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Servier's Shire Oncology Buy Gives Base For US Expansion

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While many observers focused on the effect the sale of its oncology business to Servier SA will have on Shire PLC, which is expecting a takeover offer from Takeda Pharmaceutical Co. Ltd., the deal is also a significant one for the privately held French group and its hopes to become a major player in cancer on both sides of the Atlantic. *(Also see "Shire's Suitors: Takeda, Pfizer Seen As Likely To Bid; Amgen Could Enter Fray" - Scrip, 6 Apr, 2018.)*

Servier is paying $2.4bn in cash for the unit, a price that is a little higher than analysts at Deutsche Bank and Jefferies had expected – the brokers had net present value (NPV) estimates of $2.1bn and $2.3bn respectively. For its money, the Suresnes-headquartered firm is getting Oncaspar (pegaspargase), a component of multi-agent treatment for acute lymphoblastic leukemia (ALL), ex-US rights to Onivyde (irinotecan pegylated liposomal formulation), used as combination treatment for metastatic pancreatic cancer post gemcitabine-based therapy, as well as calaspargase pegol which is under FDA review for the treatment of ALL, and two early stage immuno-oncology (I-O) pipeline collaborations. *(Also see "Servier Acquires Shire Oncology Business For $2.4bn" - Scrip, 16 Apr, 2018.)*

Servier told Scrip that one of those collaborations is with Denmark's Symphogen and relates to immune checkpoint modulators. The other is with US company Precision Biosciences, looking at allogeneic CAR-T cell candidates.

The acquisition is something of a coup for Servier. Jefferies pointed out in an investor note April 16 that the process to divest Shire's oncology business reportedly began in January, "with multiple strategic buyers identified across the US, Europe and Japan," and as well as advancing its reach in cancer, Servier president Olivier Laureau said in a statement that the deal allowed the firm to establish "a direct commercial presence in the US," with products being marketed through a newly created subsidiary.

The US is key to the French company's future plans and in February this year, it opened the Servier BioInnovation office in the heart of the life sciences hub of Cambridge, Massachusetts. The new facility will identify new R&D opportunities and expand business development and licensing activities across the pond.

The company is no stranger to US pacts in oncology. Servier licensed the allogeneic CAR T-cell candidate UCART19 to Pfizer Inc. in 2015, having itself bagged the rights from Cellectis SA), and has been collaborating with the US behemoth on the frozen, 'off-the-shelf' T cell product in Phase I trials for ALL. Earlier this month, Pfizer transferred its CAR-T assets to newly-formed Allogene Therapeutics Inc. and Servier and Allogene aim to start mid-stage studies of UCART19 in 2019 – the latter will have US rights and Servier will hold them elsewhere. *(Also see "'We Jumped' At Opportunity To Take On Pfizer's CAR-T Program, Allogene's Chang Says" - Scrip, 4 Apr, 2018.)*

Servier also has strategic research alliances with Harvard University and the Massachusetts Institute of Technology

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from the editor

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It's interesting that even now that a couple of larger acquisition deals have been signed in the sector, they cannot be directly attributed to the Trump tax reform that was expected to herald an M&A boom.

Switzerland-based Novartis' $8.7bn acquisition of gene therapy specialist AveXis (as reported in last week's issue) and French Servier's $2.4bn purchase of Shire's oncology business (see cover story) will help boost the M&A tally for 2018, but big US firms repatriating billions of dollars in cash have yet to make their move. Is it possible that firms will prioritize the short-term gratification of shareholders through dividends and stock buy-backs over big-ticket punts on other businesses?

Over in R&D land, the American Association for Cancer Research in Chicago is providing the backdrop for yet another spin of immuno-oncology's wheel of fortune. As Emily Hayes reports on p4, this time Merck & Co is enjoying its moment in the sun with Keytruda looking to be in poll position in the large – and lucrative – first-line non-small cell lung cancer market. On the other hand, Bristol-Myers Squibb's data for Opdivo were disappointing: as one firm's star rises, the other's descends. In next week's issue we will bring you further coverage from the conference.

We're more than half way through April now, and that means that it won't be long before the deluge of first-quarter results hits; our coverage will begin in next week's issue, or you can get a head start right away by checking out www.scripnews.com.

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Hanmi is set to focus on other assets in its innovative drug pipeline after it ends development of novel lung cancer drug olmutinib amid ZAI Lab's recent cancellation of a licensing agreement with the South Korean pharma.

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The Swiss developer of a Phase III potential first-in-class antibiotic for Pseudomonas infections plans to list on the Swiss Stock Exchange, SIX, underlining the unmet need for better drugs for nosocomial pneumonia, and also the upturn in the bourse's popularity for European IPOs.

Venture Funding Deals: MedImmune Spinout Viela Lands $250m Series A
https://bit.ly/2J9aGHo
Also China's JW Therapeutics nets $90m for cancer cell therapy, including backing from biotechs Celgene and WuXi. Meanwhile, Foghorn sounds out a $50m A round for its gene trafficking technology applications.

Finance Watch: VC Investment Soars In Q1, Putting Biopharma On Track For A Record Year
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Pharma and biotech companies raised $4.6bn in the first quarter, exceeding the 2017 quarterly average by $1.4bn. But while the money invested soared, the number of companies funded sank. In public financings, MorphoSys commences US IPO and Mylan sells $1.5bn in notes.

inside:

Servier Acquires Shire Oncology Business For $2.4bn

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With **Shire PLC** in the crosshairs of a number of major pharma companies, with Japan's **Takeda Pharmaceutical Co. Ltd.** thought to be the leading potential bidder, the company has sold its oncology business to France's **Servier SA** for $2.4bn. The disposal of the oncology franchise might make the company less attractive an acquisition target.

Commenting on the deal, Shire CEO Flemming Ornskov said: "While the oncology business has delivered high growth and profitability, we have concluded that it is not core to Shire's longer-term strategy. We will continue to evaluate our portfolio for opportunities to unlock further value and sharpen our focus on rare disease leadership with selective disposals of non-strategic assets."

Servier has agreed to acquire Shire's oncology business for a total consideration of $2.4bn in cash upon completion. In 2017, the oncology business generated revenues of $262m. The total consideration represents a revenue multiple of 9.2 times 2017 revenues.

"The proceeds from the transaction increase optionality and Shire's board will consider returning the proceeds of the sale to shareholders through a shareholder-approved share buyback after the current offer period regarding Takeda's possible offer for Shire concludes," added Ornskov.

Servier, which has previously stated its ambition to be major oncology player, views the transaction as an essential step in its evolution to establish a direct commercial presence in the US and strengthen its portfolio of marketed products in the territories where it is already present. Shire's oncology teams will join Servier after the closing.

The transaction covers in-market products *Oncaspar* (pegaspargase), a component of multi-agent treatment for acute lymphoblastic leukemia (ALL) and ex-US rights to *Onivyde* (irinotecan pegylated liposomal formulation), a component of multi-agent treatment for metastatic pancreatic cancer post gemcitabine-based therapy. The portfolio also includes *Calaspargase Pegol* (Cal-PEG), which is under FDA review for the treatment of ALL, and early stage immuno-oncology pipeline collaborations.

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Merck's Keytruda Enjoys Clean Sweep In Lung Cancer

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Merck & Co. Inc.'s PD-1 inhibitor *Keytruda* has emerged as the clear winner in non-squamous non-small cell lung cancer (NSCLC), with consistent and striking survival data for the combination of the drug with chemotherapy in the Phase III KEYNOTE-189 study, leaving an uncertain future for **Bristol-Myers Squibb Co.**'s competing *Opdivo/Yervoy* combination.

On April 16, the American Association for Cancer Research (AACR) meeting featured full data from landmark studies in first-line metastatic NSCLC. Merck's KEYNOTE-189 study compared Keytruda (pembrolizumab) with doublet chemotherapy – **Eli Lilly & Co.**'s *Alimta* (pemetrexed) and cisplatin or carboplatin vs. the chemo combo alone in non-squamous NSCLC – and Bristol's CheckMate-227 study tested its PD-1 inhibitor Opdivo (nivolumab) with its CTLA-4 inhibitor Yervoy (ipilimumab) in squamous and non-squamous NSCLC.

There were some noteworthy differences in trial design. For example, crossover was permitted for placebo patients with verified

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and becoming a leading player in cancer is one of the goals that Laureau hopes to achieve by 2021. Those goals include the launch of a new molecular entity every three years, maintaining its position in cardiology (according to him, currently number two in Europe and eighth worldwide) and attaining sales of €5bn, up from €4.15bn in 2016/17.

FOUR AGREEMENTS

Last year, four oncology agreements were inked, including an I-O licensing deal with Germany's Pieris Pharmaceuticals Inc. and a CAR-T collaboration with fellow French group Transgene. As a result of these deals and in-house research, the share taken by oncology in Servier's R&D spend has jumped in two years from 14% to 37% last year and should reach 50% within the next two years.

It has three anticancer drugs on the market in Europe – Muphoran (fotemustine) for melanoma and cerebral tumors, Pixuvri (pixantrone) for the treatment of adults with multiply relapsed or refractory aggressive non-Hodgkin's B-cell lymphoma and Lonsurf (trifluridine/tipiracil) for metastatic colorectal cancer. Servier told Scrip it is pursuing new indications with Lonsurf, such as gastric cancer and earlier-stage colorectal cancer.

CROWDED MARKET

Analysts at Datamonitor Healthcare believe that the crowded nature of the colorectal cancer market means that Lonsurf will struggle to gain significant uptake, not least due to competition from immunotherapy blockbusters such as Merck & Co. Inc.'s Keytruda (pembrolizumab), Bristol-Myers Squibb Co.'s Opdivo (nivolumab) and further down the line Roche's combination of Tecentriq (atezolizumab) and Cotellic (cobimetinib), although the Swiss major did halt enrollment for a Phase II study for the combo last week after four patient deaths were reported.

In terms of the oncology pipeline, as well as UCART19, Servier also has high hopes for flotetuzumab, a humanized dual-affinity re-targeting (DART) protein which is being co-developed with MacroGenics and is in early-stage trials for acute myeloid leukemia and myelodysplastic syndromes.

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disease progression in KEYNOTE-189, whereas no crossover was allowed between treatment groups in CheckMate-227.

Results for both trials were published the same day in the *New England Journal of Medicine*; positive top-line results had previously been released for both trials.

'ABSOLUTELY' STANDARD OF CARE

The many positive data points across the board in KEYNOTE-189 included an overall survival (OS) benefit with a very strong hazard ratio of 0.49. This result was quite "extraordinary" and "exceeded expectations," as a 0.70 or 0.75 hazard ratio on this endpoint would have been considered by experts to be a major advance, said Roy Herbst, chief of medical oncology at the Yale Cancer Center and Smilow Cancer Hospital, discussing results at the AACR meeting, being held April 14-18 in Chicago.

Noting that the overall survival data were positive across study groups regardless of PD-L1 expression, Herbst said that the Keytruda/chemo combination is "absolutely" now the standard of care in first-line, non-squamous NSCLC.

Bristol's CheckMate 227 study is more complex in its design and interpretation. In February, the company announced that it had changed the design to feature progression-free survival (PFS) as a main efficacy measure in a subset of patients with a high level of tumor mutation burden, instead of using PD-L1 expression.

At the AACR meeting, the company reported that in patients with high tumor mutation burden, defined as 10 mutations per megabase, the median PFS was 7.2 months for Yervoy/Opdivo versus 5.5 months for pemetrexed with cisplatin or carboplatin, a statistically significant result, with a hazard ratio of 0.58. Overall survival data are not yet mature.

