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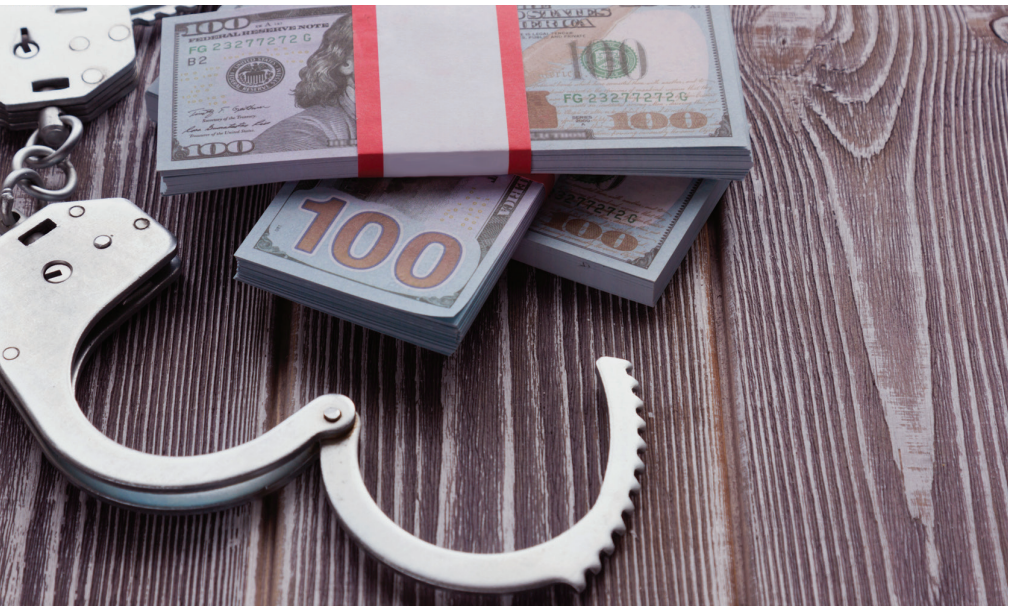

Pfizer Consumer Combo Deal Frees Capital For GSK Pharma Investment

ELEANOR MALONE eleanor.malone@informa.com

The planned all-equity arrangement to combine the consumer health businesses of **GlaxoSmithKline PLC** and **Pfizer Inc.** will create greater visibility around the capital structure for GSK's pharma and vaccines business and ultimately, by de-levering – or reducing the debt ratio of – that business, free up resources to invest in its R&D pipeline. So said GSK's management on an investor call to outline the details of the transaction, which will see the GSK and Pfizer consumer businesses coming together in a joint venture with combined sales of £9.8bn.

The new consumer company will become the leading OTC business globally. *(Also see "GSK And Pfizer Start Consumer JV For Different Reasons, Aim For Similar Goals" - HBW Insight, 19 Dec, 2018.)*

GSK CEO Emma Walmsley noted that the UK big pharma is paying a premium to become the controlling partner in the JV, which will enable it to manage the exit, which GSK is currently envisaging as a demerger of its equity interest to GSK shareholders and a UK listing of the separate consumer business within three years of the closing of the transaction. This will enable the two parts of GSK's business – pharma/vaccines and consumer – "to purse their own long-term strategic and capital allocation priorities" and facilitate the de-leveraging of the pharma/vaccines business.

"Strengthening GSK's pharma business and pipeline is our clear priority," emphasized Walmsley, who noted that the company had assessed Pfizer's consumer business when it was up for sale by auction but had walked away because paying cash did not fit with GSK's capital allocation priorities. CFO Simon Dingemans said the de-levering of the pharma/vaccines business would create "significantly greater flexibility for future investments." This is because, upon separation, the consumer health company with its "more durable cash flows" will be able to take on a higher leverage, enabling a reduction in the leverage of the newly distinct pharma/vaccines business.

Asked if there was a possibility the full demerger could take place before three years were up, Walmsley said it was "important that we take a bit of time to do this right." Having learned from the global integration of the **Novartis AG** consumer business previously "exactly what it takes," she said the consumer business would want to execute the integration "very well whilst at the same time delivering operating performance" first, without "everybody distracted around the notion of a separation." Nevertheless, GSK retains the right to decide exactly when it demerges, whether that be sooner than 2022 or up to five years from the deal closure. It can also decide if it will sell all or part of its JV stake in an IPO. Meanwhile, the larger consumer business will continue to contribute cash flow to pharma pipelines in the interim period.

Walmsley acknowledged that there have been certain synergies with the consumer business that have benefited its pharma/vaccines business, such as the launch of its *Shingrix* vaccine, which took advantage of the consumer busi-

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BROUGHT TO YOU BY THE EDITORS OF **PHARMASIA NEWS**, **START-UP** AND **SCRIP INTELLIGENCE**

Going, Going, Gone
BMA sells consumer arm to Taisho for $1.6bn (p4)

Javelin Misses Mark
Bavencio failure casts shade on treatment for ovarian cancer (p7)

Winner Takes All
China drug price discounts hit international pharma hard (p17)

from the executive editor

alex.shimmings@informa.com

Welcome to the first issue of 2019, where we round up the biggest news to happen over the Christmas and New Year break. Despite the holidays there was no shortage of pharma and biotech news, including a major rearrangement for GlaxoSmithKline and Pfizer's consumer health businesses. The ultimate aim for GSK is to free up capital to invest in its pharma business. CEO Emma Walmsley noted that the UK big pharma was paying a premium to become the controlling partner in the JV, which will enable it to manage its exit. See front cover for more details.

AstraZeneca had a busy run up to Christmas with two approvals, the first (in China) for roxadustat partnered with FibroGen for anemia in chronic kidney disease (p11). This first-in-class oral inhibitor of HIF-PHI has the potential to replace erythropoietin stimulating agents such as Amgen's *Epogen*. AZ's other approval was an extension for leading PARP inhibitor *Lynparza* into first-line ovarian cancer (p10). These positives compensated for yet another disappointment with tremelimumab, this time in the EAGLE study (p5).

Merck KGAA and partner Pfizer Inc. also hit a stumbling block in immuno-oncology, pulling the plug on the Phase III JAVELIN Ovarian 100 study of Bavencio in first-line ovarian cancer (p7).

Eli Lilly, meanwhile, set out its plans to turn its recent raft of new launches into blockbusters (p13), while there were changes at the top of Swiss firms Novartis and Roche (p18-20), setting the scene for a busy 2019. Happy New Year!

Scrip

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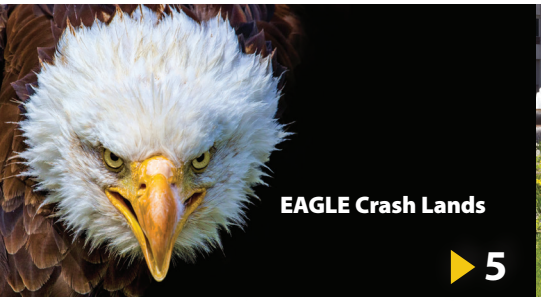

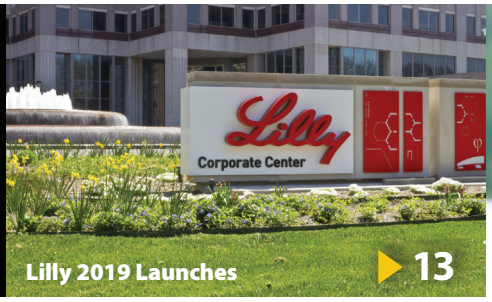

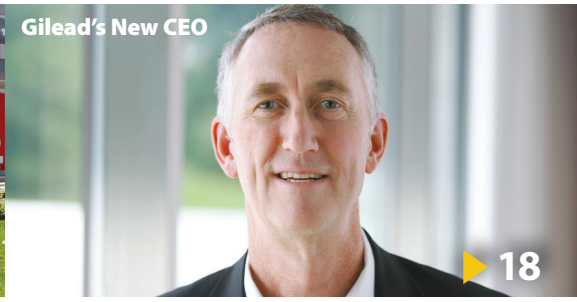

exclusive online content

Novartis Pruned Pipeline Producing Attractive Respiratory And Neurology Fruits

ALEX SHIMMINGS alex.shimmings@informa.com

Analysts are looking forward to a strong growth phase for **Novartis AG** based on its current drivers *Cosentyx*, *Entresto* and *Aimovig*, as well as around 11 upcoming launches expected in the next three years, as CEO Vas Narasimhan's new regime beds in.

While there were no major surprises during the Swiss major's first R&D day since Narasimhan took the role of CEO early this year, analysts were reassured overall by the level of detail given during the four-hour meeting in London last month that reaffirmed confidence in the direction the company is taking. "It is a catalyst-rich pipeline in the near-term" said Tim Anderson at Wolfe Research in an investor note.

Products nearing the market that stood out were the oral treatment for severe asthma fevipiprant (QAW039), the two multiple sclerosis treatments siponimod (BAF312) and ofatumumab (OMB157), as well as the potential of canakinumab in immuno-oncology.

Among the other products highlighted by management were those coming out of its advanced therapy platforms brought into the company through various acquisitions, particularly the gene therapy product AVXS-101 for spinal muscular atrophy (SMA) which is bidding fair to shake up treatment for that terminal disease.

Published online 13 December 2018

To read the rest of this story go to: https://bit.ly/2s0iLla

inside:

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ness's presence in the retail OTC/pharmacist market. However, the overall group structure created difficulties in giving the pharma business access to capital. "Obviously, this deal today just vastly outweighs the benefits of those synergies and there's tremendous opportunity to create value for shareholders and to support the pharma priority," the CEO commented.

On investing in pharma M&A, Walmsley noted that the company had already stated this was an intention, as evidenced by the recently announced acquisition of **Tesaro Inc.** for its oncology drug *Zejula* (niraparib). *(Also see "GSK Embraces PARP Promise With Tesaro Buy" - Scrip, 3 Dec, 2018.)*

"We do expect to continue doing further in-licensing partnerships, and indeed out-licensing some of our portfolio," she said, adding that today's deal and future separation creates further capacity for business development in future. "Rx is going to be significantly less levered, and therefore better able to invest when within three years we come to the point of split." How the company decides to invest at that point will depend to some extent on the progress of the current pipeline, which will in the meantime benefit from greater investment opportunity, management explained.

Analysts at Deutsche Bank recognized that the spin-out of the combined consumer business into an independent entity would deleverage the pharma/vaccine business in terms of debt, but warned in a Dec. 19 note that "this will leave the pharma/vaccines business more exposed to the ultimate [HIV drug] dolutegravir patent expiry (2027/29; >40% of profits) and thus more dependent on success in reinvigorating its pharma pipeline."

Published online 19 December 2018

GSK/Pfizer Consumer Health Combination Key Points

Ownership Split of Joint Venture: GSK 68%, Pfizer 32%
Proforma 2017 Sales Of Combined Consumer Group: £9.8bn ($12.7bn)
GSK: $9.2bn
Pfizer: $3.5bn
Creates the world's leading OTC company, with 7.2% market share
2017 Consumer Health Business Operating Margins:
GSK 17.6%
Pfizer 17.3%
New CEO: Brian McNamara, current head of GSK Consumer Healthcare

FUTURE OUTLOOK
Completion Date: Second half 2019
Demerger via UK listing within three years
2022 Forecast Operating Margin %: mid-20s
Cost synergies: £0.5bn annually by 2022
Total cash costs of deal: £0.9bn
Non-cash charges: £0.3bn
Anticipated Proceeds From Asset Divestments, to cover costs: £1bn
Initial Net Debt Ratio Post-Separation: 3.5-4.0 X aggregate adjusted EBITDA for JV's last four quarters

Bristol-Myers Squibb Sells French Consumer Health Unit UPSA To Taisho For $1.6bn

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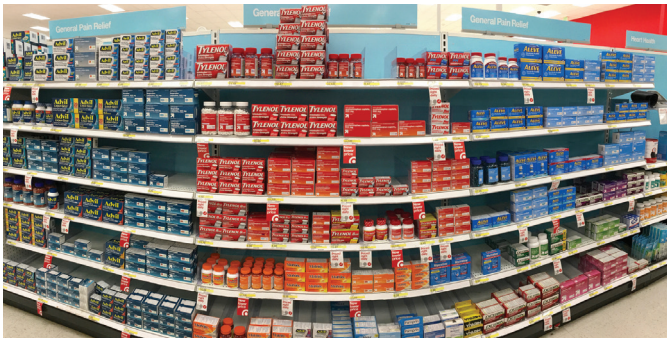
Six months after effectively putting its French over-the-counter drugs business UPSA up for sale, **Bristol-Myers Squibb Co.** has agreed to sell it to Japan-based healthcare group **Taisho Pharmaceutical Co. Ltd.** for $1.6bn and thereby allow the US big pharma to concentrate on developing and selling lucrative prescription drugs, particularly for cancer.



