted exclusively in patients in China, who were much less heavily treated with existing drugs compared to bb2121, making comparisons difficult.

Now Janssen and Legend are set to unveil data from a Phase Ib arm of the CARTITUDE-1 study conducted in US patients.

Like its rivals, the partners are starting off trials in patients who have stop responding to several lines of existing treatment.

Patients on the trial will have received at least three prior regimens, including a proteasome inhibitor (PI), an immunomodulatory drug (IMiD), and an anti-CD38 antibody, and have documented disease

The BCMA-targeting race in multiple myeloma

GSK and Celgene/bluebird lead the pack

	CANDIDATE	APPROACH	STATUS
Phase III			
bluebird/Celgene	bb2121	CAR-T	Completing pivotal KarMMa trial
Phase II			
GSK	belantamab mafodotin	Antibody Drug Conjugate	FDA filing by end of 2019
Janssen/Legend	JNJ-4528 (LCAR-B38M)	CAR-T	Data from US study CARTITUDE at ASH
Celgene (Juno)	JCARH125	CAR-T	Potential update at ASH
Amgen	AMG420	Bispecific	Potential update at ASH
Phase 1			
Sanofi/Regeneron	REGN5458	Bispecific	Dose escalation study expected at ASH
bluebird/Celgene	bb21217	CAR-T	Update expected at ASH

Data: Bernstein Therapeutics, Scrip

progression within 12 months of starting the most recent therapy, or are double refractory to an IMiD and PI.

Analysts at Bernstein say the Phase Ib study is likely to produce data at the congress from around 60 patients with perhaps 6-15 months of follow-up.

Bernstein expects comparable objective response rates (ORR) to prior CAR-Ts of 80% or above, though cautions that drawing conclusions on median progression-free survival (PFS) could be difficult given the relatively small number of patients who are a more than a year post-treatment with the one-time therapy.

The Phase Ib is primarily focused on safety and establishing the recommended dose for a pivotal Phase II trial.

This puts the candidate some way behind GSK and bluebird and Celgene, who expect to file in late 2019 and early 2020 respectively, both anticipating approval and launch next year.

Analysts expect the market leading treatments to earn over $2bn in peak annual sales, though with so many candidates vying for space, it is difficult to predict how the market will pan out.

For Janssen, its CAR-T candidate would add to its presence in the field: its fast-growing blockbuster Darzalex (daratumumab) is on track to earn $3bn this year as it rapidly progresses towards becoming a standard first-line therapy in myeloma. *(Also see "Sanofi Myeloma Drug Shines But Darzalex Dominates Still " - Scrip, 3 Jun, 2019.)*

It's unclear just how much of a challenge the BCMA-targeting agents will mount against Darzalex and other existing myeloma therapies. Their penetration into earlier lines of treatment will be closely linked to the depth and durability of response in patients, as well as questions of cost and safety, which remain to be resolved across the field.

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Roche Discontinues Duchenne Hope At Interim Analysis

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Late-stage clinical trial failures in Duchenne muscular dystrophy continue to plague this therapeutic sector, with Roche discontinuing its RG6206 (RO7239361) program. The decision emerged on 6 November in communications Roche addressed to the patient community, and quickly spread to the internet.

A pre-planned interim futility analysis of the Phase II/III SPITFIRE study of RG6206 (talditercept alfa), an anti-myostatin adnectin, indicated the compound was "highly unlikely to demonstrate clinical benefit as defined by meeting the primary endpoint (change from baseline in the North Star Ambulatory Assessment (NSAA) total score versus placebo)," Roche said.

The double-blind, placebo-controlled study involved boys with DMD who were ambulatory and was initiated in 2017,

> Other companies have also found Duchenne muscular dystrophy therapies difficult to develop.

and completed enrolment in July 2019. RG6206 was being given once weekly by subcutaneous injection, and because it binds to myostatin, it was hoped that it would increase muscle mass – usually, myostatin stops muscles growing too large, and an initial clinical study suggested that it did increase lean muscle mass.