NSCLC is expected to account for close to half of the total immuno-oncology (IO) market and Keytruda secured the first and only monotherapy approval in first-line metastatic NSCLC in October 2016 in patients with at least 50% PD-L1 expression, adding to its approval in second-line NSCLC for all levels of expression. The combination of Keytruda and pemetrexed also secured FDA approval for first-line NSCLC. On April 9, the drug solidified its lead in NSCLC with data from the KEYNOTE-042 first-line lung cancer study supporting Keytruda as a monotherapy in patients with at least 1% PD-L1 expression.

Bristol's Opdivo infamously failed as a monotherapy in first-line NSCLC in the CheckMate 026 study, which was stratified by PD-L1 expression, though a retrospective analysis showed a benefit for those with high TMB.

MERCK'S LEAD WILL WIDEN

Merck's KEYNOTE-189 data are strong enough to support full regulatory approval in the US, Japan, and EU, and will continue to widen the first-line lead held by Keytruda, Datamonitor analyst Dustin Phan commented to *Scrip*. "At this point, Merck & Co appears to be the clear winner due to the availability of OS data for both single-agent Keytruda and Keytruda plus chemotherapy in the first-line setting," Phan said.

Overall survival data from CheckMate-227 will be necessary to better understand the potential impact Opdivo plus Yervoy will have on treatment trends in first-line NSCLC, the analyst added. These data are expected at the end of 2018 or early 2019.

PERFORMANCE ACROSS PD-L1 LEVELS

Both Keytruda and Opdivo demonstrated performance across PD-L1 subgroups and good safety relative to the comparator arms.

The KEYNOTE-189 study included 616 patients with previously untreated metastatic NSCLC with all levels of PD-L1 expression and no EGFR or ALK mutations. *(Also see "Merck Hits IO Bullseye With Keytruda Combo In First-line Lung Cancer" - Scrip, 16 Jan, 2018.)* After a median 10.5 months follow-up, OS at 12 months was 69.2% for the Keytruda/chemo combination versus 49.4% for the placebo-controlled chemo comparator.

"Improvement in overall survival was seen in all PD-L1 categories that were evaluated," Leena Gandhi, director of thoracic oncology at the Perlmutter Cancer Center at New York University, and colleagues reported in the *NEJM*.

Median PFS for the Keytruda arm was also superior at 8.8 months vs. 4.9 months.

Herbst said that for all endpoints and subgroups evaluated in the study, there were significant benefits except for PFS in patients with less than 1% PD-L1 expression, which is "cause for a little concern." However, he added, overall survival was significantly better in this group and that trumps PFS.

"So this is something to keep in mind as we move forward but I don't think it's a major limitation of the study," Herbst .

Furthermore, safety was similar – the rate of severe adverse events (AEs) was 67.2% for the Keytrda arm vs. 65.8% for placebo. The KEYNOTE-189 investigators and Herbst both flagged the rate of acute kidney injury in the Keytruda/chemo arm (5.2% vs. 0.5%). "In the pembrolizumab-combination group, acute kidney injury was of grade 3 or higher in 8 patients (2.0%); at the time of this analysis, acute kidney injury of grade 3 or lower had resolved or was resolving in 9 of 19 patients," the *NEJM* article states.

But the signal is not likely to be a deterrent, analysts concluded. "Safety was not an issue, except for the curious finding of more frequent kidney injury with chemo combo. On balance, the data is clean, except performance of the control arm was worse than historical precedent would have predicted, providing [Merck] with a beneficial tailwind," Bernstein Research analyst Tim Anderson said in an April 16 note.

"The only drawback is that grade 3-5 AEs occurred in ~67% of both arms, but were mostly chemo related (nausea, anemia, fatigue). However, efficacy drives treatment choice. [Merck] can offer Keytruda + chemo in healthier patients, and Keytruda monotherapy in sicker patients," BMO Capital Markets analyst Alex Arfaei said in an April 16 note.

Anderson said that the data confirm that Merck will remain in the driver's seat in terms of IO penetration into the all-important first-line lung cancer market, which has been forecast to be worth $7.5bn by 2021, for the PD-1/L1 segment.

Herbst said that the study that had supported the accelerated approval of the combination in first-line NSCLC – KEYNOTE-21G – was small and consequently the regimen was not used as much as it could be, although Merck has had a strong launch into the first-line setting. *(Also see "Merck's Keytruda Claims Market Leadership In First-line Lung Cancer" - Scrip, 30 Jul, 2017.)* "Everyone was waiting for the results we heard today," he noted.

Merck Laboratories Chief Medical Officer Roy Baynes commented to *Scrip* that the study asked simple questions and was remarkably clean, with a high degree of consistency, "the mark of a robust trial."

Like Herbst, Baynes expects an uptick in use.

"It's clear that data does drive practice – as it should, because it's good for patients," Baynes said.

BRISTOL DATA DISAPPOINTS

Bristol's CheckMate 227 was a multi-arm study of 1,739 patients that randomized patients based on PD-L1 expression to treatment with Opdivo and a low dose of Yervoy (1 mg/kg), double platinum chemotherapy, Opdivo monotherapy or Opdivo/chemotherapy. *(Also see "Bristol Debuts Opdivo/Yervoy Data In New First-Line Lung Cancer Bid" - Scrip, 5 Feb, 2018.)* The study included all levels of PD-L1 expression but excluded patients with EGFR and ALK mutations.

Results were reported by Memorial Sloan Kettering oncologist Matthew Hellman and colleagues in the *NEJM*.

Bristol was originally going to evaluate efficacy based on performance in PD-L1 subsets but wound up pooling parts of the trial and using PFS in a subset with high TMB as a coprimary endpoint – 299 participants (130 on Opdivo/Yervoy and 160 on double chemotherapy). **Foundation Medicine Inc.**'s FoundationOne CDx assay was used to assess PD-L1 and tumor mutation burden in the study.

Those with higher tumor mutation burden (TMB ≥10 mut/Mb) had significantly longer PFS, with 42.6% alive at one year in the Opdivo/Yervoy arm, versus 13.2% for chemotherapy. The objective response rates (ORR) in these patients were 45.3% for Opdivo/Yervoy vs. 26.9% for chemotherapy.

The benefit for the IO combination was broadly consistent regardless of PD-L1 expression or histology (squamous vs. non-squamous), investigators reported.

The one-year PFS rate of about 13% is very low for chemo; in TMB-unselected patients one-year PFS with chemo ranges from 25%-35%, BMO Capital's Arfaei commented.

Anderson commented that TMB is an emerging but still highly unconventional biomarker. "In 'low TMB' patients, the combination did worse than chemotherapy by itself. This is in stark contrast to MRK's '189 data, whose combination did better than chemotherapy in all segments, and the magnitude of the benefit in all of these segments was impressive," he said.

On the safety front, the rate of severe adverse events for Yervoy/Opdivo was 31.2% vs. 36.1% for chemotherapy.

MERCK ON TOP, AS EXPECTED

Analysts also expressed concern about data from CheckMate 227's Opdivo monotherapy arm.

"The Opdivo monotherapy section in the *NEJM* describes how mPFS with Opdivo monotherapy is essentially no better than chemotherapy by itself in PDL1+ patients using a TMB cutpoint at >13 [13 mutations per megabase]. It is difficult for us to interpret this data, but harkening back to the failed CM-026 study, it leaves open the possibility that Opdivo monotherapy may just not be as good as Keytruda monotherapy – for some unknown reason – a possibility we have often been dismissive of," Anderson said.

Analysts had expected Merck to emerge in a better position relative to Bristol at the AACR meeting, with robust survival data from KEYNOTE-189, and believe it may be hard for Opdivo to rebound in the important lung cancer indication.

One consolation for Bristol is the April 16 approval by FDA of the Opdivo (3 mg/kg)/Yervoy (1 mg/kg) combination in first-line renal cell carcinoma patients at intermediate and poor risk (about 75% of the population). The combination had demonstrated an overall survival benefit regardless of PD-L1 expression in the CheckMate 214 study, which tested the regimen against **Pfizer Inc.**'s tyrosine kinase inhibitor *Sutent* (sunitinib).

Opdivo has historically held the lead in the IO market, and brought in $4.9bn across all indications in 2017. But times seem to already be changing. In the fourth quarter, Keytruda drew almost level with just under $1.3bn, compared to $1.36bn for Opdivo. Keytruda's full year 2017 sales were $3.8bn. As of the firm's Feb. 2 earnings call, in the US roughly 55% of Keytruda sales came from lung cancer, with about 15% from melanoma and 5% each from bladder and head and neck cancers. *(Also see "Buoyed By US Tax Reform, Merck Plans $12bn In Capital Investments" Scrip, 2 Feb, 2018.)*

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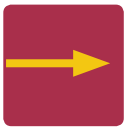

Merck's Keytruda Set For Expanded Use As Lung Cancer Monotherapy: https://bit.ly/2H5AwQb

Encouraging Survival Data For Lynparza in Metastatic Breast Cancer

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Although the Phase III OlympiAD study wasn't powered to show a statistically significant effect on survival, updated overall survival (OS) data from the trial are "another encouraging marker" for the use of **AstraZeneca PLC/Merck & Co. Inc.**'s PARP inhibitor, *Lynparza* (olaparib) in BRCA-mutated, HER2-negative metastatic breast cancer, the companies say.

The final OS results from the OlympiAD study found that Lynparza therapy was associated with a median OS of 19.3 months, compared with 17.1 months in patients treated with chemotherapy (HR 0.90; 95% CI 0.66-1.23; p = 0.513), the companies report. The analysis, presented at the American Association for Cancer Research (AACR) meeting in Chicago on Apr. 15, 2018, also showed that at final OS data cut-off (64% maturity), nearly 13% of patients remained on Lynparza and no patients remained on chemotherapy.

Previously presented results from OlympiAD in mid-2017 showed that Lynparza was the first PARP inhibitor found to control disease in this group of patients in a Phase III study. Lynparza met the primary endpoint of extending progression-free survival (PFS) when compared with a physician's choice of chemotherapy (capecitabine, eribulin or

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vinorelbine) in patients with germline BRCA-mutated (gBRCAm) HER2-negative metastatic breast cancer.

The current OS analysis supports the PFS endpoint and reinforces the importance of identifying BRCA status to optimize metastatic breast cancer management, the companies said. They entered an agreement in July 2017 to collaborate on the co-development and co-commercialization of Lynparza.

The current analysis also suggest there is no statistically significant difference between the effect of Lynparza and physician's choice chemotherapy on OS in patient subgroups divided on the basis of whether they had prior chemotherapy or prior platinum chemotherapy or on the basis of their receptor status.

US APPROVAL IN JANUARY

The OlympiAD results were the basis for the US FDA granting approval on Jan. 12, 2018, for the expansion of Lynparza's indication to include the treatment of patients with metastatic breast cancer who have a mutated BRCA gene, the first such approval globally. Previously Lynparza was indicated for ovarian cancer. The breast cancer additional indication has also been submitted for approval in the EU.

Gaining the first approval for a PARP inhibitor in breast cancer was considered crucial for Lynparza, so that it can get established in the marketplace before other PARP inhibitors that are in Phase III in the condition gain approvals, Datamonitor Healthcare analysts noted at the time. Not yet approved PARP inhibitors being evaluated in breast cancer in Phase III studies include **Pfizer Inc.**'s talazoparib, with the Phase III EMBRACA study expected to be completed in the first quarter of 2018, and **AbbVie Inc.**'s veliparib, which is being evaluated in HER2-negative metastatic or locally advanced unresectable BRACA-associated breast cancer.

There is currently no cure for patients diagnosed with metastatic breast cancer, and only 26.9% of patients survive for five years after diagnosis. Last year, sales of Lynparza rose by 36% to $297m, but the product is likely to come under increased pressure in ovarian cancer from two other recently approved PARP inhibitors, **Tesaro Inc.**'s *Zejula* (niraparib) and **Clovis Oncology Inc.**'s *Rubraca* (rucaparib).

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Can Pharmas Come Out Unscathed As China-US Trade War Escalates?