Buying OTC Unit UPSA From BMS will complement Taisho's product portfolio

The acquisition of UPSA will be complementary to Taisho's product portfolio and will allow it to establish a platform in Europe to expand its operations in the region, the company said when announcing their proposed transaction.

DEAL DETAILS

Bristol-Myers Squibb and Taisho have a history of doing deals together. In 2009, Taisho entered the OTC market in certain Asian countries through the purchase of **PT Squibb Indonesia** from Bristol-Myers Squibb. The subsidiary of Taisho is now known as **PT Taisho Pharmaceuticals Indonesia Tbk.**

UPSA operates in 60 markets, primarily in Europe, serving a variety of consumer health segments such as pain relief, cough and cold, and vitamins, minerals and supplements.

Paris-based UPSA's leading brands include the *Fervex* (acetaminophen/vitamin C/pheniramine) cold and flu products, *Effer-algan* (acetaminophen) analgesics and *Donormyl* (doxylamine) sleep aids.

In 2017, it was third in France's self-care product sales, with a market share of around 6% by value. It made a concerted effort to strike out from its French base in 2016 by creating UPSA International.

REFLECTS DIVESTMENT TREND

The transaction, announced Dec. 19, coincided with news that **Pfizer Inc.** and **GlaxoSmithKline PLC** are revamping their consumer health divisions under a giant deal that will see painkiller brands *Panadol* and *Anadin* bought under one roof.

The deals reflect the continuing trend of large-cap pharma divesting non-core assets to focus on high-margin prescription drugs and continues the consolidation wave in the consumer health sector, notably **Procter & Gamble Co.**'s acquisition of **Merck KGAA**'s consumer health business for $3.8bn and GSK's acquisition of **Novartis AG**'s stake in their consumer health joint venture earlier this year for $13bn. *(Also see "Merck KGaA Down-Plays Further Deals After Consumer Health Sell-Off" - Scrip, 19 Apr, 2018.)*

Bristol-Myers Squibb has in recent years sold-off all but a small part of its global OTC portfolio.

Most recently, **Reckitt Benckiser Group PLC** in 2016 exercised its option from a 2013 agreement between the firms, acquired a basket of BMS's OTC brands and a manufacturing facility in Latin America. *(Also see "Reckitt Deals Feed OTC Domination Plan" - Pink Sheet, 18 Feb, 2013.)*

BMS's latest deal is structured in the form of a "put option" agreement and subject to Bristol-Myers Squibb's exercise of the put option following information and consultation processes with relevant employee representative bodies. Deutsche Bank Securities, Inc. and Jefferies LLC acted as exclusive financial advisors to BMS. Kirkland & Ellis LLP, Freshfields Bruckhaus Deringer LLP and Baker & McKenzie acted as its legal advisors.

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EAGLE Crash Lands: AstraZeneca's Imfinzi/ Tremelimumab Continues To Disappoint

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AstraZeneca PLC's IO combination of *Imfinzi* and tremelimuab has failed in a Phase III study in head and neck cancer. Neither Imfinzi (durvalumab) monotherapy nor Imfinzi/ tremelimumab combination treatment met the primary endpoint of overall survival in patients with recurrent or metastatic head and neck squamous cell carcinoma (HNSCC) that had progressed following platinum-based chemotherapy, in the EAGLE trial. Studies continue in first-line head and neck cancer.

The company emphasized that the failed trial had studied the therapies in a "hard-to-treat" indication with a very poor prognosis. EAGLE was a randomized, open-label, multi-center global Phase III trial of the programmed cell death ligand 1 (PD-L1) inhibitor Imfinzi as monotherapy or Imfinzi with the cytotoxic T-lymphocyte-associated protein 4 (CTLA4) inhibitor tremelimumab compared with standard of care chemotherapy. It included patients who had progressed following standard-of-care chemotherapy, regardless of their PD-L1 tumor status. According to the trial record on clinicaltrials.gov, it enrolled 736 patients across 169 sites globally.

AstraZeneca said the safety and tolerability profiles for Imfinzi and Imfinzi/ tremelimumab were consistent with previous experience. Recruitment into EAGLE and KESTREL (the ongoing trial in first-line HNSCC) had been put on hold following bleeding events for a few weeks in 2016.

"This is certainly a disappointing outcome for AstraZeneca as the failure of this trial will keep Imfinzi from being approved for previously treated metastatic head and neck cancer patients, a setting with high unmet need," commented Hardik Patel, oncology therapeutic area director at Datamonitor Healthcare. "There were secondary endpoints listed for the trial which looked at survival in PD-L1+ and PD-L1- patients, but since nothing was mentioned in the press release about this subgroup analysis, it's reasonable to assume no significant OS benefit was observed in either of these subpopulations either."

However, he noted that "all is not lost for Imfinzi in head and neck" as another Phase III trial continues.

Top-line results from KESTREL in first-line HNSCC are expected in the first half of 2019. Analysts at Jefferies said in a Dec. 7 note that they had expected peak sales in HSNCC overall of $500m for Imfinzi, with the first-line setting pegged as the larger contributor to sales. Nevertheless, they pointed out that **Merck & Co. Inc.**'s programmed death receptor 1 (PD-1) inhibitor *Keytruda* (pembrolizumab) has already shown an overall survival benefit in first-line use.

Datamonitor Healthcare has forecast that the market for head and neck cancer therapies (around 90% of head and neck cancers are squamous cell carcinomas) will rise from $906m in 2017 to $2,817m in 2026, with PD-1/PD-L1 inhibitors taking the lion's share at $2,375m in sales in the US, Japan and the five major EU markets of Spain, France, Germany, Italy and the UK. At present, the primary targeted therapy is **Eli Lilly & Co./Merck KGaA/ Bristol-Myers Squibb Co.**'s *Erbitux* (cetuximab), an epidermal growth factor receptor (EGFR) inhibitor, which was approved in 2006.

Keytruda was the first PD-1 immunotherapy to be approved by the FDA in HNSCC; it is approved in recurrent or metastatic disease that has progressed following platinum-based chemotherapy. Bristol-Myers Squibb's *Opdivo* (nivolumab) is also approved in that indication, having shown an overall survival improvement in previously treated patients as a monotherapy.

In July 2018, Keytruda also was shown in the KEYNOTE-048 study to extend survival as a first-line treatment in patients expressing PD-L1, compared with standard of care with Erbitux and platinum chemotherapy plus 5-fluorouracil.

However, it failed to demonstrate an overall survival benefit in previously treated patients in a confirmatory trial (KEYNOTE-040) following accelerated approval in this population. "Therefore, Imfinzi may still have success in the first-line despite failure in previously treated patients," commented Datamonitor Healthcare's Patel.

With Opdivo also being developed in combination with BMS's anti-CTLA4 antibody *Yervoy* (ipilumab) in the first-line setting, AstraZeneca could face a strong competitive threat in the first-line setting should KESTREL succeed, Patel noted.

Imfinzi has failed a couple of other Phase III trials recently. November 2018 saw its failure both as monotherapy and in combination with tremelimumab in stage IV lung cancer in the MYSTIC trial, which also had overall survival as a primary endpoint. In April the combination failed to produce progression-free or overall survival benefits in late-stage treatment of advanced non-small cell lung cancer, as studied in the ARCTIC trial. Data from the EAGLE trial will be presented at a future medical meeting, AstraZeneca said.

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AZ Goes Into The MYSTIC And Finds Positives For Imfinzi

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Less than a month after confirming its closely-watched MYSTIC lung cancer trial of *Imfinzi* (durvalumab) plus tremelimumab had failed, **AstraZeneca PLC** has presented the full results from the study which suggest that there may still be a place for the PD-L1 inhibitor as a first-line treatment for the disease.

In November, AstraZeneca confirmed that in MYSTIC, Imfinzi in combination with the firm's investigational anti-CTLA-4 antibody tremelimumab improved neither overall survival (OS) nor progression-free survival (PFS) compared with platinum-based standard of care chemotherapy in previously untreated patients with stage IV (metastatic) non-small cell lung cancer (NSCLC) in patients expressing PD-L1 at 25% or above, representing 488 of the 1,118 total enrolled. However, in a full analysis presented at the ESMO Immuno-Oncology 2018 congress in Geneva Dec. 13, study author Naiyer Rizvi of the Columbia University Medical Center in New York noted that while not reaching statistical significance, Imfinzi monotherapy gave a clinically meaningful median OS improvement of 16.3 months compared to 12.9 months with chemotherapy in patients with 25% or greater PD-L1 expression.

However, arguably of more interest were the results of an exploratory analysis which examined survival according to the biomarker of high or low tumor mutational burden (TMB) in the blood – 16 or more mutations per megabase was defined as high and fewer than 16 as low.

TMB evaluation was performed in more than 70% of patients, of whom 40% had high TMB and for those patients OS was 16.5 months with the Imfinzi/ tremelimumab combination versus 10.5 months with chemotherapy; OS with Imfinzi alone was 11 months. The proportion of high TMB patients alive at two years was 39% with the combo, 30% with Imfinzi and 18% with chemotherapy, while in those with low TMB, OS was 8.5 months with Imfinzi plus tremelimumab, 12.2 months with Imfinzi and 11.6 months with chemotherapy.

There has been much debate as to whether TMB is a valid biomarker to guide treatment with immunotherapy and Rizvi acknowledged that the results of the exploratory analysis in MYSTIC needed to be validated in a future trial. However, he noted that TMB is measured with a simple blood test "and might be an easy way to select patients for this treatment," adding that **Bristol-Myers Squibb Co.**'s high-profile CheckMate 227 trial this year showed that a subset of patients with NSCLC with high TMB (measured at 10 or more mutations per megabase rather than 16 in MYSTIC) and low PD-L1 expression who were treated with the firm's PD-1 inhibitor *Opdivo* (nivolumab) and CTLA-4 inhibitor *Yervoy* (ipilimumab) had better PFS.

Hesham Abdullah, head of immuno-oncology, global medicines development at AstraZeneca, said in a statement that "we are eager to continue following the science to fully understand the role of both PD-L1 and TMB as biomarkers to help select patients that may benefit from our I-O medicines." He added that the company is encouraged to see that Imfinzi monotherapy activity "is consistent with the anti-PD1 class in previously-untreated patients with Stage IV NSCLC" and "the apparent association between high blood TMB and response to immunotherapy observed in this exploratory analysis warrants further investigation."

Beyond MYSTIC, AstraZeneca's other stage IV first-line NSCLC trials include PEARL (just Imfinzi) and the tremelimumab combo studies NEPTUNE and POSEIDON, with initial readouts expected in the first and third quarters of 2019, respectively. Those studies may offer more insight into how valid TMB is as a biomarker.

The stage IV setting is a difficult one for AstraZeneca and other I-O players given the dominant market position of Merck & Co's *Keytruda* (pembrolizumab) plus chemo which has shown both a PFS and OS

benefit in all comers and does not require any testing. In MYSTIC, the TMB data was gathered using a device made by Guardant Health and the two companies have just announced a deal to develop blood-based companion diagnostic tests for AstraZeneca's oncology portfolio including Imfinzi and *Tagrisso* (osimertinib), its third-generation EGFR inhibitor for advanced NSCLC.

In an investor note, BMO Capital Markets analyst Alex Arfaei wrote that Merck "is unlikely to be meaningfully surpassed" by the PD-1+CTLA-4 combos from AstraZeneca and Bristol in metastatic NSCLC, and its "significant lead should make Keytruda more difficult to displace." He does expect competition to increase for Merck in first-line NSCLC in 2020 and beyond, however, and BMO's forecasts assume the US giant leading with 40% peak market share, and AstraZeneca having around 10%. How important the stage IV lung cancer indication would be for Imfinzi is debatable and earlier this year initial data from the ARCTIC study showed that the Imfinzi/tremelimumab combo failed to produce either a PFS or OS benefit when used in the late-stage treatment of advanced NSCLC patients. However, AstraZeneca has carved out a sizeable niche for the drug in stage III NSCLC, a space where the company has a monopoly and recent updated data from the PACIFIC study showed a 32% OS benefit in those patients. *(Also see "ARCTIC Chill Descends On AstraZeneca's Imfinzi/Treme Combo In NSCLC" - Scrip, 24 Apr, 2018.)* *(Also see "AstraZeneca's PACIFIC Update Bolsters Imfinzi's Lead In Stage III Lung Cancer" - Scrip, 25 Sep, 2018.)*

Earlier this month, a combination of Imfinzi and tremelimuab failed in the Phase III EAGLE study in head and neck cancer. Another late-stage study in that indication, KESTREL, is ongoing, with topline results expected in the first half of next year.