The NSAA scale was being used to measure changes in functional motor ability. No safety signals have been seen in the study, and RG6206's safety profile was similar to that seen in previous trials.

A DIFFICULT AREA

RG6206 was originally developed by Bristol-Myers Squibb Co. as BMS-986089, and was licensed to Roche in April 2017. Under the agreement, Roche was to pay BMS an upfront of $170m, and BMS was eligible for potential milestone payments of up to

$205m and tiered double-digit royalties if it was commercialized.

Other companies have also found Duchenne muscular dystrophy therapies difficult to develop. Last year, Pfizer Inc. reported that it was discontinuing its Phase II myostatin/GDF-8-targeted antibody, domagrozumab, which failed to show a significant treatment effect, and was switching to evaluating a gene therapy approach to the disease.

Summit Therapeutics PLC also reported that its utrophin modulator, ezutromid, failed to meet endpoints in a Phase II study.

Analysts at Informa Pharma's Datamonitor Healthcare estimate there were more than 180,000 patients with DMD worldwide in 2017, and a wide variety of targets are being evaluated for new therapies. Sarepta Therapeutics Inc.'s Exondys 51 (eteplirsen) and PTC Therapeutics Inc.'s Translarna (ataluren) are already marketed for the disease in some countries, while Sarepta and Pfizer have gene therapy-based approaches to therapy in clinical studies.

INFORMING PATIENTS

Roche has made efforts to inform patients in a way that would allow their concerns to be addressed. It says it has notified all clinical trial sites and investigators are now in the process of informing study participants and families about the discontinuation. The company will also hold two global community webex online meetings on 8 November, and share the results of the interim analysis at upcoming congresses.

The discontinuation involves both RG6206 studies, that is the open-label extension study of the Phase Ib/II THUNDERJET study, and the Phase II/III SPITFIRE study. The US patient advocacy group, Parent Project Muscular Dystrophy, said it was disappointed to learn about the decision.

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Big Pharma Advances Efforts In TB But Pricing Stays Key Concern

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The 50th Union World Conference on Lung Health in India heard a string of encouraging announcements that provide hope for new and more affordable treatments for tuberculosis (TB), the infectious disease estimated to be one of the top 10 causes of death worldwide.

The meeting, which brought together clinicians and public health workers, health program managers, policymakers, researchers and advocates working in the area of lung disease, with a focus specifically on the challenges faced by low-and lower-middle income populations, was inaugurated in Hyderabad by the vice-president of India, M Venkaiah Naidu.

The opening ceremony was, however, disrupted by activists, survivors and the humanitarian group Médecins Sans Frontières demanding price cuts for new treatments for drug-resistant TB – Johnson & Johnson's bedaquiline, Otsuka Pharmaceutical Co. Ltd.'s delamanid and the TB Alliance's pretomanid - to ensure access to hundreds of thousands of patients around the world who "desperately" need these medicines. TB kills more people every year than any other infectious disease.

The conference, which ran from 30 October to 2 November, was also preceded by the first ever Survivors Summit convened by the Union that provided a platform for dozens of survivors of TB and lung disease facilitating a more co-ordinated global advocacy movement.

Scrip pieced together some of the key developments emerging from the conference, including Sanofi's pact to drop prices of its antimycobacterial rifapentine (sold as Priftin) by over 60%, the final analysis of the Phase IIb study for GlaxoSmithKline PLC's promising TB candidate vaccine and the US National Institutes of Health (NIH) trial to assess treatments for preventing people at high risk from developing multidrug-resistant tuberculosis (MDR-TB).

J&J also shared a series of initiatives to build capacity, improve access and health outcomes for TB patients in India.

SHARP DROP IN RIFAPENTINE PRICE

As part of an agreement with Unitaid, the global health initiative to fight AIDS, TB and malaria, Sanofi agreed to cut the price of rifapentine by around 67% to $15 from the current $45 for a three-month treatment course.

The volume-based agreement will allow main development partners supporting TB prevention, such as the Global Fund, President's Emergency Plan For AIDS Relief, United States Agency for International Development and Stop TB Partnership's Global Drug Facility, to make it much more widely available through their programs with governments in 100 low-income and middle-income countries.