BRIAN YANG, ANJU GHANGURDE & IAN HAYDOCK

A tetchy trade war between the US and China looks set to escalate, with rising rhetoric and potential further tariff action on both sides. The pharma sector is keeping a close eye on developments, although – while some drug products have been included so far – some analysts expect the actual impact on companies and exporters to be limited.

Responding to the latest US move to slap proposed tariffs on Chinese exports of 1,300 products worth $50bn, China promptly said it would add similar tariffs on 106 products originated from the US. But to the relief of many pharma executives, the products subject to the planned 25% duties were mainly soybeans (the biggest single US export to China), cars and smaller aircraft, comprising some of the major items imported to China from the US.

China had earlier targeted $3bn in US exports after US President Donald Trump's initial move to hit Chinese steel and aluminium with new tariffs.

In the ongoing tit-for-tat, Trump has meanwhile proposed placing higher tariffs on another $100bn worth on Chinese goods, asking the US Trade Representative to look at the appropriateness of such a move and possible specific product targets. The president described China's trade practices as "illicit" and claimed they had cost "millions of American jobs".

In the pharma sector, China's weak intellectual property protection and "unfair" practices such as local testing requirements and quality tests for imported commercial products have largely deterred patient access to innovative new drugs, claim US industry groups.

China's restriction of cross-border transport of materials and data for clinical studies, for one, along with China's Pharmacopeia that favors local makers, continue to add unnecessary burdens and delay time-to-market of innovative therapies, pointed out the US biotech industry group BIO in a statement submitted to the USTR's 301 investigation last September.

USTR Robert Lighthizer said that Trump's new instructions to look at additional tariffs were "appropriate" given the need to eliminate "unfair [Chinese] acts, policies, and practices. The main US complaint in the wider dispute, besides the impact on the US economy, is that it wants China to better respect intellectual property rights across the board, and sees as unfair some China moves to acquire technology and protect its multiple domestic industry sectors.

LIMITED IMPACT?

Nevertheless, a US industry group advocating for generic drug makers, the Association for Accessible Medicines, sees a potential impact of higher drug prices in the US. "We are concerned that the proposed tariffs may lead to increased costs of manufacturing for generics and biosimilars and thus higher prescription drug prices for patients in the US" said the group in a statement.

Analysts are less concerned. They pointed out that many of the Chinese active ingredients and biologic products listed by the US for the potential higher 25% tariffs actually have little impact on the pharma industry in China.

US companies using many of the targeted Chinese exports, ranging from antibiotics to vitamins, have their manufacturing sites outside the US, in countries such as India. "We know that many of the big generic players actually have their manufacturing facilities ex-US (India etc.) and the import [by the US from China] of API [active pharmaceutical ingredient] bulk materials go to the Indian manufacturing sites etc…and not to US, " noted Evercore ISI senior analyst Umer Raffat in an April 4 note.

Furthermore, a large bulk of the APIs imported from China are mainly antibiotics and vitamin C, while the list of APIs in Trump's sights in the planned tariffs on the $50bn in goods is comparatively narrow, added the analyst. "The list of APIs included on this Trump proposed tariff list is NOT very exhaustive and thus, it doesn't appear that it would have much impact to generic players."

Generics firms aside, biologics manufacturers including insulin companies in China are also likely to see limited or no impact from the planned new US tariffs. An executive of Chinese major domestic insulin maker, **Gan & Lee**, told *Scrip* that the Chinese export of insulin APIs to the US is small and the effect would be limited.

The Evercore ISI analysis shows that US firm **Eli Lilly**, a major insulin producer, has expressed no impact so far, given that its products are made in the US.

One Chinese API maker that could have some impact, given that it has a number of approved in the US, is **Zhejiang Hisun Pharmaceutical Co. Ltd.**. The firm has 18 APIs approved by the FDA, including oncology injections (such as doxorubicin and cytarabine), which are covered by the planned US tariffs.

Economists estimate the total value of all the products on the planned US list (which remains subject to a final hearing in mid-May) accounted for just 0.4% of China's total GDP in 2017. China's new tariffs amount to merely 0.3% of the GDP of the US, noted US Secretary of Commerce Willbur Ross in an interview with CNBC.

Nevertheless, as the US runs a roughly $375bn goods trade surplus (buying $506bn in total) with China, it potentially has more head room to inflict hurt through further tariffs, although a key question is what the price (literally) to consumers will be and what political fallout may occur. For instance, there has already some blow-back from the politically influential US agricultural sector over the planned new foodstuff tariffs in China.

For its part, China has said it is not worried about a trade war but would like to avoid escalation through negotiations, showing no intention to back down. Despite the current standoff, some observers say both sides have more to gain from negotiations.

For China, the options seem to be fewer if foreign buyers and other countries decide to step into the foray, providing the supplies or scooping up US goods, although China's state-controlled economy might allow state-owned enterprises to absorb more losses without shareholder pressure, if indeed more tariffs on exports are imposed by the US.

Indian firms are also keeping a close eye on the goings on in the US-China trade tit-for-tat. Any serious escalation could potentially imply some trickle-down gains for Indian generic companies, though not many in the Indian industry expect the US-China stand-off to escalate into a full-blown trade war, at least yet. And for now, not getting caught in the crossfire when two large economies spar may be an equally relevant strategy for India – that appears to be the general take away from some sections of industry.

Industry veterans underscore that any immediate or headline-grabbing gains accruing to Indian firms as a result of the US-China tariff tussle are unlikely – much could depend on how US firms deal with costlier Chinese APIs that go into their formulations.

Dilip Shah, secretary general of the Indian Pharmaceutical Alliance, which represents leading domestic firms, explains that effecting any change of API source is not easy under the FDA rules – it's both "costly and time-consuming", he notes - and hence US firms that rely on Chinese APIs are unlikely to shift immediately.

"They [US firms] may rely on raising formulation prices to compensate for the loss arising from duty paid APIs. Indian companies using own/indigenous APIs in their formulations may benefit from the head room provided by the US companies for better [formulation] prices," Shah told *Scrip*.

But he emphasized that the real impact would be visible only three to six months after the tariffs are enforced, if and when. "As of now, it is only a proposal. If they are implemented, Indian companies would benefit, but not before 2019."

US OVERSEAS MANUFACTURING

But what about companies like **Mylan NV** that appear to be in sweet spot given their India manufacturing base? Shah notes that President Trump has also been targeting US companies which are manufacturing overseas for the US market. "This includes many non-pharma companies. Mylan will fall in this category," he said.

But others like Dr. Ajit Dangi, president and CEO of Danssen Consulting, believe that it is more likely to be "status quo" for India amid the US-China sparring. He notes that many Indian pharma companies have, in the past few years, developed indigenous or alternative supply of APIs and these companies will see "little impact".

However, with Indian firms still grappling with US FDA issues related to GMP non-compliance and data integrity (although there is positive declining trend, he notes), companies are unlikely to gain significantly from the ongoing "so called trade war".

"From the pharmaceutical industry point of view, India has to worry more about intellectual property rights-related issues than tariffs," said Dangi, a former director general of the Organization of Pharmaceutical Producers of India, which represents the foreign firms.

FLEXING AND POSTURING?

For the most part, though, Indian experts believe that the US-China wrangling won't stretch into the long term. In addition to reports of ongoing trade negotiations between the two nations, China has also said that it will appeal to the World Trade Organization for intervention.

In contrast to some other observers, Salil Kallianpur, a former executive vice president at GlaxoSmithKline India and co-founder and partner of The Digital Transformation Lab, said: "Also, in retaliation, China can impose tariffs that will be far more damaging to the US. So, I expect this to die down once the political rhetoric fades away." He also observed that while the US targeted many Chinese made APIs, in retaliation, China hasn't done the same so far.

"They [China] seem to have included only a few chemicals in their list which is unlikely to impact the US pharma market, if at all. This can be viewed as a concession given that the US market is the largest in terms of pharmaceuticals and the Chinese will probably negotiate hardest to get that section off the [US] list. The Chinese move of 'being kind' to US pharma may be handy leverage in this bargain," Kallianpur added.

Danssen's Dangi also believes that strategically too, taking on two powerful countries like China and Russia and also a belligerent nation like North Korea is likely to harm US more than these countries. "These are regimes that can take snap decisions without worrying about any negative impact on the survival of their respective leaders. With the world's largest stockpile of foreign exchange, China also has staying power. The US-China scenario, therefore, looks more like muscle flexing and posturing."

CHANCE TO TALK?

So far, neither China and the US have finalized a date for implementing any new tariffs, leaving the door open for more negotiations. The hope is that the two sides will be able to reach concessions to avoid a full-blown trade war..

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Pfizer's Essential Health Leadership On Why US Biosimilars Will Take Off – Eventually

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Pfizer Inc. is in the biosimilar market for the long game, despite the commercial challenges it has faced with its first biosimilar to launch in the US – *Inflectra* (infliximab-dyyb). That was the message the company's Essential Health leadership set out during a briefing on the company's biosimilar strategy at Pfizer's New York headquarters April 10.

"The market for biosimilars is alive and it's real and it's here to stay," Essential Health Group President Angela Hwang said. Hwang took over the top leadership role for Pfizer's Essential Health business late last year, succeeding John Young in a broader leadership reorganization of Pfizer's top ranks. Young moved up to head Pfizer's Innovative Health business while Albert Bourla moved up to be chief operating officer.

Hwang previously was global president and general manager of Pfizer's Inflammation & Immunology business, experience that suits her well now as Pfizer tries to get Inflectra off the ground in the nascent market for biosimilars in the US. Inflectra, which launched in late 2016, was the first biosimilar version of **Johnson & Johnson**'s *Remicade* (infliximab) to launch in the US.

The early challenges Inflectra has faced have put a spotlight on what could be a big road block to the commercial uptake of biosimilars in the US. With no interchangeability requirements for biosimilars in the US, brand drug manufacturers have the leverage to simply lower the price of their drug and negotiate preferred formulary access with payers for the brand product, which has substantially larger volumes and thus larger impact on payers' budgets. J&J has taken a hit on sales of Remicade in the last year because it is offering higher rebates, but it has effectively blocked Inflectra from the market. Inflectra generated $419m in 2017, whereas Remicade generated $6.3bn.

Pfizer has filed a lawsuit against J&J claiming the company's contracting strategy for Remicade is anti-competitive, alleging the company threatened to withhold rebates on Remicade if Inflectra was reimbursed. The outcome of that lawsuit could have implications for future biosimilar launches.

Inflectra had a 5.6% share of the infliximab market by volume at the end of 2017, Pfizer said, with about half of that coming from highly-integrated payer systems like the Department of Veterans Affairs and Kaiser Permanente, which have been more receptive to providing access to Inflectra. **Aetna Inc.** added Inflectra to its commercial formulary effective Jan. 1, and Pfizer noted that it is making slow progress on the market access front.

Regardless of the slow launch of Inflectra, the long-term potential of biosimilars is too large to ignore, Global President-Europe, AfME and Biosimilars Richard Blackburn said.

"We are confident about the future," Blackburn said. That optimism is fueled by the increasing role of biologics in treating patients and increasing health care costs. Biologics are expected to represent global sales of roughly $360bn by 2025, with about one-third of those sales no longer subject to market exclusivity, according to Pfizer.

"As you get into the next decade you start to see the really big potential savings," Blackburn said. "We believe the market will form and we are optimistic."

But the US market for biosimilars is not going to take off without some nudging, he added. "There is a continued need for education," he said. "There's got to be fair and equal access to the medicines … There needs to be a consensus around what is reasonable pricing."

"The sorts of savings that can be achieved in the solid oral generic space will not be achievable in this space, and if that's what stakeholders strive for we will find that companies are unable to make money, and we won't see the successive waves of new compounds coming to market."