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Merck KGAA/Pfizer's Bavencio Failure Casts More Shade On Immunotherapy For Ovarian Cancer

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Merck KGAA and partner **Pfizer Inc.** are pulling the plug on the Phase III JAVELIN Ovarian 100 study of their PD-L1 checkpoint inhibitor *Bavencio* (avelumab) in first-line ovarian cancer on the advice of an independent data monitoring committee, the companies announced Dec. 21.

JAVELIN Ovarian 100 was a three-arm study testing Bavencio with carboplatin/paclitaxel chemotherapy followed by monotherapy maintenance treatment vs. Bavencio maintenance treatment after chemotherapy vs. chemotherapy followed by observation.

The goal was superiority on progression-free survival for either one of the Bavencio-inclusive arms vs. chemotherapy/observation.

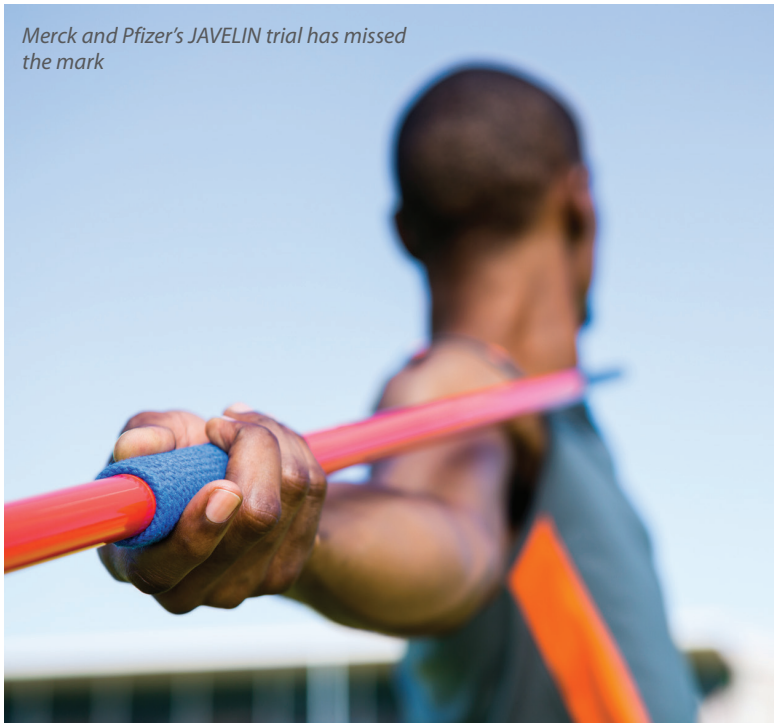
Data from a planned interim analysis of the trial did not support the study's initial hypothesis, the companies explained.

"While detailed analyses of the data are ongoing, no new safety signals were observed, and the safety profile for avelumab in this trial appears consistent with that observed in the overall JAVELIN clinical development program," they said.

Checkpoint inhibitors have not worked very well as single agents in early-stage studies of ovarian cancer, but there have been some promising signs of activity and a lot of hope that they will prove more efficacious when used as parts of combination regimens.

Many trials of various combinations are ongoing in ovarian cancer and the JAVELIN studies are the first late-stage trials involving immunotherapies in ovarian cancer to report results.

"These are certainly negative results for both Bavencio and the immunotherapy class in general. The development of immunotherapies in ovarian cancer has lagged behind other indications partly because ovarian malignancies have traditionally been considered non-immunogenic. These clinical results seem to further that notion," Datamonitor analyst Zach McLellan commented in an interview.



Merck and Pfizer's JAVELIN trial has missed the mark

The partners plan to continue with the Phase III JAVELIN Ovarian PARP 100 study, a first-line trial testing Bavencio with chemotherapy followed by maintenance with the combination of Bavencio and Pfizer's PARP inhibitor *Talzenna* (talazoparib), which has US FDA approval for BRCA-mutated breast cancer. Other earlier-stage studies of avelumab as part of additional combinations are ongoing.

Bavencio is FDA-approved for metastatic Merkel cell carcinoma and second-line metastatic bladder cancer.

The drug has been at the lead of immunotherapies being developed for ovarian cancer. In November, however, Merck KGaA and Pfizer announced that Bavencio failed to improve progression-free survival or overall survival as a monotherapy or in combination with chemotherapy in the Phase III JAVELIN Ovarian 200 trial of platinum-resistant or refractory patients. *(Also see "Merck KGAA/Pfizer's Anti-PD-L1 Bavencio Loses An Opportunity In Ovarian Cancer" - Scrip, 19 Nov, 2018.)*

It was thought that patients would respond better to immune checkpoint inhibitors in earlier lines of therapy, but that does not seem to be the case after the JAVELIN Ovarian 100 readout, McLellan said.

"There is always the potential for post-hoc subgroup analyses to find patients that benefit, but the failures are stacking up for Bavencio in ovarian cancer," the analyst added.

Although the JAVELIN Ovarian PARP 100 study of Bavencio with Talzenna in a similar setting is ongoing, potential mechanistic synergy between checkpoint inhibitors and PARP inhibitors is yet to be proven.

Other ongoing Phase III combination studies involving immunotherapies include IMagyn050 of **Roche**'s anti-PD-L1 *Tecentriq* (atezolizumab) with the VEGF inhibitor *Avastin* (bevacizumab), FIRST of **Tesaro Inc.**'s PARP inhibitor *Zejula* (niraparib) with the company's in-house PD-1 inhibitor TSR-042 and ATHENA, which tests **Clovis Oncology Inc.**'s PARP inhibitor *Rubraca* (rucaparib) with **Bristol-Myers Squibb Co.**'s PD-1 inhibitor *Opdivo* (nivolumab). *(Also see "Ovarian Cancer Pipeline Review: Sponsors Plan Frontline Punch, Smart Combinations" - Scrip, 7 Dec, 2018.)*

Published online 31 December 2018

ECLIPSE: J&J's Tremfya Beats Novartis' Cosentyx For Long-Term Psoriasis Clearance

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Johnson & Johnson's IL-23 inhibitor *Tremfya* beat **Novartis AG**'s IL-17A inhibitor Cosentyx on a long-term, 48-week primary endpoint in psoriasis in the Phase III ECLIPSE study, but was not superior on a range of secondary measures.

First-in-class Tremfya (guselkumab), partnered with **MorphoSys AG**, was approved for psoriasis in the US in mid-2017 and is in Phase III for psoriatic arthritis. (*Also see "J&J's First-In-Class Tremfya Poised To Join A Crowded Psoriasis Market" - Scrip, 14 Jul, 2017.)*

The biologic has a lot of ground to make up versus its formidable competitor Cosentyx (secukinumab), which was cleared by the FDA in 2015 for psoriasis and later for psoriatic arthritis and ankylosing spondylitis. Cosentyx has become an important product for Novartis, generating more than $2bn in 2017 sales.

Psoriasis in general has become a very competitive market dominated by TNF inhibitors and new classes of drugs, but until the ECLIPSE results reported on Dec. 12, no head-to-head data have been available for IL-23 versus IL-17 inhibition.

The Phase III results were presented in an obscure setting – the third Inflammatory Skin Disease Summit in Vienna, Dec. 12-15.

The ECLIPSE trial tested Tremfya versus Cosentyx in 1,048 patients with moderate-to-severe plaque psoriasis. Both drugs were given by subcutaneous injection. After an initiation period with an intense dosing regimen, Tremfya was given every eight weeks and Cosentyx every four weeks, per labeling.

The primary endpoint was non-inferiority based on the proportion of patients achieving a Psoriasis Area Severity Index (PASI) 90 response (meaning 90% reduction on this score) at week 48. On this measure, 84.5% on Tremfya had a PASI 90 response vs. 70% for Cosentyx, a statistically significant result ($p<0.001$).

There also were six secondary endpoints assessed at 12 and 48 weeks *(see table opposite)*. The sequentially fixed study design (NCT03090100) dictated that if Tremfya was superior on the first major secondary endpoint, the others could be assessed for superiority.

In actuality, Tremfya was non-inferior, but not superior, to Cosentyx on the first major secondary endpoint, which was PASI 75 at weeks 12 and 48. On this measure, 84.6% on Tremfya hit the mark vs. 80.2% on Cosentyx.

Consequently "p-values for all the subsequent major secondary endpoints were considered nominal," J&J said in a statement.

On the safety front, researchers reported toxicity profiles for both products that were consistent with registration trials and current prescribing information. The serious adverse event (AE) rate was 6.2% for Tremfya vs. 7.2% for Cosentyx. Six cases of serious infections were reported for Tremfya vs. five for Cosentyx. The treatment dropout rate was 5.1% for Tremfya and 9.3% for Cosentyx.

COSENTYX HAS BIG LEAD

It remains to be seen how the results will impact the market. The performance of both products has pleased investors, but Cosentyx holds a big lead over Tremfya.

In 2018, Novartis reported sales of $750m for Cosentyx in the third quarter, up 37% from the year-ago period. Novartis Pharmaceuticals CEO Paul Hudson commented during the company's Oct. 18 earnings call that the product is a significantly larger asset compared with last year and has leverage with payers, so Novartis is comfortable with the outlook for 2019.

J&J reported $171m in Tremfya sales for the third quarter. Execs said during the company's earnings report that more than 25,000 US patients already are on Tremfya and that the product has taken 5.8% market share in psoriasis to date. J&J did not break out sales for Tremfya in 2017, although it did report "other" immunology sales of $85m worldwide, up from $25m in 2016.

EFFICACY RESULTS IN ECLIPSE, MODERATE-TO-SEVERE PSORIASIS			
Endpoint	J&J's Tremfya	Novartis' Cosentyx	P-value
PRIMARY ENDPOINT			
PASI 90 at 48 weeks	84.5%	70%	p<0.001
FIRST MAJOR SECONDARY ENDPOINT			
PASI 75 at weeks 12 and 48	84.6%	80.2%	P<0.001 for noninferiority; p=0.062 for superiority
OTHER SECONDARY ENDPOINTS, P-VALUES CONSIDERED NOMINAL, AS SUPERIORITY NOT SHOWN ON FIRST SECONDARY ENDPOINT			
PASI 100 at week 48	58.2%	48.4%	Nominal p<0.001
Investigator's Global Assessment (IGA) Score of 0 (cleared) at week 48	62.2%	50.4%	Nominal p<0.001
IGA score 0 or 1 (cleared or minimal disease) at week 48	85%	74.9%	Nominal p<0.001
PASI 75 at week 12	89.3%	91.6%	p<0.001 for non-inferiority
PASI 90 at week 12	69.1%	76.1%	p=0.127 for non-inferiority

J&J STRESSES LONG-TERM EFFICACY

J&J stresses the long-term disease control possible with Tremfya. The response-over-time curves in ECLIPSE show that there was a strong initial effect with Cosentyx, but that it peaked at 20 weeks and fell consistently from 24 weeks to 48 weeks, investigators reported.

Response at 12- and 16-week time points for the new classes were important for pivotal studies, dictated partly by the fact that the drugs were compared to placebo and it wouldn't be ethical to withhold treatment from the comparator arm for very long, Bruce Randazzo, J&J senior director of clinical research, dermatology, said in an interview.

The company included early endpoints in ECLIPSE, but sees durability over 48 weeks as more important for patients, as it's disappointing to get a response and lose it and have to switch to a different treatment.

"Shifting gears is a big deal," said Randazzo, who is a practicing dermatologist.

ECLIPSE provides a "crystal-clear picture" of how the drugs perform in the same population with the same analysis tools and identical assessors, the exec said. "We are hopeful this will be very encouraging to people [regarding] the use of Tremfya. Keeping patients under control in psoriasis has always been the greatest challenge. We have a variety of drugs even beyond biologics that are very effective in the short term. It's long-term management of psoriasis that really presents a substantial challenge," he said.