A report in the local media in India indicated that rifapentine has been registered in the country and that Sanofi has initiated pricing discussions with the Indian government.

Shorter treatment regimens like rifapentine find favor with healthcare agencies due to better adherence by patients. Previously, preventive TB therapy took six to 36 months and uptake and compliance has been low. A rifapentine-based regimen shortens treatment to 12 weekly doses in combination with isoniazid and is recommended by the World Health Organization.

GSK TB VACCINE – SUSTAINED PROTECTION

GSK's tuberculosis candidate vaccine M72/AS01E continued to show promise, with final results confirming its efficacy level and acceptable safety profile in a three-year clinical trial conducted in sub-Saharan African regions.

Final analysis of the Phase IIb study, sponsored by GSK and conducted in partnership with the International AIDS Vaccine Initiative (IAVI), were published on 29 October in the *New England Journal of Medicine (NEJM)* and presented at the Hyderabad conference. The vaccine efficacy at month 36 was 49.7%, details of the study indicated.

The results are consistent with the primary analysis done after two years of follow-up and published in the NEJM in September last year.

The study was conducted in TB-endemic regions – Kenya, South Africa and Zambia – and covered 3,573 HIV-negative adults. Those who received two doses of either M72/AS01E or placebo 30 days apart were followed for three years to detect evidence of pulmonary tuberculosis disease. The final analysis indicated that 13 participants in the vaccine group developed active pulmonary tuberculosis compared to twice the number in the placebo group.

Among participants who received the vaccine, an increased M72-specific immune response was sustained through three years.

NIH PHOENIX TRIAL

Other interesting developments pertaining to the prevention of TB reported at the conference include the US National Institutes of Health's (NIH) plans for a Phase III multidrug-resistant TB (MDR-TB) prevention trial, known as PHOENIx, in certain high burden countries including India.

PHOENIx MDR-TB, short for Protecting Households on Exposure to Newly Diagnosed Index Multidrug-Resistant Tuberculosis Patients, will compare the efficacy and safety of delamanid versus isoniazid for preventing confirmed or probable active tuberculosis during 96 weeks of follow-up among high-risk household contacts of adults with MDR-TB.

In June, the NIH had indicated that it expects the study to include more than 27 sites in at least 12 countries, including Botswana, Brazil, Haiti, India, Kenya, Peru, the Philippines, South Africa, Tanzania, Thailand, Uganda and Zimbabwe.

Separately, Matthew Saunders from the Imperial College, London, provided results from a cluster randomized trial in Peru demonstrating the benefits of socioeconomic interventions to optimize the completion of TB screening and preventive therapy among household members in TB-affected households, a statement from the conference said.

ACTIVISTS/SURVIVORS DISRUPT CONFERENCE

Meanwhile, activists, MSF and TB survivors made themselves heard at the conference, disrupting a number of sessions at the event. They demanded price cuts for bedaquiline, delamanid and pretomanid to ensure that these medicines can reach those who need them; some were reported to have even called for "freedom from patents" on Otsuka's delamanid.

The prices of drug resistant-TB regimens are currently estimated to range between $1,040 and $11,680 depending on the treatment length and combination of drugs needed and MSF has been demanding that J&J cut the price of bedaquiline to no more than $1per day ($30 per month/$180 for a six-month treatment course).

In the case of delamanid, the humanitarian group has, in addition to price cuts, sought that Otsuka issue a non-exclusive license to the Medicines Patent Pool to allow generic firms to enter the fray to produce affordable versions of the drug.

MSF also argued that the Global Drug Facility's recently announced global access price of $364 for a six-month treatment course of pretomanid was too high and believes that a complete DR-TB treatment course should be available at no higher than $500 per person. The US Food and Drug Administration in August approved pretomanid tablets in combination with bedaquiline and linezolid (BPaL)] for the treatment of a specific type of highly treatment-resistant TB of the lungs. The GDF's price would mean that the lowest global price for a six-month course of BPaL regimen is $1,040.