Some payers have pointed out that one reason Inflectra has not been able to overcome the market access barrier is because the price is simply not low enough, though Pfizer disagrees with that view. The average sales price (ASP) of Inflectra in the US is about 17% lower than Remicade. Average sales prices are what drug manufacturers report to the Centers for Medicare & Medicaid Services for drugs reimbursed under Medicare Part B and reflect the average prices including rebates and discounts. Pfizer also talked about offering discounts on the wholesale acquisition cost (WAC) of Inflectra of 25% to 40%.

US Biosimilars General Manager John Kennedy insisted the price of Inflectra is not the issue, since Pfizer has seen strong uptake of Inflectra in the closed payer systems that are reimbursing the drug.

"Anti-competitive tactics like J&J's exclusionary contracting need to be stopped," he said. "I'm convinced there is very significant long-term potential for biosimilars in the US, but now's the time to make sure there is a market that is receptive to them."

AN EARLY LEADER

Pfizer is an early leader in biosimilars, a position it acquired with the $17bn deal to buy **Hospira Inc.** in 2015. Hospira had amassed one of the largest biosimilar pipelines in the industry at the time in part through a collaboration with South Korea's **Celltrion Inc.**, which gave it rights to several biosimilar drugs, including Inflectra. In addition to Inflectra in the US, Pfizer also markets *Nivestim*, biosimilar filgrastim, and *Retacrit*, biosimilar epoetin, in Europe.

Pfizer has a biosimilar version of Roche's breast cancer blockbuster *Herceptin* (trastuzumab) pending at the US FDA with action anticipated in the first half of 2018, and two other applications, for biosimilar *Epogen* (epoetin alfa) and *Neupogen* (filgrastim), that have been filed with the agency. The Neupogen application was accepted by FDA in November, while Pfizer resubmitted the Epogen application in November after receiving a complete response letter from the US regulator. Four other biosimilar versions are in late-stage development: *Humira* (adalimumab), *Rituxan* (rituximab), *Avastin* (bevacizumab) and *Neulasta* (pegfilgrastim). Five undisclosed biosimilars are in preclinical development, Pfizer said.

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Mylan Poised To Launch Its First US Biosimilar

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Mylan NV has developed an impressive pipeline of biosimilars, but whether it can turn those products into commercial successes on the big stage that is the US market remains a question. Now, after many years of investment, the company seems close to getting the chance to launch its first biosimilar in the US, a version of **Amgen Inc.**'s *Neulasta* (pegfilgrastim).

Mylan showcased its biosimilar pipeline during an investor day in New York City April 11. The company has 11 biosimilar products, including insulins, in clinical development through partnerships with **Momenta Pharmaceuticals Inc.**, **Biocon Ltd.** and others, and another 10 in preclinical development. The expansive pipeline Mylan has amassed highlights the strategic decision the company made nearly a decade ago to prioritize biosimilars and complex small molecule generics as it sought to move into segments of the generic drug market with higher barriers to entry.

CEO Heather Bresch spoke in an interview with *Scrip* earlier this year about how those investments and other diversification strategies have positioned Mylan to navigate what has become a challenging US market for generic drugs.

The question now is if those investments are going to pay off in the near-term. The company was the first to market with a generic version of **Teva Pharmaceutical Industries Ltd.**'s 40mg version of the multiple sclerosis backbone *Copaxone* (glatiramer) last year, and is also hoping to be the first to market with a generic version of **GlaxoSmithKline PLC**'s asthma blockbuster *Advair* (fluticasone/salmeterol) later this year.

Neulasta could be its first biosimilar to launch in the US, though it would not be Mylan's first biosimilar approved by FDA. The agency approved Mylan's version of the **Roche**'s breast cancer drug *Herceptin* (trastuzumab) as *Ogivri* in December, a biosimilar developed with Biocon. The launch timeline, however, is dependent on a patent settlement agreement with Roche and has not been disclosed.

The regulatory progress on these various hard-to-replicate products has helped Mylan regain some credibility with investors after the *EpiPen* pricing scandal, and a corresponding revenue hit, that played out in 2016 and 2017, but how these products perform commercially in the market is now the big question on the minds of investors.

Some of the first bisoimilars to launch in the US have underwhelmed, like **Pfizer Inc.**'s *Inflectra*, the first biosimilar version of **Johnson & Johnson**'s *Remicade* (infliximab) to launch and which has faced market access challenges. Mylan has said it does not expect any material revenues from biosimilars until 2019, but Bresch said she is confident in the long-term commercial opportunity for biosimilars.

"I think that necessity certainly is going to drive biosimilar uptake" she told investors. "I don't think it's going to be 90% [penetration] probably anytime soon, nor necessarily should it be, but I do believe there's going to be uptake."

NEULASTA ON TRACK FOR JUNE

The application for biosimilar Neulasta is on track for FDA approval by the June 4 action date, Head of R&D Arnd Annweiler said. If it is approved, it would be the first biosimilar version of Neulasta to launch in the US and it would be quite an accomplishment since several companies have filed regulatory applications for biosimilar pegfilgrastim with the FDA that have been returned with complete response letters. Mylan was one of them, along with **Sandoz International GMBH**, **Coherus BioSciences Inc.** and **Apotex Inc.**

Neulasta generated $3.93bn in the US in 2017, so being the first biosimilar to compete in the space could be a lucrative opportunity.

Annweiler said Mylan has responded to all of the FDA's questions, including labeling questions, and is awaiting FDA action. He said he does not expect the FDA will convene an advisory committee to review the application as some industry observers have speculated given the high number of CRLs the agency has issued so far on proposed biosimilars to Neulasta.

When it comes to commercializing Neulasta, Bresch said she is encouraged by the profile of the neutropenia drug, because of the acute nature of the product.

"It's not a maintenance medication, so it has new patients coming in and out of that drug constantly versus a product like Copaxone." The company has not disclosed sales of its Copaxone generic.

ON ADVAIR: "NOT IF, BUT WHEN"

As for the timeline for generic Advair, President Rajiv Malik sounded perhaps less confident about FDA approval on or before the June 27 action date, though he insisted the company is encouraged by FDA's progress on the application.

Mylan had a meeting with the FDA March 1 to discuss outstanding questions, which the company has since answered, he said. "We are now waiting to hear from FDA," he said. "There might be some more clarification they might need, but there is nothing sticking out." Mylan is moving ahead with commercialization plans for the product, which it plans to market as *Wixela Inhub*, and Malik said the question is "not if but when."

Separately, the company is targeting a regulatory filing with the FDA for a generic version of **AstraZeneca PLC**'s competing asthma drug *Symbicort* (budesonide/formoterol) in mid-2018.

LEAP-FROGGING

One of the biggest opportunities for biosimilars is **AbbVie Inc.**'s *Humira* (adalimumab), the top-selling drug in the world six years running. All of the biosimilar players have their eye on the Humira prize, though AbbVie's extensive patent estate for the drug so far has held off biosimilar competition in the US to 2023 in two patent deals with Amgen and **Samsung Bioepis Co. Ltd.**. In Europe, the situation is different, with the first versions of adalimumab expected to enter the market in October 2018.

Mylan has a biosimilar version of adalimumab in Phase III development with Biocon, but announced a new deal April 11 with **Fujifilm Kyowa Kirin Biologics Co. Ltd.** for an adalimumab product that could get to the market faster.

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Mylan Looks To Expedite Biosimilar Humira in EU Through Kyowa Deal: **https://bit.ly/2HHAz1K**

How Is Pharma Spending Tax Savings? Not On Drug Pricing, Sen. Booker Says

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New Jersey Senator Cory Booker issued a report on April 10 noting that 10 big pharma and biotech companies have decided to use their windfalls from last year's tax reform legislation for stock buybacks and other investments rather than reducing the prices for their drugs.

On the same day, **Pfizer Inc.** and **Amgen Inc.** both announced significant infrastructure investments, in line with how the companies have said they will spend some of the increased cash on hand.

Booker's report did not offer any suggestions for how pharma companies might use their tax savings to offset high drug prices and didn't acknowledge that other industries haven't been asked to use the money they've saved to cut the costs of their goods and services.

However, it detailed various drug price increases for 2018. Pfizer, for instance, raised prices – before rebates and discounts negotiated with payers – for 116 products by 3%-9.5% in late 2017 and early 2018. Several companies, however, recently have disclosed either flat or small increases or small decreases after rebates and discounts.

The report did note that the biopharma industry's investments in stock buybacks outpace other sectors, while also conceding that some biopharma expenditures will benefit employees, fund research and development, and create new jobs.

President Donald Trump and the Republican-led Congress promised sweeping tax reforms late last year and delivered the Tax Cuts and Jobs Act in December. The legislation benefited corporations in many ways, including a reduction in the corporate tax rate from 35% to 21%, a repeal of the alternative minimum tax, and changes in the way that companies report and pay taxes on foreign profits and cash, making it less costly to spend overseas cash in the US.

Pharma's investments in buybacks, capital expenditures, employees (via wages, bonuses and pensions), R&D, business development and donations are funded by some significant tax cuts, but probably even more so by bringing cash home from overseas (*see table below*).

TAX REFORM'S IMPACT ASSESSED

Booker – a Democrat who has been known as a supporter of the pharma industry, which employs hundreds of thousands of people in New Jersey – said he asked his staff to put together a report on how biopharma companies plan to spend their tax savings as part of his effort to assess the impact of tax reform "on working families, including patients struggling to afford their prescription medications."

The Senator's staff looked at various media, analyst and government reports as well as the fourth quarter 2017 earnings conference

Top 10 US Biopharma Companies' Projected Tax Rate Cuts And Cash Held Overseas

COMPANY	EFFECTIVE TAX RATE CHANGE 2017-2018 *	EX-US CASH END OF 2016 +	% OF TOTAL CASH HELD OVERSEAS +
Pfizer	Reduced from 20% to about 17%	$22.5bn	90%
Merck	Estimated at 19%-20% versus 19.1% in 2017 (22% in 2016)	$21.9bn	85%
J&J	Projected range of 16.5%-18% versus 17.2% in 2017	$41.3bn	96%
Gilead	Down to 21%-23% from 24.5% in 2017	$27.4bn	85%
AbbVie	9% in 2018, but increasing to 13% over the next five years, but much lower than 18.9% in 2017	$7.4bn	90%
Amgen	Lowered to 14%-15% from 18%	$35.9bn	94%
Bristol	Fairly static at 20%-21% versus 21%	$8bn	88%
Lilly	Falling from 20.5% to 18%	$9.8bn	87%
Celgene	Rising to about 18% from 16%	$6.1bn	77%
Mylan	17.5%-19% versus 18% in 2017	NA	NA

Sources: *Earnings statements and conference call transcripts. +Credit Suisse analyst note from Nov. 29, 2017 (Mylan was not included).

call transcripts for the 10 large US-based biopharma companies: Pfizer, Amgen, **Merck & Co. Inc.**, **Johnson & Johnson**, **Gilead Sciences Inc.**, **AbbVie Inc.**, **Bristol-Myers Squibb Co.**, **Eli Lilly & Co.**, **Celgene Corp.** and **Mylan NV**.

The report cites a Morgan Stanley analysis projecting that US companies across industries will spend 43% of their tax savings on stock buybacks. And while an estimated $200bn has been committed to stock buybacks this year by businesses of all types, five of the top 10 biopharma companies have said they will spend a combined $45bn to repurchase shares.

PhRMA said the companies 'cherry-picked for inclusion' in Booker's report 'committed at least $23bn to research and development and capital projects, such as new US manufacturing facilities that will drive domestic economic development and job growth and billions more to unspecified projects'

Pfizer, Merck, AbbVie and Amgen committed $10bn each for buybacks, and Celgene said it would spend $5bn to buy its stock. But while J&J was more focused on dividends than share repurchases, Bristol-Myers and Mylan emphasized buybacks announced in 2017, while Gilead and Lilly said they plan to repurchase shares, but did not provide specifics.