NOT A TOTAL ECLIPSE

Jefferies analyst Peter Welford said in a Dec. 12 note that ECLIPSE is "certainly not total for Cosentyx."

The analyst cited the lack of superiority for Tremfya on secondary endpoints and called attention to the PASI 75 response at week 12, which was numerically better for Novartis' drug – 91.6% vs. 89.3%. Furthermore, PASI 90 at week 12 also was numerically better for Cosentyx – 76.1% vs. 69.1%, he noted.

The results confirm a slightly more rapid onset of response with Cosentyx and early responses are important to patients, Welford said. "These results imply that Cosentyx remains a good option for moderate-to-severe psoriasis patients that want to achieve more rapid skin clearance, in our view," he said.

Novartis downplayed the risk of ECLIPSE during an April 19 earnings call. When asked about the threat it posed, Hudson said Novartis was "somewhat flattered" that J&J was taking on Cosentyx. *(Also see "Novartis Allays Concerns Over Cosentyx Sales Miss " - Scrip, 19 Apr, 2018.)*

The company repeatedly has claimed that IL-17A is the best mechanism to target and argued that the drug is uniquely positioned because it also has indications in PsA and ankylosing spondylitis.

More than two-thirds of psoriasis patients have more manifestations beyond skin – in the nails, scalp, hands, feet and joints, noted Eric Hughes, development head of immunology, hepatology and dermatology at Novartis.

"This syndrome of manifestations is very important to the patient and the fact that we can treat those different endpoints is very important," Hughes told *Scrip*, adding that the company has conducted dedicated Phase III studies for these other areas.

Hughes also pointed out that the company has safety and efficacy data for Cosentyx out to five years for three indications – psoriasis, psoriatic arthritis and ankylosing spondylitis.

"That safety and that durable response for five years is extremely important for these patients with chronic disease," Hughes said.

Sam Khalil, worldwide head of medical affairs for immunology, hepatology and dermatology at Novartis, said in an interview with *Scrip* three days before the ECLIPSE data were presented that the Swiss group also is looking at multiple indications for Cosentyx where IL-17A is the cornerstone cytokine of a disease. Khalil cited the promise shown in studies of the drug for hidradenitis suppurativa, a rare long-term skin condition.

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First-Line Ovarian Cancer Approval Solidifies Lead For AstraZeneca's Lynparza

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AstraZeneca PLC/Merck & Co. Inc.'s *Lynparza* is breaking new ground in ovarian cancer with the first approval of a PARP inhibitor as first-line maintenance therapy in BRCA-mutated ovarian cancer.

After a speedy review, the US FDA approved Lynparza (olaparib) Dec. 19 as a monotherapy in BRCA+ patients in partial or complete response to first-line platinum-based chemotherapy. The companies had announced acceptance of the filing on Nov. 12, with expectations of approval in the first quarter of 2019; the application had priority review.

Lynparza has been approved since 2014 for use as a maintenance therapy in second-line ovarian cancer. About 10% to 15% of the ovarian cancer population has BRCA mutations. Lynparza was initially approved for relapsed disease with BRCA mutations but labeling was later expanded to all comers, regardless of mutation status, in second-line maintenance.

The filing for first-line maintenance use was supported by the pivotal SOLO-1 study, which tested the drug as a monotherapy maintenance therapy in patients with BRCA mutations.

Lynparza showed a significant, 70% reduction in the risk of progression or death compared with placebo – the median progression-free survival was not reached in the test drug arm and was 13.8 months for placebo. The results were maintained long-term after the drug was stopped; investigators reported that 60% of patients on Lynparza were progression-free after three years, compared to 27% for placebo.

The results were well received at the European Society for Medical Oncology meeting and published in the *New England Journal of Medicine* in October.

First-line filings have also been submitted in Europe, Japan and China.

The new US approval gives Lynparza an edge over its PARP rivals – **Clovis Oncology Inc.**'s *Rubraca* (rucaparib) and **Tesaro Inc.**'s *Zejula* (niraparib). Both drugs are approved as maintenance therapies for second-line but not first-line ovarian cancer.

> "The new US approval gives Lynparza an edge over its PARP rivals – Clovis Oncology Inc.'s Rubraca (rucaparib) and Tesaro Inc.'s Zejula (niraparib)

Roche's VEGF inhibitor *Avastin* (bevacizumab) is another player in the first-line maintenance space. It was approved in June for use in combination with chemotherapy followed by single-agent Avastin for women with Stage III or IV ovarian cancer after initial surgical resection, but it had long been included for this use in National Comprehensive Cancer Network guidelines. *(Also see "FDA Finally Approves Avastin In First-Line Ovarian Cancer" - Pink Sheet, 13 Jun, 2018.)*

Lynparza has been taking the lead among the PARP inhibitors, due to its first-mover advantage and acceptable tolerability profile as well as AstraZeneca's strength in marketing. However, **GlaxoSmithKline PLC** will be taking over Zejula with its acquisition of Tesaro. *(Also see "GSK Embraces PARP Promise With Tesaro Buy" - Scrip, 3 Dec, 2018.)*

AstraZeneca reported $169m in worldwide sales for Lynparza in the third quarter, up more than 100% from $81m in 2017, and $438m for the first nine months (+122%) of 2018. *(Also see "Ovarian Cancer Market Snapshot: AstraZeneca's Lynparza Poised To Lead In Niche Space" - Scrip, 7 Dec, 2018.)*

AstraZeneca noted that most of Lynparza sales are from the ovarian cancer indication but the drug is also being used in breast cancer, following the January approval for BRCA-mutated disease. Clovis' reported $23m in sales for Rubraca in the third quarter and Tesaro reported $63m for Zejula.

On news of the acceptance of the Lynparza filing, Deutsche Bank analyst Richard Parkes had boosted sales projections for 2023 from $2.2bn to $2.5bn and noted that Tesaro's Phase III PRIMA study of Zejula as a monotherapy in first-line ovarian cancer, which is in all comers, is not due for release until late 2019.

Parkes estimated that the first-line BRCA mutation population is worth $1bn.

A variety of combination studies, including pairing PARP inhibitors with PD-1 checkpoint inhibitors, are ongoing in ovarian cancer. Lynparza is being tested with Avastin in first-line maintenance in the Phase III PAOLA-1 all comers study, with results due in 2019. The DUO-O study of Lynparza with AstraZeneca's PD-L1 checkpoint inhibitor *Imfinzi* (durvalumab) as first-line maintenance is set to start shortly.

Other ongoing first-line ovarian cancer trials include the JAVELIN OVARIAN PARP 100 study of **Pfizer Inc./Merck KGAA**'s PD-L1 inhibitor *Bavencio* (avelumab) with Pfizer's PARP inhibitor talazoparib, which is approved for BRCA+ breast cancer as *Talzenna*. The IMagyn050 study is testing Roche's anti-PD-L1 *Tecentriq* (atezolizumab) with Avastin.

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First Approval For AZ's Roxadustat With China Green Light

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AstraZeneca PLC's renal disease franchise has received a major boost with the news that partner **FibroGen Inc.** has bagged an approval for roxadustat to treat anemia in chronic kidney disease (CKD) patients on dialysis in China, the first country globally to approve the closely watched compound.

There is a lot of excitement surrounding roxadustat, which is a first-in-class oral inhibitor of hypoxia inducible factor-prolyl hydroxylase (HIF-PHI), as many observers believe it could replace erythropoietin stimulating agents (ESAs), notably **Amgen Inc.**'s *Epogen* (epoetin alfa) - and biosimilars thereof - as the standard of care because of an improved safety profile and the ability to eliminate the need for intravenous iron. The approval in China, which followed a priority review by the country's regulator, is based on an open-label, active-control 26-week Phase III trial in dialysis dependent-CKD patients with anemia who were previously treated with various forms of a generic ESA who were then randomized to receive either roxadustat or Epogen.

Sean Bohen, AstraZeneca's chief medical officer, said in a statement that "roxadustat is a long-awaited, first-in-class medicine" and this first approval "is a significant step towards achieving our ambition to transform care in a condition where prevalence in China is increasing." The market is potentially a big one and AstraZeneca noted that there are around 500,000 patients on dialysis in the country who may be suffering from anemia, "a number that is increasing significantly."

AstraZeneca teamed up with FibroGen in 2013 to develop roxadustat in the US, China and other selected global markets. Following this approval, AstraZeneca will manage commercialization activities in China, with FibroGen in charge of manufacturing ahead of launch which is expected during the second half of 2019.

John Houghton, global medicines leader of AstraZeneca's cardiovascular and renal medicine (CVRM) unit, told *Scrip* that the firm's commercial muscle is very strong already in China, with the company being the leading pharma multinational in the country along with **Pfizer Inc.**, but the field force will be beefed up ahead of launch. Over the last year, its medical science liaison teams have been working around the mechanism and disease state and those efforts will be ramped up; AstraZeneca will also be assisting FibroGen in medical and government affairs.

Commenting on the China approval, Jefferies analyst Michael Yee issued a note saying that it could open up "an estimated ballpark $300-500m sales opportunity not widely accounted by consensus." He noted that the approval should trigger a milestone payment, pointing out that for China, FibroGen has received $43m from AstraZeneca already and is entitled to up to $334m of additional payments, much of which could be paid this quarter. Yee also pointed out that an approval in China for the larger non-dialysis population is expected later in 2019, when regulators complete the inspections of clinical trial sites. Stating that the green light marks one of the first times that a multinational pharma will begin selling its blockbuster medicines in China before the US and Europe, he added that the approval "provides some positive read-through to the upcoming US/EU studies and should build confidence on roxadustat's overall efficacy/safety profile."

Attention will now shift to the US, where roxadustat is expected to be filed in the first half of next year. Yee said that Phase III top-line efficacy data from a US study is expected in the coming weeks, followed by key major adverse cardiovascular events (MACE) safety data by March/April. He added that the key is to show both non-inferiority to Epogen on safety and efficacy for dialysis and superiority to a placebo on efficacy in non-dialysis and at least noninferior on safety, claiming that "the 'home run' scenario…would be superiority on MACE in both populations."

Houghton agreed that the safety results will be key, noting that they will involve pooled data from seven studies in both dialysis and non-dialysis patients. "The FDA were keen that we released all of it at the same time..they want to see the full picture."

Further down the line, there will be launches in other Asian as well as Latin America countries by AstraZeneca but not in Europe or Japan as FibroGen is developing roxadustat in those territories with **Astellas Pharma Inc.**, as well as in the Commonwealth of Independent States, the Middle East, and South Africa. Houghton told *Scrip* that the Astellas connection is not a problem and "we have a harmonized approach, working as a tripartite with FibroGen keeping us co-ordinated in the middle" and all the studies run by Astellas "are equally contributing to the output."

The renal area has become a strategically important one for AstraZeneca, a space Houghton knows well, joining the company nearly four years ago after having spent a decade in the area, including a period as CEO of Nephros, a medical device company focused on ultrafiltration of liquids for use in dialysis. With roxadustat and *Lokelma* (sodium zirconium cyclosilicate) for hyperkalemia, which was approved by the FDA in May, he said the company has really put its thumbprint on renal research, with more to come through the pipeline. Also, "the number of nephrologists that have joined the company in the last four years has gone through the roof," he said, "and we have a tremendous opportunity to be leaders in this area." *(Also see "AstraZeneca's Lokelma Approved In US With Label Benefits Over Veltassa" - Scrip, 21 May, 2018.)*

That would seem to be the case in terms of HIF-PHI compounds potentially getting to market. Behind roxadustat is **Akebia Therapeutics Inc.**'s vadadustat, which is in Phase III, with data expected in 2020 and **GlaxoSmithKline PLC** and **Kyowa Hakko Kirin Co. Ltd.**'s daprodustat.