TB ALLIANCE-MACLEODS PARTNERSHIP FOR PRETOMANID

Just ahead of the conference the non-profit drug developer, TB Alliance, announced a deal for a non-exclusive license to the Indian firm Macleods Pharmaceuticals Ltd. to manufacture pretomanid as part of the three drug BPaL regimen. Pending regulatory approvals, Macleods will commercialize pretomanid in about 140 countries and territories.

Pretomanid was developed by the TB Alliance, which had in April this year struck a collaboration with Mylan NV to make the drug accessible for use in specific drug regimens for pulmonary tuberculosis. Mylan has an exclusive license agreement for commercializing pretomanid for use in the BPaL and BPaMZ (bedaquiline, pretomanid, moxifloxacin and pyrazinamide) regimens in high-income markets.

Dr Mel Spigelman, president and CEO of the TB Alliance, told *Scrip* that Mylan has submitted a New Drug Application for pretomanid to the Drugs Controller General of India (DCGI) and that the Alliance and Mylan are working with the DCGI to "expedite the path to get this important product to Indian patients in need". (*An exclusive interview with the TB Alliance will appear soon in Scrip.)*

Activists, however, are demanding greater transparency in the overall terms of the TB Alliance's deal with Mylan. "There isn't enough clarity on the territories covered, the patent application on the combination regimen, terms of compassionate use," one healthcare activist told *Scrip*.

Activists also suggested that the Indian regulator could perhaps consider doing a risk-benefit analysis and choose to seek additional data on pretomanid, since the current situation is vastly different from some years ago when there were no treatments for MDR-TB.

"It's not an easy situation for the regulator since you are faced with a regimen, not just a drug. Trial waivers should be an exception and not the norm," the activist emphasized.

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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, 1–7 NOVEMBER 2019

Event Type	Lead Company/Partner	Drug Name	Indication	Comments	Change To LOA (%)	LOA (%)
Phase III Updated Results	Actinium Pharmaceuticals, Inc.	Iomab-B (I-131 apamistamab)	Acute Myeloid Leukemia	SIERRA; Encouraging Data	0	37
Phase III Updated Results	Takeda Pharmaceutical Co	TAK-003 vaccine	Dengue Fever Prevention	TIDES; Met Endpoints	0	63
Phase III Updated Results	FibroGen/AstraZeneca/Astellas	roxadustat	Anemia Due to Chronic Renal Failure, Dialysis-Dependent	HIMALAYAS; Met Primary Endpoints	0	73
Phase III Updated Results	Akebia Therapeutics, Inc.	vadadustat	Anemia Due to Chronic Renal Failure, Dialysis-Dependent	J03; Clinically Effective	0	61
Phase II/III Updated Results	Rhythm Pharmaceuticals, Inc.	setmelanotide	POMC, LEPR Deficiency Obesity	Improved CV Parameters	0	65
Phase II/III Updated Results	BioCryst Pharmaceuticals, Inc.	BCX7353	Hereditary Angioedema	APeX-S,2; Stabilized Attack Rates	-1	62
Phase II/III Updated Results	Bellerophon Therapeutics, Inc.	INOpulse (nitric oxide)	Pulmonary Hypertension with Interstitial Lung Disease	iNO-PF; Clinical Benefit	34	49
Phase III Top-Line Results	Supernus Pharmaceuticals, Inc.	SPN-810	Attention Deficit Hyperactivity Disorder	CHIME 1 (Pediatric); Missed Primary Endpoint	-9	43
Phase III Top-Line Results	Scynexis, Inc.	ibrexafungerp	Vulvovaginal Candidiasis	VANISH 303; Positive Results	0	66
Phase III Top-Line Results	Allena Pharmaceuticals, Inc.	reloxaliase	Hyperoxaluria, Enteric	URIROX-1; Met Primary Endpoint	-5	57
Phase III Top-Line Results	AB Science S.A.	masitinib	Asthma, Severe	AB07015; Positive Results	0	68
Phase III Trial Initiation	Regeneron Pharmaceuticals, Inc.	Eylea (aflibercept)	Retinopathy Of Prematurity	BUTTERFLEYE; Vs Photocoagulation	0	51
Phase III Trial Initiation	Supernus Pharmaceuticals, Inc.	Oxtellar XR (oxcarbazepine)	Bipolar Disorder	Monotherapy	51	51
Phase III Trial Announcement	Novo Nordisk A/S	concizumab	Hemophilia A and B	Explorer 8; Patients Without Inhibitors	0	60