Booker's staff also noted that the top 10 companies announced plans to spend tax savings and repatriated cash on pensions, bonuses and salaries for current employees as well as on acquisitions, debt reduction, capital projects, R&D and charitable contributions.

BIOPHARMA EXPENDITURES BEYOND BUYBACKS

Among companies that provided specifics for such expenditures, Merck announced $12bn will be spent over five years on capital projects plus other business development, R&D, employee and Merck Foundation expenditures. Pfizer committed $5bn for its capital projects in the US over five years as well as $500m for the company's US pension plan, $100m for one-time bonuses to non-executive employees and $200m for the Pfizer Foundation.

Also, AbbVie revealed $2.5bn will go toward capital projects plus $350m in charitable contributions, $750m for its pension fund, and additional spending on employee compensation and R&D. Amgen committed $3.5bn for capital expenditures (with 75% spent in the US), $300m for Amgen Ventures, $100m for the Amgen Foundation and other funding for wages, business development and R&D. Lilly said it would spend $2bn to reduce its debt, but didn't provide specifics about plans to bolster investments in its existing assets and future business development.

Amgen, which announced plans to construct a next-generation biomanufacturing facility in Rhode Island on April 10, told *Scrip* when asked about the same-day Booker report suggesting pharma companies spend their tax windfalls on drug price decreases that: "Amgen is committed to working with the Administration, Congress and the entire health care community to continue to find ways to promote innovation and bring medicines to patients that address some of the world's most serious diseases."

The company noted that its first-of-its-kind biomanufacturing facility – funded by money freed up by tax reform – will create "approximately 150 additional highly-skilled manufacturing jobs and approximately 200 construction and validation jobs."

Pfizer also announced a big capital expenditure on April 10 when it said the company signed a 20-year lease for 15 floors in The Spiral, an office building under construction in New York City. Pfizer's plan to relocate its headquarters from a building it owns and intends to sell was first revealed in September 2016, a Pfizer spokeswoman told *Scrip*, noting that the move will provide "an improved, more modern and more collaborative work environment for colleagues."

The Pharmaceutical Research and Manufacturers of America (PhRMA) said the companies "cherry-picked for inclusion" in Booker's report "committed at least $23bn to research and development and capital projects, such as new US manufacturing facilities that will drive domestic economic development and job growth and billions more to unspecified projects. This investment builds on the 376,000 jobs supported directly and indirectly by the biopharmaceutical industry in New Jersey alone."

PhRMA noted the "billions in commitments" for bonuses, salaries and pensions as well as investments in venture capital, R&D, business development and charitable contributions, "including increased aid for rebuilding Puerto Rico." The industry group also pointed out that Booker's assessment did not capture billions more in US investments publicly reported by biopharma companies excluded from the report.

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Pfizer Advances Duchenne Drug As It Prioritizes Gene Therapy

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Pfizer Inc. is stressing its commitment to the development of gene therapy for rare diseases by moving a Duchenne muscular dystrophy candidate into the clinic, after distancing itself from development of the portfolio it had built around allogeneic chimeric receptor T-cell (CAR-T) cellular therapies.

Pfizer recently announced the transfer of CAR-T assets gained in 2014 and 2015 from **Cellectis SA** and **Servier SA** to the start-up **Allogene Therapeutics Inc.** The new company debuted April 3 with a portfolio of 17 off-the-shelf CAR-T candidates obtained from Pfizer, including the Phase I candidate UCART19, and management from former CAR-T pioneer **Kite Pharma Inc.**. Pfizer notes that it will continue to participate financially and strategically in the development of the CAR-T portfolio through a 25% ownership stake in Allogene, as well as by holding two seats on the company's board of directors.

On April 12, Pfizer, announced the start of a Phase Ib study of its mini-dystrophin gene therapy candidate, PF-06939926, in boys with Duchenne muscular dystrophy (DMD), a genetic disorder caused by a lack of the dystrophin protein that causes muscle degeneration.

Pfizer's candidate is a recombinant adeno-associated virus vector serotype 9 (AAV9) based capsid that carries a truncated or shortened version of the human dystrophin gene (mini-dystrophin) under the control of a human muscle specific promotor.

Pfizer noted that the trial is the first recombinant adeno-associated virus vector-based gene therapy program to enter the clinic following the company's 2016 acquisition of **Bamboo Therapeutics Inc.**, through which it gained candidates for neuromuscular diseases.

The candidate is differentiated from other drugs developed for Duchenne in that it provides a correct copy of the mini-dystrophin gene, which addresses the underlying cause of disease for patients broadly, Bob Smith, senior vice president for Pfizer Innovative Health's global gene therapy business for rare diseases, explained in an interview.

The study will involve a test of a single intravenous infusion of the candidate in 12 ambulatory boys aged 5 to 12 years with DMD. The trial will run at up to four clinical research sites in the US, and early data are expected in the first half of 2019, after all patients have been evaluated for a full year post-treatment.

"In addition to evaluating safety and tolerability, the study will evaluate measurements of dystrophin expression and distribution, as well as assessments of muscle strength, quality and function. As part of the screening process, potential candidates for treatment will be tested to confirm a negative result for antibodies against the adeno-associated virus serotype 9 (AAV9) capsid and for a T-cell (immune) response to dystrophin," the company said.

A BIG PLAYER

Pfizer notes that it has invested to create end-to-end capabilities to design novel AAV vectors and to build capacity to manufacture gene therapy products, including a $100m investment in an expansion of a manufacturing facility in Sanford, N.C. to allow commercial development of gene therapies.

The big pharma has been investing in both gene therapy and rare disease research. The DMD program is part of Pfizer Innovative Health's rare disease unit, which includes therapies for hematology, neuroscience, and inherited metabolic disorders. With understanding of genetic defects, the company is prepared to use its gene therapy platform to fundamentally address causes of these rare monogenetic diseases; rather than treating a symptom or manifestation of disease, it can directly address the underlying cause and hopefully restore those patients to a normal physiologic state, Smith said.

Pfizer is partnered with **Spark Therapeutics Inc.** on the Phase I/II PF-06838435, a gene therapy derived from an adeno-associated virus that is designed to deliver the human coagulation factor IX gene (AAV8-hFIX19 vector) to liver cells in patients with hemophilia B, per a 2014 deal. The company is also partnered with **Sangamo Therapeutics Inc.**'s on a Phase I/II hemophilia A gene therapy program and preclinical program in amotrophic lateral scelerosis.

Research suggests potential for gene therapy in ocular disease, hematologic indications and now more complicated neuromusculoskeletal and central nervous system diseases, Smith noted.

"We think this is very exciting field of science and its highly innovative and hopefully the early successes seen with more advanced clinical programs will lead to further investment by companies like ourselves and across the field to continue to potentially develop these potentially transformative therapies for patients," the exec said

According to an analysis by Datamonitor, Pfizer was one of the most active big pharmas in terms of gene therapy partnering deals sealed between 2012 and 2017.

At $645 million, Pfizer's 2016 acquisition of Bamboo Therapeutics for recombinant adeno-associated virus vectors for neuromuscular diseases ranked third in value during that period.

The biggest deal was **Shire PLC**'s unsolicited August 2015 purchase of **Baxalta Inc.**, valued at $30bn, which gave it access to the factor VIII gene therapy SHP654 for hemophilia. The second largest deal in the space was **Gilead Sciences Inc.**'s purchase of CAR-T specialist Kite Pharma for $11.9bn in August 2017.

The field of gene therapy has reached a tipping point through the work of academic centers across the globe, through spin-outs of Bamboo Therapeutics and other companies, and with the recent approval of the first gene therapy – Spark's *Luxturna* (voretigene neparovec-rzyl) for a rare inherited type of blindness, Smith said.

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Pfizer's Axitinib Disappoints As RCC Adjuvant Therapy
https://bit.ly/2J9v8la

FDA Reversal Puts Alkermes Depression Drug Back On Track For January Approval

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Alkermes PLC investors woke up to a pleasant surprise April 16 with news the US FDA has accepted a new drug application (NDA) for the company's depression drug candidate ALKS 5461, reversing an earlier refuse-to-file (RTF) action. The FDA's change of heart was made quickly enough to keep the application on the original user fee time clock of Jan. 31, 2019 set by the original submission.

Such a quick reversal is unusual for the FDA, particularly for an RTF, which generally suggests something is fundamentally missing from the submission. In this case the RTF, announced April 2, surprised many investors because management had been talking confidently about FDA acceptance and approval. CEO Richard Pops sounded downright blindsided by the RTF on a call with investors the day it was announced.

Alkermes' stock tanked on the news, dropping 33% to close April 2 at $45.23, after management said the RTF cited insufficient evidence of efficacy for ALKS 5461 and the FDA requested additional clinical trial data. The expectation was that the delay would be quite lengthy, a significant setback given that several drugs are in late-stage development for depression.

With the positive turn of events, Alkermes regained some ground, opening 12% higher at $47.77, though investors probably still are questioning what the FDA's waffling means for the review ahead. In the case of this decision, investors only get to hear the company's perspective on the change, as the FDA does not comment on pending applications. Alkermes closed up 4% at $44.43.

ALKS 5461 is under review for major depressive disorder in patients with an inadequate response to standard antidepressants. ALKS 5461 is a novel oral medicine that acts as an opioid system modulator. It is a fixed-dose combination of the partial mu-opioid receptor agonist and kappa-opioid receptor antagonist buprenorphine and the mu-opioid receptor antagonist samidorphan.

Late-stage drug development is heating up in depression, with several new mechanisms of action headed toward regulatory filing. Among them are **Johnson & Johnson**'s esketamine for treatment-resistant depression and **SAGE Therapeutics**' brexanolone for postpartum depression.

One of the things that was surprising about the RTF is that ALKS 5461 had a fast track designation from FDA, which is granted for drugs that treat serious conditions or address unmet medical needs and means Alkermes had lots of opportunities to communicate with the FDA about the content and timing of the submission.

At the same time, the registration strategy was considered risky by some investors, because it was based on the results of a single Phase III trial after two prior Phase III trials had failed. Alkermes initiated a rolling NDA submission for '5461 in August 2017, while a second Phase III trial is ongoing.

"We welcome this action by FDA," Pops said in an April 16 call with investors. "When we received the RTF, it was immediately apparent to us – the stated basis for the refuse-to-file was inconsistent with the content of the NDA and our prior interactions with the agency."

He added, "We were hopeful that these differences could be resolved following conversations with them, and to FDA's credit that is precisely what occurred."

HURDLES TO COME

While Alkermes might be back on the original user fee timeline, it still has plenty of hurdles to jump over before ALKS 5461 reaches the market. Investors are likely to remain skeptical until there is more clarity from the FDA. The drug also is expected to face an FDA advisory committee review in the fourth quarter, the company indicated.

Barclays analyst Douglas Tsao noted in an April 16 research note that the review still could be challenging. "Given the political nature of the current FDA administration, we could see a scenario where normal-course review for ALKS 5461 felt more 'appropriate' than controversy raised by an RTF, especially considering the product's fast track designation and medical need for innovation within the indication," he said. "However, we continue to feel Alkermes is long from out of the woods on ALKS-5461 and will need to continue to engage with FDA during review with potential for the ongoing Phase III to play a role in any potential approval decision."

Credit Suisse analyst Vamil Divan said he was originally optimistic on the approval based on the positive pooled analysis of the three Phase III trials and the fast track designation, but changed his launch timeline forecast to 2022 following the RTF. Now, in an April 16 note he said, "this sudden turnaround from the FDA re-instills some of our confidence, but we acknowledge that is an unusual situation."

As Pops explained it, the RTF was triggered by "facial deficiencies" in the application, meaning missing information or clear inadequacies: insufficient evidence of overall effectiveness and inadequate bridging data between ALKS 5461 and the reference drug buprenorphine. He said the FDA was misguided on both accounts.