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Celltrion's Global Ambitions On Track As Third Biosimilar Approved In US

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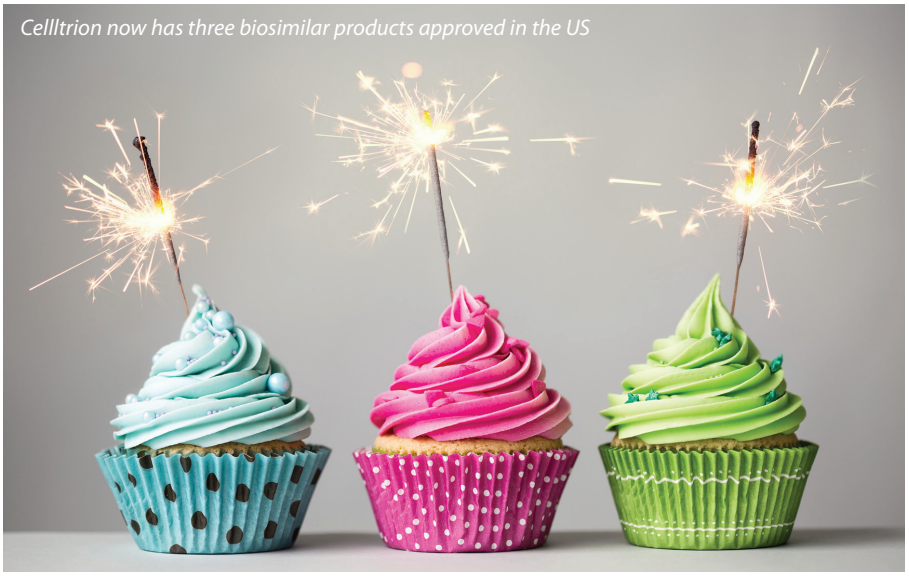
Celltrion Inc. has received the US FDA's regulatory approval for its third biosimilar product, *Herzuma* (trastuzumab-pkrb), adding to the earlier green lights in this market for the South Korean firm's biosimilar infliximab *Inflectra/Remsima* and biosimilar rituximab *Truxima*.



Celltrion now has three biosimilar products approved in the US

The new approval in the world's largest pharma market is seen as crucial to further cement the company's commercial leadership in the global biosimilar market and to help meet its longer term vision to grow into a top global biopharma firm. Receiving approval from the FDA is regarded as receiving recognition of the world-class development and production technology and quality of its products; Remsima/Inflectra was approved in the US in 2016 and Truxima this November.

"Biosimilars are of growing importance to the oncology community and the approval of Herzuma may provide more patients access to this important therapy," Celltrion CEO Woosung Kee said in a statement. "This is our second oncology biosimilar approval in the US in the past month, which reinforces the goal for all of our approved products - providing broader treatment options for patients and the providers who treat them."

HUGE MARKET, BUT LIMITED INDICATIONS

The market for Herzuma is potentially huge. Annual sales of **Roche**'s original trastuzumab product *Herceptin* are estimated to be CHF2.7bn ($2.72bn) in the US and CHF7.1bn globally. More widely, in 2017 global sales of Herceptin plus original *Remicade* (infliximab) and *Rituxan* (rituximab) together totaled KRW24tn ($21.2bn), while their combined US sales reached about KRW14tn.

However, Herzuma was approved this time - following a Complete Response Letter (CRL) in April - only for HER2+ breast cancer, missing out on some of original Herceptin's other indications including HER2+ metastatic gastric cancer and gastroesophageal junction adenocarcinoma, apparently due to ongoing litigation involving Genentech/Roche and biosimilar developers.

The first biosimilar trastuzumab to be cleared in the US, **Mylan NV**/**Biocon Ltd.**'s *Ogivri*, was approved around a year ago for these other indications, reflecting the multiple settlements with biosimilar developers (including Mylan) that have so far been reached by Genentech.

Once Herzuma is launched, Celltrion expects it to provide a new treatment opportunity to patients while reducing US health authorities' financial burden.

The company expects the product to rapidly replace Herceptin, as trastuzumab is dominating the treatment of HER2+ breast cancer patients, and given that other HER2+ breast cancer drugs development are expected to be highly priced and have limited approved indications, and so are seen as unlikely to compete with Herzuma.

Although it is unclear which trastuzumab biosimilar will lead the US market, Celltrion is counting on Herzuma's potential. While Ogivri has been approved it has not been launched yet in the US.

Meanwhile, **Amgen Inc.** and **Allergan PLC**'s biosimilar trastuzumab ABP980 received a CRL from the US FDA in June, while the user fee date has also been extended for **Samsung Bioepis Co. Ltd.**' version of the molecule, SB3. Pfizer has been asked by the FDA to submit additional data on its biosimilar PF-05280014.

CELLTRION SAILING SMOOTHLY IN EUROPE

Celltrion has been benefiting in other major markets from first mover status in antibody biosimilars, and its three approved products are sailing smoothly in Europe. Remsima's market share there reached 54% this year, while that of Truxima - which launched in Europe in April last year - stood at 32%.

Herzuma, which debuted in May this year *(Also see "Celltrion's Trastuzumab Biosimilar Gets EC Nod" - Scrip, 15 Feb, 2018.)*, is rapidly increasing its European market share by winning tender orders from countries like France.

Celltrion touted that the success of its three biosimilars in Europe was the outcome of synergies from its accumulated distribution and sales-know how, as well as improving credibility within the medical community based on its clinical data.

However, as multinationals begin to speed up their development of biosimilars, competition in the sector in general is

becoming fierce, and this impact is starting to be reflected in pricing. In response, Celltrion slashed the price of Truxima in Europe earlier this year and reported worse than expected third quarter earnings. *(Also see "Celltrion Hit By Truxima Price Cut, Temporary Utilization Rate Drop " - Scrip, 13 Nov, 2018.)*

As a result, carving out a favorable position in the US market has become ever more crucial for the Korean firm.

LOWER PRICES KEY TO US SUCCESS?

Based on its experience in Europe and know-how from first mover status, Celltrion is aiming to grow in the US biosimilars market through its partnerships with **Teva Pharmaceutical Industries Ltd.** and **Pfizer Inc.** It expects Teva's strong oncology network to help lead Truxima and now Herzuma's success in the market; the Israeli generics firm is already distributing drugs such as *Trisenox* (arsenic trioxide), *Bendeka* and *Treanda* (both bendamustine) in the US, Celltrion noted.

Demand for biosimilar versions of oncology drugs is seen as particularly strong in the US due to the generally high prices of anticancer biologics, with US breast cancer patients generally known to require about $80,000 annually if treated with Herceptin, Celltrion said. This can lead to serious financial difficulties for some as treatment costs continue to rise, leading some patients to even give up treatment.

In Europe, Celltrion said there had even been a patient death while waiting for the administration of trastuzumab amid prolonged reimbursement disputes.

The US environment for biosimilars appears to be turning more favorable, and the US government appears to be actively moving to resolve issues stemming from high drug prices. Following the announcement of the Biologics Price Competition and Innovation Act (BPCIA) in 2009, it released the American Patients First policy this year to speed up supply of prescription drugs at lower prices.

The US has also announced steps to promote innovation and competition in biologics, as well as to put additional efforts into encouraging usage of biosimilars.

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From the editors of PharmAsia News.

Lilly's New Year Resolution: Make New Launches Into Blockbusters

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Eli Lilly & Co. has had a big run delivering new drugs to the market, launching 10 new drugs in the last five years. Now the company's big goal is to turn those launches into blockbuster-level commercial successes and continue the pattern of bringing more novel agents to market.

Lilly held an investor event in New York Dec. 19, splashing the company logo across the façade of the New York Stock Exchange. It was the first time senior management has given a major commercial and R&D update since May 2016, and the company's top leadership team has largely changed in that time, including CEO Dave Ricks, Chief Financial Officer Joshua Smiley, Chief Scientific Officer Dan Skovronsky, Biomedicines President Christi Shaw and Oncology President Ann White.

While the update held little in the way of big surprises, the company did release 2019 financial targets, exceeding consensus estimates, and provided smaller updates on important catalysts ahead.

The big takeaway was that while Lilly has successfully executed on the goals it laid out to investors back in 2016, the company needs to build traction with some of those new drug launches and continue the R&D momentum.

10 LAUNCHES IN FIVE YEARS

Management highlighted improvements in the company's R&D productivity that have yielded 10 new drugs in the five years from 2014 to 2018 versus only one new drug in the prior five-year period, and that one was a commercial flop, the blood thinner *Effient*.

"We said we would launch 20 new molecules in the decade from 2014 to 2023. Well, we're halfway through that decade and we're halfway to our goal," Ricks said. "Over the last five years, we've launched 10 new products and we expect to launch two more in 2019 with the remaining eight coming between 2020 and 2023."

The 10 new launches include the diabetes drugs *Trulicity*, *Jardiance*, and the long-acting insulin copycat *Basaglar*; the IL-17 blocker *Taltz*; the JAK inhibitor *Olumiant*; the oncology medicines *Verzenio*, *Cyramza*, *Portrazza* and *Lartruvo*; and the newest, the CGRP inhibitor *Emgality* for migraine.

The company also could launch two new drugs in 2019 that have already been filed with the FDA, nasal glucagon for hypoglycemia and lasmiditan for acute migraine.

(Also see "Lilly's Lasmiditan NDA Review Could Hinge On US FDA's Migraine Guidance" - Pink Sheet, 25 Nov, 2018.) In addition, Lilly is hoping to secure FDA approval for a new indication for *Emgality* (galcanezumab) for cluster headaches.

Newer drugs are expected to account for 45% of total pharmaceutical sales in 2019, making up for headwinds like the loss of the erectile dysfunction drug *Cialis* to generic competition and US pricing pressure.

"Our new product revenue growth highlights our ability to translate R&D productivity into top-line growth by leveraging our commercial capabilities," Ricks said.

But while the company has several older medicines and insulins that are consistent blockbusters, some of the new drugs have a way to go to get there. *Trulicity* (dulaglutide), a once weekly GLP-1 agonist, has been stellar, generating $2.27bn in the first nine months of 2018. However, some recent launches have been slower, like *Taltz* (ixekizumab) and *Verzenio* (abemaciclib), coming to market behind big successes – **Novartis AG**' *Cosentyx* (secukinumab) and **Pfizer Inc.**'s *Ibrance* (palbociclib), respectively.

Olumiant (baricitinib) isn't expected to be a big contributor to the top-line in the short-term. The oral JAK1/2 inhibitor was approved by the FDA for moderate-to-severe rheumatoid arthritis in June, but only at the less effective 2 mg dose (the higher 4 mg dose was held back due to concerns over safety). *(Also see "Lilly Prices Olumiant For JAK Battle, But Misses*

Approval For Higher Dose" - Scrip, 2 Jun, 2018.) Nonetheless, Lilly is developing Olumiant for other indications like atopic dermatitis, alopecia and lupus, and it continues to see big prospects for the drug longer-term.

Emgality also launched behind competitors, but Lilly was able to narrow the timeline to just a few months. *(Also see "Migraine Market Gets Competitive With Second, Third CGRP Inhibitor Launches" - Scrip, 9 Nov, 2018.)*

IMPROVING FIRST-IN-CLASS PRODUCTIVITY

Despite R&D productivity improvements, being second- or third-to-market with a new drug can be an enormous disadvantage. Skovronsky said that delivering first-in-class drugs to the market is one of his top priorities as the head of Lilly's R&D.

"Despite tremendous progress, despite being able to move quickly through late-stage development with success of differentiated molecules, so many of our important molecules have not been first-in-class," he said. The reason wasn't because Lilly was slower in development or because its scientists didn't see the promise of the targets until after competitors, he said.

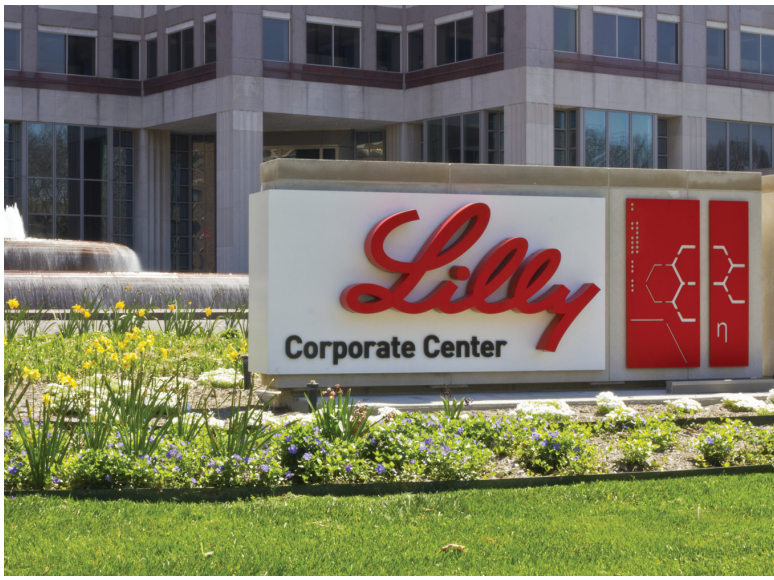
"Where we were slow is in translating those scientific insights, those innovations in a laboratory into proof-of-concept data for patients, and so that's where we seek to improve," he said. "We have the potential to shave years off of that stage of development, and if we can do that, we can more consistently bring molecules that are first-in-class."