Source: Biomedtracker | Informa, 2019

Halozyme's Spotlight Shifts To Enhanze Exclusively After PEGPH20 Fails In Phase III

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Halozyme Therapeutics Inc.'s only clinical drug candidate PEGPH20 will exit the stage – along with the company's oncology operations – now that the drug has failed to show an improvement in overall survival versus the standard of care in pancreas cancer in the Phase III HALO-301 clinical trial. The spotlight now will focus entirely on the Enhanze drug delivery platform as Halozyme restructures to support its existing partners, including two with product approvals anticipated next year.

The San Diego-based company announced on 4 November that while first-line treatment with PEGPH20 in combination with Celgene Corp.'s Abraxane (nab-paclitaxel) and gemcitabine had better response rates than Abraxane and gemcitabine alone among patients with metastatic pancreas cancer, overall survival – the primary endpoint for HALO-301 – was just 11.2 months for the three-drug combination versus 11.5 months for the two-drug combo (HR=1, p=0.9692).

PEGPH20 also did not improve progression-free survival or duration of response versus the first-line metastatic pancreas cancer standard of care.

As a result of the drug's Phase III demise, Halozyme said that it will halt PEGPH20 development and close its oncology operations to focus solely on the Enhanze platform through which the company uses its recombinant human hyaluronidase enzyme (rHuPH20) to enable subcutaneous delivery of intravenously delivered medicines or to reduce the number of injections needed for subcutaneous drugs.

"Unlike most biotechnology companies that experience a clinical trial setback, Halozyme has a clear, value-creating strategy going forward, which is to focus on our high-growth, high-margin Enhanze drug delivery technology," Halozyme CEO Helen Torley said in a 4 November call with analysts and investors. "As a result of that, we are immediately initiating a restructuring to halt development of PegPH20 and close our oncology operations."

PEGPH20 utilized rHuPH20 to break down hyaluronan that accumulates around tumors and was being tested in patients whose tumors had high levels of hyaluronan. Torley said during the call that Halozyme will inform Genentech Inc. about the HALO-301 results, since the Roche subsidiary is testing its PD-L1 inhibitor Tecentriq (atezolizumab) with PEGPH20 in Phase I combination studies in pancreas and other cancers.

With PEGPH20 off the table, Halozyme will reduce its headcount by 55%, or 160 employees, bringing its workforce to 120 people; 12 people will continue to market the company's only commercial product Hylenex (hyaluronidase human injection), which is used to improve the dispersion and absorption of other injected drugs, among other uses. About 80% of the layoffs will be completed by January 2020.

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APPOINTMENTS

Executive	To Company	New Role	From Company	Previous Role	Effective Date
Michael C. Hanley	Aeglea BioTherapeutics	Chief Commercial Officer	Esteve Pharmaceuticals	Chief Commercial Officer and Vice President	4-Nov-19
Ravi M. Rao	Aeglea BioTherapeutics	Chief Medical Officer	GlaxoSmithKline plc	Vice President, Global Medical Affairs Head, Immunology and Specialty Franchise	4-Nov-19
David A. Hollander	Aerie Pharmaceuticals Inc	Chief Research and Development Officer	Ora Inc	Chief Medical Officer and Senior Vice President	30-Oct-19
Kleem Chaudhary	Checkmate Pharmaceuticals	Chief Business Officer	Biogen	Head, Business Development and Licensing	31-Oct-19
James D. Watson	Imago BioSciences	Chief Business Officer	Sigilon Therapeutics Inc	President, Sigilon Islet Cell Therapy and Chief Business Officer	4-Nov-19
Ester Baiget	Novozymes AS	Chief Executive Officer and President	Dow Industrial Solutions	Business President	1-Feb-20

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