Pops noted that the question on insufficient evidence did not reflect a complete understanding of the NDA submission, so "we directed FDA to the relevant information in the NDA." As for the bridging issue, Pops said that was addressed in a pre-NDA meeting with the FDA and addressed in the submission. "We raised this with FDA and they agreed that this is not the basis for an RTF," he said. "Both of these issues will be addressed within the context of the review." Alkermes confirmed that it did not file the NDA over protest, which is something the FDA's guidance permits if a sponsor wants to proceed with a filing despite FDA objections.

It's unusual for the FDA to reverse a RTF decision, though this is the second time it has changed course in the last year under an FDA Commissioner that is considered more industry-friendly. Last July, the FDA rescinded its decision on **Amicus' Therapeutics**' migalastat, an oral drug for Fabry disease, after originally saying the application required a new 12-month gastrointestinal study. However, in this instance, there were eight months between when the RTF was announced and reversed.

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FDA Asks For Third Phase III Trial On RGN-259

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Although the FDA has accepted all safety data from two Phase III trials of dry eye treatment candidate RGN-259, the agency wants the drug's backers to conduct an additional Phase III trial to further demonstrate its efficacy, a requirement that will push back its prospects for approval in treating a condition with high unmet medical need that affects more than 344 million patients globally.

The RGN-259 setback was announced on April 9 by **RegeneRx Biopharmaceuticals Inc.** and South Korea's **GtreeBNT Co., Ltd**, who are jointly developing the candidate therapy in the US and Canada for ophthalmic indications through their **ReGenTree LLC** joint venture.

News that an additional Phase III trial is needed follows the release in November of mixed results from ReGenTree's second pivotal Phase III clinical trial (ARISE-2) in the US of RGN-259 for the treatment of dry eye.

ARISE-2 was not successful in duplicating the results of ARISE-1, where the study population was limited and less diversified and the mixed results fanned doubts over whether RGN-259 would be approved for the general dry-eye population.

ARISE-3 TO START THIS YEAR

Those doubts will grow after news that the FDA wants an additional Phase III evaluation done for RGN-259 before it can progress further down its planned regulatory pathway.

"Although the FDA is requiring an additional Phase III trial (ARISE-3) to further demonstrate efficacy in both signs and symptoms of dry eye in a larger patient population, all safety data from ARISE-1 and ARISE-2 were accepted by the FDA; no additional nonclinical efficacy and safety studies are required by the FDA, and the company's chemistry and manufacturing control plans for the drug substance and drug product were considered complete and acceptable for NDA submission," ReGenTree's CEO Won Yang said in a statement, adding: "ReGenTree is now planning to initiate the ARISE-3 trial this year."

RGN-259 is a sterile, preservative-free eye drop formulation manufactured using blow-fill-seal technology that has as its active pharmaceutical ingredient the novel compound thymosin beta 4 (TB4), a 43-amino acid peptide occurring naturally in all tissues.

There are two main types of dry eye disease: aqueous tear-deficient dry eye where the lacrimal glands fail to produce enough of the watery component of tears to maintain a healthy eye surface; and evaporative dry eye which may result from inflammation of the glands that produce the lipid or oily part of tears needed to slow evaporation and keep the tears stable.

Dry eye disease is currently treated mainly with artificial tears, corticosteroid drops, cyclosporine drops, or tear-stimulating drugs, like cholinergics.

In the US, there are only two main prescription drugs currently approved for dry eye disease: **Allergan PLC**'s *Restasis* (cyclosporine) and *Xiidra* from **Shire PLC**. The number of available therapies does not increase drastically outside the US, analysts say.

ReGenTree said it would be attending upcoming ARVO (The Association for Research in Vision and Ophthalmology) 2018 annual meeting on April 29-May 3 in the US "to work with key opinion leaders as well as meet with potential strategic partners."

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Sanofi Underpins Vaccine Strategy With New Manufacturing Facilities

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Following a €170m ($209.4m) expansion of a French manufacturing facility last year, **Sanofi** has now announced it is to spend Can$500m (US$397m) on the expansion of a Canadian vaccines manufacturing facility, underpinning the big pharma's commitment to vaccines, that includes seasonal flu vaccines and a roster of new potential vaccines in development.

The new Toronto facility will be one of Sanofi's largest-ever investments in a single building, and will increase the company's capacity to meet the growing demand for pediatric and booster vaccines, the company announced on Apr. 12. The building will take place at the Canadian headquarters of Sanofi's vaccines business unit, **Sanofi Pasteur**, in Toronto.

The facility will be able to produce antigens used in diphtheria and tetanus vaccines, and a five-component acellular pertussis (5-acP) antigen. Vaccines accounted for around 15% of Sanofi's sales in 2017, at €5.1bn, and exhibited growth of around 14% at constant exchange rates compared with those in 2016.

Sanofi also has a number of new potential vaccines in its R&D pipeline, including a recombinant subunit tuberculosis and a AIDS/HIV vaccine in Phase II, and a herpes simplex virus type 2 (HSV-2) vaccine and a respiratory syncytial virus (RSV) vaccine in Phase I.

Additional indications are being sought for a high-dose quadrivalent inactivated flu vaccine (*Fluzone QIV HD*), and, in the US, for a pediatric hexavalent vaccine (DTP- HepB-Polio-Hib), in infants.

However, in December Sanofi ended the development of a *Clostridium difficile* vaccine, after interim analysis of a Phase III trial indicated that the study had a low probability of meeting its primary objective.

In Oct. 2017, Sanofi Pasteur said it would expand a vaccine manufacturing facility in Val de Reuil, France, to supply the quadrivalent seasonal flu vaccine, *VaxigripTetra*. The vaccine contains two A strains (A/H1N1 and A/H3N2) and two B strains (B/Victoria and B/Yamagata) of influenza virus, as recommended by the WHO. The French facility will be completed in 2021 and will start producing vaccines in 2022.

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Orchard To Use Divested GSK Rare Disease Gene Therapies To Grow Globally

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Orchard Therapeutics says it will benefit hugely from **GlaxoSmithKline PLC**'s decision to sell its rare disease portfolio to the three-year old UK biotech, and that its gene therapy programs will remain unencumbered by the 19.9% equity stake and board position that GSK will receive in return.

Britain's biggest drug maker said on April 12 that it would transfer its rare disease gene therapy drugs to privately held Orchard Therapeutics, making good on the promise made last July by GSK CEO Emma Walmsley to reduce GSK's pharmaceuticals portfolio and launch a consequent review of its rare disease unit.

The transaction includes the transfer to Orchard of GSK's *Strimvelis*, a gene therapy approved in Europe in 2016 that involves a patient's bone marrow cells being removed and modified outside the body to produce working ADA enzyme. Also included are two late-stage clinical programs in ongoing registrational studies for metachromatic leukodystrophy and Wiskott Aldrich syndrome, and one clinical program for beta thalassaemia.

Orchard will also acquire rights to exclusively license three additional preclinical programs from Fondazione Telethon and Ospedale San Raffaele upon completion of clinical proof of concept studies for mucopolysaccharidosis type 1 or Hurler syndrome, chronic granulomatous disease and globoid cell leukodystrophy.

"Since we announced our intent to review these medicines, our goal has been to identify the right owner who can build on what we've already achieved ... allowing GSK to focus on building its broader cell and gene therapy platform capabilities. Orchard are committed to patient access, and we're confident that this agreement combined with the ongoing relationship between the two companies will support the progression of these valuable programs," John Lepore, GSK's R&D pipeline head said in a statement explaining the move.

TRANSFORMATIONAL

Mark Rothera, CEO of Orchard Therapeutics, said he was thrilled by what the transaction promises for his young company, which was launched in 2015.

"This will transform us and accelerate our strategy to become a global, fully integrated biotech, from R&D, through to manufacturing and commercialization," Rothera told *Scrip*.

"Bringing in those GSK assets, it's a perfect fit because both companies have been using the *ex vivo* gene therapies platform and they dovetail together really well," he said in an interview.

Under the deal, GSK will receive a 19.9% stake in unlisted Orchard and get a seat on its board. GSK will also receive financial considerations in the form of royalties and commercial milestone payments related to the acquired portfolio.

"This deal is a win-win for both Orchard and GSK. We can expand our portfolio and it was important for GSK to transition these programs into a safe pair of hands – to a company like us with the right capabilities."

The deal's structure also meant Orchard did not need to use its financial resources buying GSK's rare disease portfolio.

"It certainly helped that our deal included an equity stake and future royalties and milestones down the road, and so we can invest our resources – our cash – into the operations of making these programs move forward in the clinic and then to regulatory filings," Rothera said.

Asked whether the GSK executive on Orchard Therapies' board might potentially cause problems, Rothera replied, "GSK are not going to have a controlling interest with their equity stake. It's all part of shepherding these assets in a thoughtful way from GSK through to Orchard and just having some oversight – but it's not a controlling oversight."

The future GSK board member has yet to be determined. "GSK will be confirming a nomination in due course," Rothera said.

GSK NOT TRANSFERRING STAFF TO ORCHARD

GSK said it would not be transferring R&D staff to Orchard along with the gene therapy portfolio.

"GSK will seek to redeploy staff within GSK. Throughout the process to identify a new owner for these programs, we've continued to progress ongoing activities and these same employees are likely to be part of the transition team working alongside Orchard to ensure the smooth transfer of the projects," a spokesperson for the company said..

The deal with Orchard doesn't mean GSK will completely stop investigating therapies for rare disease, the company added.

"We actually have a couple of assets targeting rare diseases in the pipeline, for example a serum amyloid P component (SAP) monoclonal antibody plus SAP deplete (CPHPC) for amyloidosis. But this deal does complete the sale of assets from GSK's Rare Disease Unit," the spokesperson said.

The transition activities involved in the transaction are to be complete by the end of 2018.

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Cellectis Collects $164m For CAR-T

French biopharma **Cellectis SA** is planning to invest about $100m to establish commercial capabilities, including a state-of-the art gene-edited cell manufacturing plant for commercial supplies of its UCART portfolio.

A further $20m is being earmarked to fund the advancement of one additional UCART candidate, while about $30m will be used to pursue new therapeutics, based on its proprietary gene-editing technology, outside the oncology field.

Fully Underwritten

The follow-on offering of 5,646,000 ADS at $31 each (grossing $175m) was fully underwritten by Goldman Sachs, Citigroup Global Markets, Barclays Capital, Nomura Securities International, Oppenheimer, and Ladenburg Thalmann.

The underwriters have up to 3 May an option to purchase an additional 846,900 ADS. If the over-allotment is fully exercised, Cellectis could see its take rise to just over $188m.

Three Programs

Cellectis expects by the end of 2018 to have three off-the-shelf CAR-T product candidates – its wholly-owned UCART123 and UCART22 programs plus UCART19, which **Servier SA** has global rights to develop and commercialize, in the clinic.

Cellectis has plans to file an IND for UCARTCS1 in multiple myeloma probably in 2019.

UCART123 is being tested in patients with acute myeloid leukemia (AML) and blastic plasmacytoid dendritic cell neoplasm (BPDCN). UCART22, which is designed for the treatment of B-acute lymphoblastic leukemia (B-ALL) and B-Non-Hodgkin lymphoma (B-NHL) is pre-IND. UCART19 is initially being developed in acute lymphoblastic leukemia (ALL).

mike.ward@informa.com, 12 April 2018

Eased Tensions On Korean Peninsula To Fuel Botanical Drug R&D?

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The herbal-derived drug sector is set to become an initial beneficiary once South Korea's relationship with North Korea improves, as the South is aiming to make use of its communist neighbor's abundant natural resources by jointly conducting research on natural products and herbal-derived drugs to beef up its global competitiveness in these sectors.