THE LATE-STAGE PIPELINE

In R&D, the big data catalysts for Lilly next year will be top-line Phase III data read-outs for the NGF inhibitor tanezumab, partnered with Pfizer, for osteoarthritis pain and chronic lower back pain. The market for a non-opioid pain reliever represents big potential, but the safety profile of tanezumab will be a big factor for getting across the regulatory barrier and commercial success. **Regeneron Pharmaceuticals Inc.** and **Teva Pharmaceutical Industries Ltd.** are also partnered on a similar drug.

Lilly is also on track to file Taltz for a new indication in radiographic axial spondyloarthritis (aXSpa) next year, and it will have top-line Phase III data on Taltz in non-radiographic aXSpa, as well data from a Phase III head-to-head trial comparing Taltz in psoriasis to **Johnson & Johnson**'s IL-23 blocker *Tremfya* (guselkumab). Lilly is developing its own IL-23 blocker, mirikizumab, and announced the initiation of a Phase III program in psoriasis patients, with the expectation for a data read-out in 2020. The company is also studying the drug in ulcerative colitis and Crohn's disease.

Lilly also announced the initiation of a broad Phase III program testing tirzepatide, a dual GIP/GLP-1 receptor agonist in development for type 2 diabetes that investors have high hopes for. In Phase II testing, the drug generated impressive improvements in HbA1C reduction and weight loss versus placebo and Trulicity. The Phase III SURPASS program will include multiple trials testing tirzepatide against various insulins as well as a cardiovascular outcomes trial. The company also unveiled plans to move the drug into Phase III testing next year in obesity and Phase II for nonalcoholic steatohepatitis (NASH).



"We're, I think, years ahead of the competition here with a medicine that has the potential to be a game-changer for people with diabetes," Skovronsky said.

The initiation of the large tirzepatide Phase III program and the mirikizumab program is expected to be a big contributor to increased R&D spending in 2019. The company expects to raise R&D spending next year to $5.6bn to $5.8bn, an increase of 7% over spending in 2018. The increase represents a "high water mark" for year-over-year increases in R&D spending, according to Smiley.

Lilly also highlighted programs in its oncology portfolio, but other than continued development of Verzenio, the main late-stage candidate is the newly acquired immuno-oncology asset pegilodecakin. Lilly gained the pegylated interleukin-10 with the $1.6bn acquisition of **Armo BioSciences Inc.**. *(Also see "$1.6bn ARMO Buy Gives Lilly Its Most Advanced Immuno-Oncology Asset" - Scrip, 10 May, 2018.)* The drug is being studied in second-line pancreatic cancer in Phase III in combination with chemotherapy, and in non-small cell lung cancer in Phase II in combination with Merck's *Keytruda* (pembrolizumab), with top-line data expected in 2019.

"Depending on the data that we get from these trials, this will inform our future development of pegilodecakin," Skovronsky said.

The oncology portfolio is one that could benefit from additional business development, White said.

"Adding to our portfolio has been a very key focus of mine already in these early days, the first few months of this role, and we do believe that there are a number of good opportunities out there," she said. Skovronsky also talked about some of the changes being made when it comes to business development. *(Also see "Lilly Ready For More Risk When It Comes To Early Deals" - Scrip, 19 Dec, 2018.)*

Lilly confirmed 2018 revenue guidance of $24.3bn to $24.5bn and issued 2019 revenue guidance of between $25.3bn to $25.8bn and earnings per share of $5.52 to $5.62. The company also raised its compound annual growth rate from 2015 to 2020 to 6%, up from 5%.

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Eisai Adds To Alzheimer's Arsenal With Anti-Tau Drug

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As **Eisai Co. Ltd.** gets ready to puts another Alzheimer's drug into the clinic, the result of a collaboration with University College London (UCL), the Japan-headquartered company has been weighing up the challenges that industry and governments face in getting access to disease-modifying agents in the future.

In an interview with *Scrip*, Nick Burgin, president and chief operating officer of Eisai EMEA, noted that in terms of unmet need and burden of disease, neurology ranks probably second after oncology and in terms of market size and commercial opportunity, dementia is rapidly growing in line with the world's rapidly aging population. There are fewer players in the neurology field compared with cancer, with a number of firms such as **GlaxoSmithKline PLC**, **Pfizer Inc.** and **AstraZeneca PLC** having exited the CNS space, and Eisai, helped by its alliance with **Biogen Inc.** and having developed *Aricept* (donepezil) to treat the symptoms of dementia caused by Alzheimer's over 30 years ago, is an industry leader. *(Also see "Neuroscience Is The Next Oncology: Why Biogen Is Doubling Down" - Scrip, 23 Nov, 2018.)*

PIPELINE

Burgin highlighted the firms' pipeline in Alzheimer's, a field which is littered with clinical failures. However they have high hopes for aducanumab, which reduces the number of amyloid plaques present in the brain and, some researchers believe, slows neurodegeneration and reduces disease progression. Due to a design change in a Phase III study, data readouts are not expected until early 2020. *(Also see "Biogen Spooks With Phase III Aducanumab Changes" - Scrip, 15 Feb, 2018.)*

Next up is a similar monoclonal antibody, namely BAN2401. New data from a closely watched Phase II trial were presented in July but the results, while declared positive, failed to convince analysts who are still waiting to see if a Phase III trial, the protocols for which are still being discussed, according to Burgin, will finally prove the amyloid hypothesis. *(Also see "Biogen, Eisai Report BAN2401 Seemingly Positive In Alzheimer's; Others Skeptical" - Scrip, 26 Jul, 2018.)*

Burgin also mentioned the beta amyloid cleaving enzyme (BACE) inhibitor elenbecestat, which potentially works earlier in the process and could be disease-modifying. He noted that recruitment for a Phase III trial was on track, with results scheduled for the end of next year. *(Also see "Eisai/Biogen Remain In BACE Race As Alzheimer's Contenders Dwindle" - Scrip, 6 Jun, 2018.)*

Aside from the Biogen alliance, Eisai recently announced the first candidate from its UCL collaboration is to enter Phase I trials for Alzheimer's early next year. E2814 is an anti-tau monoclonal antibody designed to target tau protein 'seeds' that spread between different areas of the brain as the disease advances within affected individuals.

The hope is that E2814 will prevent further build-up of neurofibrillary tangles made of tau protein in the brain and may slow the course of the disease. Andy Takle, head of Eisai Hatfield Research Laboratories which is based outside London, told *Scrip* the UCL pact, inked in 2012 for an initial six years, was part of the company's 'open innovation' strategy designed to access the latest emerging science in the dementia space.

He said he was "very pleased with the speed we have advanced the project," which started in the middle of 2014. "To have gone from concept to clinical study in just four and a half years is impressive," Takle added, saying that "both parties recognize the value of working together on projects which neither can do alone and by working outside our own four walls we can tap into world class research." The UCL partnership has been extended for a further five years to 2023.

> 'We have already had some preliminary discussions with NICE about Alzheimer's; it is very much on their radar screens,' Burgin said.

Supporting a healthy pipeline does not come cheap, especially for a company of Eisai's size and Burgin noted that Alzheimer's trials were "hugely expensive," a key reason for the Biogen partnership. He also expressed concern about the financial strain put on small to medium-sized companies who are having to put together cost effectiveness packages for payers at the same time as they are preparing filings for regulatory approvals. "We have already had some preliminary discussions with NICE about Alzheimer's; it is very much on their radar screens," Burgin said.

PATIENT ACCESS

He believes that the arrival of disease-modifying Alzheimer's therapies will have a big impact on governments' coffers, on the social care budget as well as the medicines bill, which are separate in most countries. The patient pathway to access to these innovative drugs is also going to be a challenge, Burgin noted, pointing out that the latter would be administered earlier so symptoms will be much less obvious in patients and finding the patients who will benefit most will require more PET scans to detect plaques in the brain.

Also if aducamumab and BAN2401 get to market, as biologics they will be delivered by infusion, another costly business, as are the MTI scans that will be needed to check on how well patients are responding to treatment after 12 months, said Burgin. Some markets are well resourced to cope with all these factors but others are not, he stated, and governments need to get planning quickly.

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Lupin Ends 2018 On High, Strikes Large MALT1 Deal With AbbVie

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Lupin Ltd., which has had a generally tough run in 2018, is ending the year with a bang, striking a licensing deal that is potentially valued at over $900m with **AbbVie Inc.** for an early stage asset. *(Also see "Lupin Paints Better Second Half Riding On Solosec, New US Launch Hopes" - Scrip, 1 Nov, 2018.)*

The deal will see Lupin license out its MALT1 (Mucosa-Associated Lymphoid Tissue Lymphoma Translocation Protein 1) inhibitor program to AbbVie in return for up to $947m (including an upfront payment of $30m) due on successful completion of certain regulatory, development and commercial milestones. Lupin is also entitled to double-digit royalties on the sales of the product and will retain commercial rights to the program in India.

AbbVie will have exclusive global rights to develop and commercialize Lupin's MALT1 inhibitors and the US firm intends to develop the asset across a range of hematological cancers, many with limited current treatment options. MALT1 is a protein involved in T-cell and B-cell lymphocyte activation.

Lupin's managing director Nilesh Gupta said that the deal terms were "pretty much unprecedented" for a preclinical candidate and "speak volumes about the level of science that has gone in."

"Obviously it's still a few years of development that has to go in but as and when the product comes to the market it brings a very important treatment paradigm to patients. With this compound, we have the chance to be the first to the clinic and even an opportunity to be first to market," Gupta said on a media call Dec. 24.

PARTNER OF CHOICE

Lupin's president of Novel Drug Discovery and Development (NDDD), Dr Raj Kamboj, said that the first-in-class drug discovery program was delivered exclusively by Lupin "right from concept generation" through the various stages of drug discovery and development.

In experimental studies, Lupin's molecule (LND 700110) is said to have produced a complete regression of certain tumor types and the targeted approach meant that it doesn't affect normal cells of the body.

AbbVie, Kamboj indicated, took and tested the asset extensively in its lab as well and "they found the results to be very satisfactory."

Kamboj also hinted that there may have been more parties interested in the Lupin asset, but that Lupin "wanted AbbVie to be the partner of choice."

"There is interest in the area, but we were very focused to strategically focus on AbbVie because of their development and commercialization expertise in this area," Kamboj told *Scrip* in a telephone interview

On whether other indications - MALT1 inhibitors are reported to have potential in autoimmune and inflammatory diseases – fall under the purview of the deal with AbbVie, Kamboj said: "We've given them exclusive global rights for all indications." A statement from Lupin reported Dr Tom Hudson, vice president (discovery) at AbbVie, as saying that Lupin's MALT1 program is exploring a new and innovative approach in difficult-to-treat cancers."AbbVie is committed to pursuing advanced treatment options for patients and we look forward to partnering our expertise in hematological oncology with Lupin's discovery program to offer new hope to patients," Hudson said.

Lupin has licensed its early stage oncology asset to AbbVie

LEADERSHIP POSITION?

Competition in the space, however, appears to have some big names including Novartis in the fray, though an updated position on the Swiss multinational's progress in the area could not immediately be ascertained. *(Also see "Life Science Start-Ups: Tech Transfer Deals, March 2014" - Scrip, 5 Mar, 2014.)*

On how Lupin's MALT 1 program was placed vis-à-vis others like that of **Novartis AG**, Kamboj told *Scrip*: "Based on our competitive intelligence, our program is in the worldwide leadership position today and they (AbbVie) are going to be doing their best to advance it into the clinical stages."

Earlier this year VIB, the Centre for Drug Design and Discovery of KU Leuven (CD3) and **Galapagos NV** entered into an exclusive license and collaboration agreement for the development of novel MALT1 inhibitors as therapeutics in inflammatory and/or oncological diseases.

Interestingly, Gary Deeb, Lupin's senior vice president, global licensing and business development (NDDD and biologics), maintained that there is currently no intellectual property (IP) or patents in the public domain because of how early and novel the MALT1 target is.

"Everyone is working in creating a space of IP and testing that IP in assays, animal models to see whether or not the drug works. This is the quintessential innovative component of being first in class, because you are in uncharted waters. So, it takes time to nail it and get it right," Deeb said, adding that what Lupin had done in a few years, in the innovative business, was "exceptional."

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Drug Price Waterloo: China's New Bidding Process Hits MNCs Hard

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The results of a new pilot drug price bidding scheme, announced by China's new Medical Insurance and Support Administration (MISA), sent immediate shock waves to the market, leading to instant trading halts for many publicly traded drug makers in Shanghai and Shenzhen as they were affected by the process.

Although the "winner takes all" model of highly centralized product bidding, the first ever for China, affected both domestic and international companies, underlined by a broad decline in shares prices, multinationals seemed to bear the brunt of the likely commercial hit.

The so-called "4+7" bidding scheme is named for the number of cities picked for the pilot, which will start in the four top-tier conurbations of Beijing, Tianjin, Shanghai and Chongqing, plus the seven second-tier urban centers of Shenyang, Dalian, Xiamen, Guangzhou, Shenzhen, Chengdu and Xi'an.

Under the scheme, a Joint Procurement Office bids for the supply of products at the lowest price on behalf of public hospitals in their areas.

The new bidding process is the latest move to reign in drug prices, especially for large-selling cancer and cardiovascular treatments. The latest quarterly sales figures show many major firms are continuing to grow well from local increases for established products, propelling companies such as Sanofi and Pfizer to double-digit growth in China. Sanofi saw its sales grow 18% in China compared to last year, and these were up 11% from the previous quarter. The reasons cited included a recent data forgery scandal that drove patients to imported vaccines.

One of the main reasons for the pilot, noted the MISA in its announcement, is that the regulators believe the effect of the "patent cliff" for some major older products has still not been realized in China, meaning that some off-patented originators drugs continue to command a price premium in the country.

> 'The average price reduction is 52% and the steepest cut is 96%, reflecting a significant reduction'

CUTS RANGE UP TO 96%

The results announced Dec. 6 show that the 31 selected drugs for the scheme include some widely-prescribed treatments such as **AstraZeneca PLC**'s *Crestor* (rosuvastatin), **Pfizer Inc.**'s *Lipitor* (atorvastatin), and *Norvasc* (amlodipine), and other best-selling cardiovasculars including **Merck & Co. Inc.**'s *Cozaar* (losartan) and **Sanofi**'s *Plavix* (clopidogrel), but also the CNS drug **Johnson & Johnson**'s *Risperdal* (risperidone) and **Bristol-Myers Squibb Co.**'s *Baraclude* (entecavir).

Additionally, some commonly used anticancer drugs including **Novartis AG**'s *Gleevec* (imatinib), AstraZeneca's *Iressa* (gefitinib) and **Eli Lilly & Co.**'s *Alimta* (pemetrexed) were also included in the bidding list.

Out of the total, the price bids for 25 drugs have been accepted, meaning an 81% success rate but leaving nearly 20% still to be decided.

"The average price reduction is 52% and the steepest cut is 96%, reflecting a significant reduction," noted the MISA in its statement. "[The off-patented products' prices] are now 25% lower than the average reference prices of surrounding markets, showing the effect of the 'patent cliff'," added the agency.

What's most notable in the process is the large number of multinationals to have lost bids, with only two MNCs successfully winning these, one being AstraZeneca with *Iressa* and the other BMS for *Monopril* (fosinopril). As part of the bidding scheme, however, AstraZeneca agreed to lower the price of Iressa by 76% while BMS cut its Monopril price by 68% in order to get into the game, which promises increased volumes.

Winners of the bid win the right to supply the product to the cities at the agreed price for one year, and to provide additional quantities at the same price if the original quantity is used up before this time.

PRICE WATERSHED?

But industry observers quickly pointed to a nosedive in prices for some best-selling generics that won this bidding round. One of these was amlodipine, for which branded Norvasc has seen dozens of competitors. Amlodipine tablets from a relative newcomer, Zhejing Jingxin Pharma, won the bidding this time at a price of CNY0.14 ($0.02) per tablet, roughly 97% below Norvasc's listed price of CNY5.

"Dec.6 marks the beginning of China's generics market to be taken over by [low-priced] generics, and the end of two eras, one when generics are high-priced, having high-profits and high promotion fees, and another era when branded generics dominated with large market shares," CEO of Chinese drug maker Canion Pharma Wu Jiqiang predicted in an interview with local media E-Pharma Managers.

Representatives from research-based multinational drug makers have already expressed opposition to the pilot scheme.

Jean-Christophe Pointeau, president of the R&D-based Pharmaceutical Association Committee (RDPAC), a major industry trade group representing 40 firms in China, said "it's not a right move", adding that "people can lower drug manufacturing costs, but it should not be at the expense of drug quality." The executive is the president of Sanofi Pharma China.

Addressing the quality concerns, MISA said that all 22 bid-winning drugs made by domestic firms had cleared bioequivalence testing, showing that their quality is equal to the off-patent reference products.

Despite the increase in expected volume uptake for the bid-winning products, which could partly offset lower prices, the unusually deep erosion of drug prices in the process has many worrying about a domino effect on the pharma sector.

The real impact, analysts say, could come from a ripple effect created by the sometimes shockingly steep price cuts, and the winning bid prices could be used as a reference for other products during future rounds of bidding.

"The volume [reported by each 4+7 city] may not reflect the real demand, but the prices could still be used for follow-on purchases," commented Yang Song, an analyst at Guotai Junan Securities. Shanghai, for one, has issued complementary policies to the bid that require hospitals prioritize to use the winning products, and other cities may soon follow its lead, noted the analyst.

LOOKING FORWARD

However, MISA said in its statement that the market selloff and strong reactions to the deep price reductions are an over-reaction, stressing what it sees as the transparency and fairness of the process.

"Drug price inflation has long been an issue," said the agency. "The price reduction is only a move to squeeze out inflation, and drug makers can still make a profit."

Facing fierce competition and mounting price pressures, many multinationals operating in China are now largely shunning branded generics, and are instead turning their focus to innovative new drugs that will offer better pricing power. *(Also see "Multinationals Eye Divesting Established Products In China Amid Fierce Competition, Shifting Focus" - Scrip, 25 Nov, 2018.).*

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From the editors of PharmAsia News.

Gilead Lures Roche Pharma's O'Day As CEO; Genentech's Head Will Replace Him

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After 31 years at Swiss cancer drug giant **Roche**, Daniel O'Day, an American, has decided to call it a day and move over to **Gilead Sciences Inc.** as both its CEO and chairman, bringing with him a solid CV in drug development, mergers and acquisitions.

The 54-year-old O'Day, currently CEO of Roche Pharmaceuticals, will take over on March 1 as Gilead's chairman and CEO. In the board role, he replaces John Martin, who steps down the same day, while John Milligan is leaving the chief executive role at the end of this year.

Roche said O'Day would step down from his role there on Dec. 31 but help Roche with a "smooth transition" until the end of February.

The American executive, who joined the Switzerland-based company in 1987, had a number of managerial positions while climbing the corporate ladder there, becoming its pharma head in 2012.

William Anderson, currently CEO of Roche-owned **Genentech Inc.**, will be appointed CEO of Roche Pharmaceuticals effective Jan. 1, 2019. He will be based in Basel, and report to Severin Schwan, Roche's Austrian-born CEO, becoming a member of the family-controlled group's corporate executive committee. Anderson's promotion means Genentech, which has been hit by a string of executive departures recently, will now be searching for its fifth CEO in less than a decade.

O'Day in a statement issued Dec. 10 said "I have long admired Gilead for its work to develop medicines that have fundamentally changed the way HIV and viral hepatitis are treated."

He noted the US company, founded in 1987, has since "successfully grown into a global organization, providing access to people around the world, while maintaining its focus on innovative science. Together with the board, leadership team and Gilead's 11,000 employees, I look forward to building on this."


Daniel O'Day

In a recent interview with *Scrip*, O'Day emphasized the importance that personalized healthcare will have in transforming R&D and how patients are treated. Read the full article here

His M&A record at Roche has also underscored his belief that real world evidence will become increasingly important for drug discovery and development and for successful approval by regulators and reimbursement by payers.

That can be seen in Roche's purchase in April of **Flatiron Health Inc.**, which offers research-quality electronic medical records data

which will help gain access to patients and help in the drug development and reimbursement process. *(Also see "'Watch This Space' Roche Execs Say, Outlining RWE Rationale For Flatiron Buy " - Scrip, 26 Apr, 2018.)*

ANALYSTS APPLAUD APPOINTMENT

Analysts at Mizuho Securities conducted a straw poll of investors after the news on Dec. 10. It showed two-thirds of those asked approved of Gilead's choice of O'Day as its chairman and CEO.

The choice of O'Day is the first time in the last 20 years that Gilead has put in place a CEO from outside the company. John Martin joined the US pharma in 1990 in R&D and became CEO from 1996-2016. John Milligan also joined Gilead in 1990 in R&D and became CEO in 2016.

It's also the first time in the last 20 years that Gilead has put in place a non-PhD in the CEO role. John Martin held a PhD in organic chemistry. John Milligan held a PhD in biochemistry. Gilead was founded by Michael Riordan, a medical doctor, in 1987.

"An external CEO with a non-advanced science degree may shift the company to a more operational bent. While moving from a background-deep-science CEO to perhaps a more operational one is a shift from how the company has appointed its CEOs, the company is also much larger today, so it's not necessarily a bad thing in our view," the Mizuho Securities analysts said.

They added that O'Day's hiring seemed to further indicate "that Gilead would like to further branch out in oncology ... We can probably expect more oncology deals from Gilead."

Analysts at Baird Equity Research also viewed the appointment of O'Day as a positive for Gilead.

"We have viewed the uncertainty around who would take over as CEO as a major overhang in the last few months, and see the appointment of a qualified and experienced executive to the role as a positive for Gilead heading into the new year," analyst Brian Skorney said in a Dec. 10 note to investors.

"Although Roche is diversified, there is no question oncology and immunology are the most successful franchises there. This is in line with Gilead comments that have been suggestive of a CEO with oncology expertise."

Skorney noted that "Roche has largely been absent in the cell therapy land-grab, preferring, as we do, more traditional therapeutic modalities. It will be interesting to see how Mr. O'Day speaks about the cell therapy versus bi-specific/ADC/traditional mAb debate in his new role."

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AAA President Takes Novartis Oncology Top Job, As Barrett Leaves For Biotech

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Before Liz Barrett had a chance to put her strategy into action at **Novartis AG** Oncology, she has decided to leave the role as CEO, to be replaced by **Advanced Accelerator Applications SA** (AAA) president Susanne Schaffert.

Citing personal reasons for the exit, namely that she would not be able to move her family to Basel from the US, she has accepted the role as a CEO of a US-based biotech, as yet it is not known which company she will lead.

Only in the post since February, after a high profile move from leading **Pfizer Inc.**'s oncology division, Barrett's stated priority for the Novartis division was to reinvigorate its pipeline with new brands while older assets such as *Gleevec* (imatinib) lose patent protection. In a statement, Novartis CEO Vas Narasimhan, himself only in his role since February, referred to its "pipeline of talent" when announcing that this vital position would be taken by Susanne Schaffert.

Schaffert is a Novartis stalwart, joining the company more than 20 years ago. She has spent the last six years in the oncology business in leadership roles, including region head, Novartis Oncology Europe, where she led that organization for five years.

During her tenure as oncology head, she was instrumental in the **GlaxoSmithKline PLC** oncology integration and served on the board of the Consumer Health joint venture between Novartis and GSK until early 2018. Before her time working in the oncology division, she was head of investor relations, and and before that worked in sales and marketing in both the pharmaceuticals and oncology business units.

Most recently, Schaffert was appointed president of Novartis's buy-in nuclear medicine specialist AAA, launching *Lutathera* (lutetium Lu 177 dotatate), a radioligand therapy for the treatment of certain cancers, in the US and EU.

AAA operates independently of Novartis, and Schaffert has been busy overseeing its plans for ramping up its technology platform to a broader range of tumors. *(Also see "AAA Ramps Up Lutathera Launch And Plans Expansion Under Novartis Ownership " - Scrip, 5 Jul, 2018.)*. It is currently unknown who will now lead AAA, and if the company will be brought in-house.