If the latest planned cooperative project is actually launched based on eased tensions on the peninsula, it is poised to help South Korea secure herbal drug materials, which are currently mostly imported and form an important component of medicine in the country. This is likely to help the South deal with the implementation of the Nagoya Protocol (governing access to genetic resources and the sharing of their benefits) and help it to replace biological resources from overseas, said South Korea's Ministry of Science and ICT.

Traditionally, South Korea has been actively using natural products in oriental medicine and folk remedies, but there have been limitations due to weak scientific studies in this sector and a lack of standardization of raw material ingredients.

GROWING GLOBAL DEMAND

Demand for human body-friendly natural products is rising worldwide amid an increase in chronic diseases and worries over harmful chemical substances. As a result, the global natural products market, including herbal-derived drugs and functional health foods, is emerging as a promising sector with an annual growth rate of more than 7%.

Although South Korean herbal-derived drugs have been performing relatively strongly in the country, they haven't made any significant progress in global markets in the past. However, **Dong-A ST Co. Ltd.**'s recent sizable global deals for its botanical-derived drug pipeline assets, as well as the increasing global market presence of South Korean natural product-derived cosmetics, have sparked official expectations for the potential global success of Korean natural products.

The South Korean ministry may have also picked natural products and herbal-derived drugs as the first planned joint study project with the North as doctors there are known to be widely practicing oriental medicine and herbal folk remedies, given the North's limited capabilities in, and access to, synthetic medicines. According to data from South Korea's Unification Ministry, North Korean doctors mostly use oriental (herbal) medicine to treat diseases, particularly chronic disorders, although they also sometimes use Western drugs.

North Korea is known to severely lack regular drug supplies and to suffer from regular outbreaks of uncontrolled infectious diseases.

POLITICAL CONSIDERATIONS

However, given sensitive political considerations, "The joint study with North Korea will only proceed if the relationship improves," an official at the Ministry of Science and ICT told *Scrip*. "If this project is launched, the government will proceed this with academia, industry and research institutes [in North Korea]. We want them to actively participate in this project."

However, aside from the potential cooperation in the herbal-derived drug area, it is difficult to talk about other possible joint plans with the North in the medical/pharma sector at this point, the official added, alluding to the broader political situation.

However, North Korean leader Kim Jong Un has sharply ramped up international diplomacy in recent months, and appears to be reaching out to potential allies with a recent trip to China, for instance. Kim is slated to meet with South Korean President Moon Jae-In on April 27 and with US President Donald Trump in May or June, raising hopes that there could be a positive outcome from the meetings that will ease relationships with the reclusive communist nation.

"If the joint study is conducted in the natural product sector, this will be positive in terms of usage and research of new types of natural substances," Dong-A ST's PR repre-

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sentative told *Scrip*, adding that the company will review participation in the joint study going forward.

The South-North joint study plan is part of the so-called "natural product innovation strategy for the Korean peninsula," announced by the Ministry of Science and ICT. Under the strategy, the South's government aims to develop 10 global-level natural products, including herbal-derived drugs and functional health foods, and to double the country's share in the global natural product market to 4% by 2022 from 2.2% in 2017, to buoy the value of natural products that exist on the peninsula.

The strategy is a follow-up measure to the ministry's third biotechnology nurturing plan unveiled last year, which aims to create five South Korea-developed global blockbuster drugs and sharply raise worldwide licensing out deals by 2025.

For the planned North-South program, the aim is to obtain about 4,000 types of traditional natural substances that exist on the Korean peninsula, and the South Korean government will designate a big data center for natural products to set up integrated databases including on the ingredients, structure and origin of usable natural products. North Korea is estimated to have more than 1,000 types of traditional natural substances of interest.

The South Korean government plans to seek the joint move in stages, once conditions such as the political relationship are appropriate, and to jointly conduct research on natural products with little scientific research but high potential value. South Korea will develop a screening system that can quickly analyze ingredient composition and content of the substances. It will also develop an artificial intelligence platform that can predict the natural product's mechanism of action in the human body, using big data based on papers and patents, then in the safety confirmation and evaluation stage, set up technology such as animal models that can scientifically prove the natural product's safety.

To create the innovative growth ecosystem in which companies, research institutes and colleges can collaborate, the South's government will set up a group with joint expert participants in each sector. South Korea also plans to seek joint research programs that links promising natural product materials to actual product development and supports the basic technology essential to commercialization and standardization.

The latest plan, if realized, could help reinvigorate South Korean domestic pharma and biotech companies' R&D activities in herbal-derived drugs, which haven't generated significant progress in global markets aside from the recent licensing deal reached by Dong-A ST.

In January, the company licensed out its botanical drug candidate for diabetic neuropathic pain, and also sold its botanical drug program for Alzheimer's disease to Boston-based NeuroBo Pharmaceuticals.

Dong-A also has a botanical-derived drug candidate, DA-9805, for Parkinson's disease, which is in Phase II clinical trials in the US.

Although there aren't many Korean companies that focus mainly on developing herbal-derived drugs, multiple companies such as Enzychem Lifesciences Corp. and **ViroMed Co. Ltd.** are progressing herbal-derived drug pipelines.

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From the editors of PharmAsia News.

Daiichi Demands Fortis Sale Block Until Singhs Pay

PENELOPE MACRAE

Daiichi Sankyo Co. Ltd. has asked the Delhi High Court to stall the proposed sale of Fortis Healthcare's hospital business to Manipal Health Enterprises Private Ltd until Malvinder Singh and Shivinder Singh pay $550m owed to the Japanese company from a Singapore arbitration panel's award two years ago.

Manipal's planned takeover, backed by US private equity firm TPG Capital, would be the biggest merger in India's fragmented healthcare space. Fortis is already India's second-largest hospital operator with 34 hospitals. Including Manipal's 14 hospitals, the sale would create India's largest hospital business by revenue, overtaking leading operator Apollo Hospitals Enterprise Ltd, which has 71 hospitals. The combined group would have annual revenue of INR54bn ($831m) as well as 11,000 beds compared with Apollo's 4,550.

The sale could also help close a difficult chapter in the 17-year history of loss-making Fortis, whose founders, the Singh brothers, are mired in allegations of financial fraud. But Daiichi told the Delhi High Court that Fortis' sale would mean disposal of a "key asset" and that this could hurt the Japanese company's ability to obtain the arbitration award from the debt-laden Singhs, who are the former owners of Indian generic heavyweight Ranbaxy.

The Singapore arbitration tribunal awarded the compensation to Daiichi after concluding the brothers hid vital information about the seriousness of a US probe into drug test fraud at Ranbaxy when they sold their stake to the Japanese company for $2.4bn a decade ago. The brothers, third-generation scions of a respected Indian business family, deny all wrongdoing.

The Delhi High Court asked Fortis on April 5 to submit a "counter-affidavit" in response to Daiichi's bid to block the sale until the Singh brothers pay up. The court set the next hearing for April 25.

Meanwhile, the brothers are appealing to the Singapore High Court the award by the International Court of Arbitration in Singapore. Arguments in that case were scheduled to be heard from April 9 to April 13. The Singhs have exhausted all legal avenues in India to avoid paying the arbitration award.

Daiichi's court case comes after the Fortis board approved the demerger of its hospitals business late last month to Manipal Health, which is led by Indian medical doctor and serial investor Ranjan Pai. The complex two-stage deal is due to be put to Fortis shareholders in the coming month. Manipal is currently India's fourth-largest private hospital group.

Daiichi asked the Delhi High Court to order the Singhs to deposit the arbitration award amount with interest and costs before "concluding any scheme of restructuring/transaction involving Fortis Healthcare." In addition, Daiichi has written to the Securities and Exchange Board of India, the coun-

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Vectura's Ward-Lilley On Re-Focusing On The Respiratory Sector

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UK respiratory specialty company **Vectura Group PLC** is aiming to develop a pipeline of new inhaled generic products that CEO James Ward-Lilley believes will deliver significant value over the years to come, including proprietary nebulized products and generic versions of **AstraZeneca PLC**'s *Symbicort* (budesonide/formoterol), **Boehringer Ingelheim GMBH**'s *Spiriva* (tiotropium) and **GlaxoSmithKline PLC**'s *Ellipta* portfolio, as well as the delayed generic version of GlaxoSmithKline's *Advair* (fluticasone/salmeterol), VR-315.

Vectura announced in the middle of last month that it had started development of generic versions of the Ellipta portfolio using its "Open-Inhale-Close" dry powder inhaler device, which has the potential to be used for AB-rated substitutable generics. Formulation work has started with the device, along with partnering discussions.

Such products are indicative of Vectura's refocus of its investment strategy on developing advanced generics products, and not taking on the development of high-risk early stage novel molecules, as announced at the beginning of this year. "Our strategy hasn't changed, but our investment focus has," Ward-Lilley said in a recent interview.

Instead of improving formulations of novel biotech products, or developing drug delivery devices for such new molecular entities, our "real sweet spot is found where we combine drug formulation of existing molecules with device design and our development expertise," Ward-Lilley said. "The risk profile is lower and financial return is better than entering lots of early stage NME deals that tie up the company's resources and have a lower probability of success." As a consequence of its decision to pull back from its existing NME work, it is seeking partners for its early stage novel molecule programs, including the kinase inhibitor VR588 and its co-development inhaled IL-13 biologic program.

Ward-Lilley continues to see significant market opportunities in the complex inhaled US drug-device generics market, where there are still no AB-rated directly substitutable generic devices. "It's a significant commercial opportunity, and a large patient opportunity as well, that should improve patient access to cost-effective therapies," he said. "There are also barriers to entry that include the cost of doing clinical studies and of manufacturing devices, and having the technical wherewithal and appetite to develop new inhaled substitutable generic products."

Of course, Vectura has had its own setbacks to contend with in this sector, particularly in the development of VR-315, a potentially AB-rated substitutable generic version of GlaxoSmithKline's Advair in the US, but Vectura and partner **Hikma Pharmaceuticals PLC** are not alone in this regard – similar setbacks with other potential Advair generics for the US are being experienced by other companies.

"Our experience with VR-315 has been disappointing and protracted," Ward-Lilley noted. But, he added, now "we know exactly what the FDA found to be an issue and therefore we are confident that the new study can be executed quickly and the data considered appropriate." The UK executive was referring to the March 2018 decision by the US FDA's dispute resolution process confirming the need for a second clinical endpoint study with VR-315 to be conducted. The clinical study is being started by Hikma, and data are expected to be submitted to the agency in 2019, with launch of the product, if approved, due in 2020.

There are positives to be drawn from the experience, according to Ward-Lilley. "We have gained insights and more confidence about the next wave of generic opportunities," he claimed. That next wave could include generic versions of GSK's Ellipta portfolio, including *Incruse* (umeclidinium), *Anoro* (umeclidinium/vilanterol) and *Trelegy* (umeclidinium/vilanterol/fluticasone), whose patent protection could start to run out in the mid-2020s, he added.

In addition, to the new Ellipta portfolio opportunity, continuing in Vectura's R&D pipeline are complex inhaled generics, including VR-2081, partnered with **Sandoz International GMBH**; generic versions of Boehringer Ingelheim's *Spiriva* (tiotropium) and a potential generic tiotropium/LABA product, are also in development, and the subject of licensing discussions.

Vectura is also seeking partners for proprietary nebulized products that are the lead products in a series of "enhanced" inhaled drugs. "A Phase III EU study of a new budesonide nebulizer, VR-475, should be completed by the end of 2018, and the results of a Phase II US study of a pediatric budesonide nebulizer, VR-647, should be available in the second half of 2018, Ward-Lilley noted. Partnering discussions have been started for the two products, and are expected to be completed in 2019 subject to the successful outcome of the ongoing studies.

The budesonide projects both use a desk-based *AKITA Jet* inhaler, with VR-475 being evaluated to reduce exacerbations in adult asthmatics, and to be used as an alternative to high-dose oral steroids and before the use of expensive biologic therapies. VR-647 is being evaluated to reduce treatment time in children in the US. Phase I studies confirmed the potential of VR-647 to significantly reduce the nebulisation time and dose of steroid given to children.

Vectura has also developed a mesh based hand-held *FOX* nebuliser, and the technology has been well received by patients with reductions in daily treatment times of between 45 and 60 minutes, using **Bayer AG**'s *Breelib* (iloprost) for peripheral arterial hypertension, a product launched last year in Germany.

Following-on from progress with these products, Vectura believes there are further opportunities to enhance patient outcomes with known therapies in the respiratory area, using its proprietary nebulisers. "Based on the technology validation seen with Breelib we are now moving forward with feasibility studies with other assets and products," noted Ward-Lilley. Progress in Vectura's pilot studies in this area are expected to be released in the second half of 2018.

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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

Selected clinical trial developments for the week 6–12 April 2018

LEAD COMPANY/PARTNER	COMPOUND	INDICATION	COMMENTS
PHASE III SUSPENDED			
vTv Therapeutics Inc.	azeliragon	Alzheimer's disease, mild	STEADFAST; missed co-primary efficacy endpoints.
Incyte Corp./Merck & Co. Inc.	epacadostat plus *Keytruda* (pembrolizumab)	melanoma, metastatic or unresectable	ECHO-301/ KEYNOTE-252; missed PFS primary endpoint, other studies continue.
PHASE III RESULTS PUBLISHED			
Amgen Inc.	*Prolia* (denosumab)	steroid associated osteo-porosis	*The Lancet Diabetes & Endocrinology*, Apr. 6, 2018.
PHASE III INTERIM/TOP-LINE RESULTS			
AbbVie Inc.	upadacitinib	rheumatoid arthritis	SELECT-COMPARE; met primary endpoint.
Merck & Co. Inc.	Keytruda, first-line monotherapy	non-small cell lung cancer (NSCLC), advanced or metastatic with PD-L1 expression at 1% or higher	KEYNOTE-042; overall survival improved.
Novartis AG	*Cosentyx* (secukinumab)	psoriatic arthritis	FUTURE 4; sustained clinical improvements.
Pfizer Inc.	*Inlyta* (axitinb)	renal cell cancer, adjuvant therapy post-surgery	ATLAS; disease-free survival not extended.
Drugs for Neglected Diseases initiative/Presidio Pharmaceuticals Inc./Pharco Corp.	ravidasvir plus sofosbuvir	hepatitis C with or without cirrhosis	STORM-C-1; high cure rates of affordable combo.
UPDATED PHASE III RESULTS			
Cara Therapeutics Inc.	*Korsuva* (CR845/ difelikefalin)	uremic pruritus	Reductions in itch intensity.
PHASE II INTERIM/TOP-LINE RESULTS			
Menlo Therapeutics Inc.	serlopitant	pruritus in atopic dermatitis	ATOMIK; some signs of improvement.
Therapix Biosciences	THX-TS01 (dronabinol/ palmitoylethanolamide)	Tourette's syndrome	Improved symptoms.
Adynxx Inc.	brivoligide	post-surgical pain	ADYX-004; reduced pain, opioid use.
UPDATED PHASE II RESULTS			
Aeglea Biotherapeutics Inc.	pegzilarginase	arginase-1 deficiency	Clinically relevant treatment effects.
Prometic Life Sciences Inc.	PBI-4050	Alstrom syndrome	Clinical activity.
Wilson Therapeutics AB	WTX101	Wilson's disease	Study 201; long term disease control.
Arrowhead Pharmaceuticals Inc.	ARC-520	hepatitis B	Signs of efficacy, well tolerated.
CymaBay Therapeutics Inc.	seladelpar	primary biliary cholangitis	Positive and sustained effects, well tolerated.
Reata Pharmaceuticals Inc.	bardoxolone methyl	Alport syndrome	CARDINAL; improved kidney function.
Prescient Therapeutics	PTX-200 plus paclitaxel	breast cancer, HER-2 negative	Early signs of efficacy.
Selecta Biosciences Inc.	SEL-212	chronic severe gout	Clinical activity, well tolerated.
Spectrum Pharmaceuticals Inc.	poziotinib	NSCLC, EGFR exon-20 mutant	Preliminary efficacy signs.
Viralytics Ltd.	*Cavatak* (oncolytic virus) plus checkpoint inhibitors	bladder cancer, melanoma, NSCLC	CAPRA, MITCI, STORM, KEYNOTE -200; signs of efficacy.
Innovation Pharmaceuticals Inc.	brilacidin	mucositis	Reduced incidence.

Source: Biomedtracker

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try's market regulator, to block the deal, saying it would violate Indian court orders relating to payment of the settlement.

The arbitration award is the highest ever against Indian nationals, Ananth Pathak, managing partner of P&A Law Offices, which has represented Daiichi in its Indian court battle, told the India Business Law Journal. The case is seen internationally as a test for enforcement of an arbitral award in India, a country widely regarded as a challenging and unpredictable place to do business.

The Singh brothers say the court action by Daiichi to block the sale of Fortis' hospital business is "vindictive in nature to hurt the larger stakeholders of our group."

The new combined company, Manipal Hospitals, would be listed on the Indian stock market. Some 38% would be held by Pai, who's Manipal's chief executive, while TPG would have 20.7%. But the deal, which includes sale of Fortis Healthcare's 20% stake in its diagnostics chain SRL, has left various shareholders unhappy about what they consider to be a low price.

Shares in Fortis, after a steady rise on investors' bid hopes, plunged 13.4% on March 28 to INR123.35 when the sale was announced. But the shares have leapt 15% in the past five days on hopes of another bidder, long-rumored suitor Malaysian giant IHH Healthcare, entering the fray. The shares were flat at INR141.00 on April 10. Indian media reports say the IHH is planning an all-cash counter-offer.

Under the Manipal offer, every Fortis Healthcare shareholder would get 10.83 shares in Manipal Hospitals – the new combined business – for every 100 shares held. Separately, Manipal Health will also buy a 20% stake in Fortis Healthcare's diagnostics unit SRL for INR7.2bn.

Manipal would seek to raise its holding to just over 50% by buying shares from its hospitals business, Fortis would become an investment holding firm and include in its portfolio 36.6% of SRL. Also, under the agreement, the new owners have pledged to infuse INR39bn worth of equity into the combined hospitals business.

Fortis Healthcare chief executive Bhavdeep Singh said taking into account the planned investment by Manipal in the new entity, the deal was valued at INR150bn. But that investment would further dilute the stake of Fortis Healthcare's shareholders in the new company which has stoked investor unhappiness.

India's Mint newspaper has reported some Fortis shareholders, led by India-focused hedge fund Eastbridge Capital, are banding together to oppose the deal. Analysts say even though Fortis swung to a net loss of INR190m in the third-financial quarter to December from a profit of over INR4.53bn a year earlier, shareholders want a sweeter deal.

With a struggling and underfunded public hospital system, India's private-sector healthcare is seen as a lucrative area with consultancy Deloitte projecting the healthcare market will triple in value by 2022 to reach $372bn.

Daiichi's lawyer Arvind Nigam, however, told the Delhi High Court no transaction should be permitted that would "hamper or diminish" the value of Fortis Healthcare Holding and ultimately the valuation of the brothers' holding companies RHC Holding and Oscar Investments. Daiichi's lawyers have said most of the former Ranbaxy owners' assets may be "unrealizable" as they are encumbered by debt.

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LNC Therapeutics, a French biotech company specializing in research and development for gut microbiome-based drugs, has appointed ***Dr. Georges Rawadi*** as its new CEO. His predecessor, ***Jean-Luc Treillou***, will become chairman as of July. Before joining LNC Therapeutics, Rawadi, formerly a researcher at Institut Pasteur, was vice president of business development and intellectual property and a member of the management team at Celyad. Previously, he held various business development positions at Cellectis, Galapagos, ProStrakan and Sanofi-Aventis.

Arjan Roozen has been named chief technology officer at **Zelluna Immunotherapy**, a biotechnology company specializing in T-cell receptor immunotherapies targeting a broad range of solid cancers with a high unmet medical need. Arjan previously headed up the GMP solutions and manufacturing team at Cellectis, the French cell therapy company. Before that he was at CDMO Pharmacell, recently acquired by Lonza, where he was responsible for all operational activities. Zelluna has also appointed Julia Ino as head of project management. She was previously product manager, business development and IP manager at Bone Therapeutics (Belgium).

BC Platforms, a world leader in genomic data management and analytics, has appointed ***Richard Kivel*** as its chairman. Kivel has served as a C-level executive, investor and director in both private and public companies in the biotech, bioinformatics and diagnostics sectors in the US, Europe and Asia, and is currently the managing director at Graybella Capital, a European investment fund.

Alexandra Pearce has been appointed vice president and head of regulatory affairs at the French biotech company, **Abivax** effective May 21. Pearce joins from Viramal, where she served as chief operations officer and head of regulatory affairs. Previously, she held roles as executive vice president and head of global regulatory affairs for Glenmark Pharmaceuticals Ltd.

Pneuma Respiratory Inc. has recruited ***Steven Kesten*** as president and chief medical officer as the company pursues FDA approval for a portfolio of therapeutics targeting asthma and chronic obstructive pulmonary disease. Kesten was previously VP of Respiratory Products at Boehringer Ingelheim GMBH.

The UK-based cell therapeutics company **ReNeuron Group PLC** has recruited ***Richard Beckman*** as chief medical officer. He replaces ***Julian Howell*** who has left the Company to pursue another opportunity. Before joining ReNeuron, Beckman was the chief medical officer of several innovative biotech and device firms, including Clearside Biomedical Inc., OphthoTech Corp. and Neurotech.

Rare disease company **ARVOBIO Inc.** has appointed ***Dr. Annalisa Jenkins*** to its board. Jenkins' former roles include being head of global R&D for Merck Serono and head of global medical affairs for Bristol-Myers Squibb Co. She also served as the CEO of Dimension Therapeutics, Inc., until its acquisition in late 2017. Jenkins will join as an independent director, effective immediately.

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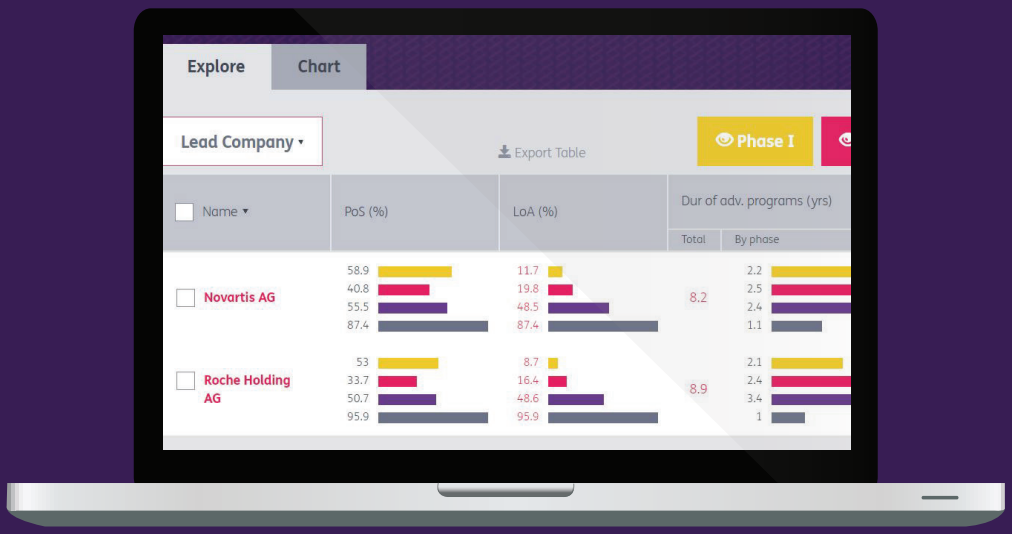

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