Liz Barrett


Susanne Schaffert

ONCOLOGY FOCUS

Schaffert is taking over at a critical juncture for Novartis and its still-to-be-proven CEO Narasimhan, as he reimagines what a large pharmaceutical company should resemble in the modern world. This includes culling the pipeline, jettisoning certain therapeutic areas altogether such as anti-infectives. *(Also see "Novartis Pruned Pipeline Producing Attractive Respiratory And Neurology Fruits" - Scrip, 13 Dec, 2018.)*

Its R&D engine now centers around six core areas: oncology, cardiometabolic, neuroscience, ophthalmology, respiratory, immune/ inflammation. While the company's recent bolt-ons, including AAA, have been in non-traditional areas such as radiopharmaceuticals and gene therapy, buying **Endocyte Inc.** for $2.1bn and **AveXis Inc.** for $8.7bn, its oncology department is still a clear commercial priority for the organization.

Datamonitor Healthcare forecasts a 2.5% compound annual growth rate (CAGR) for the division, projecting it to make more than $11bn of annual revenue for the company by 2027, making it the biggest department by far.

Novartis Oncology has 32 drugs in Phase I, 28 in Phase II and eight in Phase III.

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Menarini Owners Acquitted Of Fraud

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The brother and sister owners of Italy's largest pharma company, **Menarini Group**, have been acquitted of money laundering by the Court of Appeal in Florence. Lucia and Alberto Giovanni Aleotti had been found guilty in the Court of First Instance in 2016 and sentenced to prison. The court has now cleared them of all charges and ordered that about €700m that had been seized from the defendants be restored to them.

Menarini board member Carlo Colombini expressed satisfaction that the ruling "recognized the complete inexistence of the alleged fraud against the Italian National Health System." He noted that it had been reconfirmed that "Menarini products have never been sold at 'inflated' prices, acknowledging therefore the company's complete business integrity."

A spokesperson for the Aleotti family stated: "We are satisfied that Lucia Aleotti and Alberto Giovanni Aleotti have been acquitted by the Court of Appeal of Florence for all of the accusations made against them. Many years have gone by since this distressing case began, but finally the judge has acknowledged that the Menarini stakeholders were in no way involved in the matters for which they have been wrongly accused. Now Lucia and Alberto Giovanni Aleotti will be able to continue focusing on the growth of the Menarini Group which today has more than 17,000 employees and which, despite not being directly involved in the court case in any way, has most certainly suffered both damages and serious negative repercussions on the company image on an international level as a result of this judicial enquiry."

Lucia Aleotti, who stepped down as Menarini's chair in March 2018 to be replaced by Novartis's former chief ethics, compliance and policy officer Eric Cornut, and her brother had been accused of various crimes including money laundering and defrauding the health service by overcharging for medicines. In 2016 they had initially been handed sentences of 10 and a half and seven and a half years, respectively, for tax fraud, but cleared of other accusations including overcharging the Italian health system. Their mother Massimiliana Landini had also initially been accused of money laundering but was cleared by the Court of First Instance in 2016.

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Summit Hits The Heights With Billionaire Backing

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Summit Therapeutics PLC, and the world of antibiotics research, have been boosted by the news that US healthcare entrepreneur and billionaire Bob Duggan is paying $25m to take a large stake in the UK firm.

Duggan, who was CEO and chairman of **Pharmacyclics Inc.** before it was sold to **AbbVie Inc.** for $21bn in 2015, has agreed to pay $1.60 each for over 15.6 million American Depositary Shares in Summit, representing a 32% premium to the latter's stock price when it closed on the Nasdaq on Dec. 14. The purchase will push his stake up in the company from just 0.2% to a whopping 48.8%.

Getting Duggan on board is a major coup for Summit. At Pharmacyclics, the billionaire oversaw the development of the blood cancer drug *Imbruvica* (ibrutinib), a blood cancer drug which made more than $2.5bn in sales for AbbVie in the first nine months of the year, plus another $1.9bn for partner **Johnson & Johnson**.

Now heading up his own private investment firm, Summit said that Duggan's focus "is on patient-friendly breakthrough therapies to the resolution of complex healthcare situations, including the urgent need to develop new antibiotic treatments." It added that the entrepreneur holds Summit's management team and its strategy "in high regard."

Duggan "is a seasoned healthcare entrepreneur and investor whose proposed investment into our company speaks volumes about the potential that our new mechanism antibiotics have in addressing serious infectious diseases," said the Oxford-based firm's chief executive Glyn Edwards. "We are thrilled with his commitment to Summit and look forward to advancing our programs…and showing significant advantages over current standards of care."

In an interview with *Scrip*, Edwards said that the first specific contact with Duggan came at the JP Morgan healthcare conference in San Francisco two years ago. Duggan had links with Summit's home town, having invested in a couple of Oxford University start-ups, and was very interested in the company's antibiotics programs but was "less comfortable" with a Duchenne muscular dystrophy program it was running in partnership with **Sarepta Therapeutics Inc.**

However, in June this year, Summit's utrophin modulator ezutromid failed as a potential treatment for DMD in a Phase II trial and the company refocused as an anti-infectives specialist. It was then that Duggan "reached out to us, as he thought our antibiotics programs looked really good – he feels the advancement of the field is really important for mankind and given that valuations are so beaten up, he also believes he can make a good return," Edwards said.

> Duggan's focus 'is on patient-friendly breakthrough therapies to the resolution of complex healthcare situations, including the urgent need to develop new antibiotic treatments'

He added that after the demise of the DMD candidate, some advisors had suggested that Summit's management team was too good to focus on antibiotics and should look at other therapeutic areas, "but this was like a red rag to a bull. We believe it is a huge opportunity where there is a clear unmet medical need at one end and lots of innovative science at the other, but the middle bit of investment has been lacking." *(Also see "A Call To Action On Antibiotic Development" - Pink Sheet, 5 Dec, 2018.)(Also see "'Slow Money As Bad As No Money' – SMEs Struggle For Superbug Funds" - Scrip, 9 Nov, 2018.)*

Now Summit is building up a roster of long-term investors, of whom Duggan, who has other investments in the antibiotics space, is the first. However, the proposed deal is slightly complicated by the fact that under UK financial rules (Summit is also listed on the London Stock Exchange's AIM), a shareholder who owns more than 30% of a company's shares is required to make a general offer to other investors. However Summit is asking shareholders to vote in favor of waiving that requirement, known as Rule 9, at a meeting on Jan. 4, 2019.

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

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

PIPELINE WATCH, 14–20 DECEMBER 2018

Stage Of Event	Lead Company/Partner	Drug Name	Indication	Comments	Change To LOA (%)	LOA (%)
Phase III Published Results	Bayer/Amgen	Nexavar (sorafenib)	Desmoid Tumors	NEJM, Dec. 20, 2018	0	35
Phase IIIb Top-Line Results	Teva Pharmaceutical Industries Ltd.	Ajovy (fremanezumab)	Migraine Prophylaxis	FOCUS; Met Primary And Secondary Endpoints	0	100
Phase III Top-Line Results	Saniona AB/Medix	tesofensine	Obesity	Viking (Mexico); Met Primary And Secondary Endpoints	-	-
Phase III Top-Line Results	Evofem Biosciences, Inc.	Amphora (L-lactic acid, citric acid, potassium bitartrate)	Contraception	AMPOWER; Met Primary Endpoint	11	71
Phase III Top-Line Results	Puma Biotechnology, Inc.	Nerlynx (neratinib)	Breast Cancer, HER-2 Positive Metastatic, Third-Line	NALA; Encouraging Results	0	100
Phase III Top-Line Results	Roche Holding AG	satralizumab	Neuromyelitis Optica	SAkuraStar (Monotherapy); Met Primary Endpoint	1	68
Phase III Top-Line Results	AstraZeneca PLC/FibroGen/Astellas	roxadustat	Anemia Due to Chronic Renal Failure, Dialysis-Dependent And Dialysis-Independent	HIMALAYAS, SIERRAS, ROCKIES, ANDES, OLYMPUS; Met Primary Endpoints	5	68
Phase III Top-Line Results	AstraZeneca PLC/Merck & Co	Lynparza (olaparib)	Ovarian Cancer	SOLO 3; Improved Objective Response Rate	0	100
Phase III Top-Line Results	Pfizer/Astellas	Xtandi (enzalutamide)	Prostate Cancer, Metastatic, Hormone-Sensitive	ARCHES; Met Primary Endpoint	0	100
Phase III Top-Line Results	Supernus Pharmaceuticals, Inc.	SPN-812	Attention Deficit Hyperactivity Disorder	P302 (Low Dose Adolescents); Met Primary Endpoint	0	62
Phase II/III Updated Results	Catalyst Biosciences, Inc.	marzeptacog alfa	Hemophilia A and B	MAA-201; Reduced Bleeds Observed	0	30
Phase III Trial Initiation	Galapagos NV	GLPG1690	Idiopathic Pulmonary Fibrosis	ISABELA 1, 2; An AutoTaxin Inhibitor	50	70

Source: Biomedtracker | Informa, 2019

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Edwards explained to *Scrip* that Rule 9 "is a very sensible rule," as it helps to stop "takeovers by stealth" where potential buyers did not have to make offers to existing investors. He noted that Duggan has the means to acquire Summit but he has no desire to interfere with the running of the company, hence the move to waive Rule 9, and the initial feedback from shareholders about his future participation has been very supportive.

Assuming investors vote with the board and back Duggan's investment, the money will help Summit begin patient enrolment into the Phase III clinical trial of ridinilazole for the treatment of *Clostridium difficile* infection. Announcing its financials for the first nine months of 2019 last week, the company said it would initiate the late-stage program in the first quarter of 2019 on the back of Phase II studies which showed ridinilazole reduced recurrence rates by 59% versus standard of care vancomycin in patients with *C difficile* infection.

Edwards noted that the space has suffered a lack of truly new mechanisms of action, and the most recently approved antibiotics got regulatory green lights simply by showing non-inferiority to older products, which in turn has made it difficult to get significantly better prices for the newer offerings. However, the Phase III trial of ridinilazole is being designed to show superiority and its narrow spectrum of activity, which wipes out specific organisms but leaves the patient's microbiome unaffected, is a major advance, he said, acknowledging that Summit has had "a few manufacturing issues" but is ready to start the studies.

Summit noted that it has also been receiving funding for ridinilazole from the US government agency BARDA (the Biomedical Advanced Research and Development Authority), which committed a further $12m in August of an up-to-$62m award, bringing the total of committed BARDA non-dilutive funding to $44m. The company had cash and equivalents of £13m (about $16m) at the end of October but the Duggan money means that operations will now be funded through to the end of January 2020.

Some of the cash will also go towards completing investigational new drug application-enabling studies for SMT-571, Summit's gonorrhea candidate. Up to $4.5m was awarded by the US funding vehicle CARB-X (Combating Antibiotic Resistant Bacteria Biopharmaceutical Accelerator) in July 2018 to support the preclinical and Phase I development of SMT-571.

The extra funds will also be used to accelerate the development of treatments for hospital-acquired infections caused by ESKAPE (*Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa* and *Enterobacter* species) identified by Summit's proprietary Discuva platform.

Summit also noted that chief financial officer Erik Ostrowski is to step down from the role at the end of the month to pursue another, as yet undisclosed, opportunity. Edwards had warm words for the outgoing CFO, saying he led Summit through several successful financings, including its US initial public offering, "was instrumental in building out our US operations, and has been a key strategic contributor to the company." *Published online 17 December 2018*

APPOINTMENTS

Executive	To Company	New Role	From Company	Previous Role	Effective Date
Yu Liu	Compass Therapeutics	Chief Medical Officer	Pfizer Inc	Vice President and Head, Clinical Development	19-Dec-18
Nitya Ray	CytoDyn Inc	Chief Technology Officer	Actinium Pharmaceuticals Inc	Executive Vice President and Head, Product Development	29-Dec-18
Arjun Desai	InSightec Ltd	Chief Strategic Innovation Officer	Johnson & Johnson Innovation	Vice President and Chief Operating Officer	10-Dec-18
Colin Freund	Modra Pharmaceuticals BV	Chief Executive Officer	QUE Oncology Inc	Chief Executive Officer	19-Dec-18
Edwin De Wit	Modra Pharmaceuticals BV	Head, Oncology Development	Celsion Corp.	Senior Vice President and Head, Medical, Europe	19-Dec-18
Nancy Wyant	Stoke Therapeutics	Vice President and Head, Clinical Operations	BeiGene USA Inc	Vice President, Clinical Operations	18-Dec-18
Shamim Ruff	Stoke Therapeutics	Senior Vice President, Regulatory Affairs and Quality	Sarepta Therapeutics	Chief Regulatory Affairs Officer and Senior Vice President, Head, Quality	18-Dec-18

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

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