Collaboration
Bristol teams up with billionaire-backed Parker Institute on IO (p8)

Exclusive Interview
Genentech's early cancer technology scout talks partnering (p10)

Expert View
Payers want deep discounts to make biosimilars worth their while (p12)

Scrip
scrip.pharmamedtechbi.com
7 April 2017
No. 3848
Pharma intelligence | informa

Shutterstock: funnyangel

Sanofi/Regeneron Choose Access Over Price With Dupixent Launch

The FDA approved the IL-4/IL-13 inhibitor March 28 in a win for Sanofi and Regeneron. The companies set the biologic's price at $37,000 per year, which is lower than many biologics on the market for psoriasis.

JESSICA MERRILL jessica.merrill@informa.com

Sanofi and Regeneron Pharmaceuticals Inc. will launch *Dupixent* (dupilumab), the first targeted biologic for atopic dermatitis, at a wholesale acquisition cost of $37,000 per year – a price the companies actively discussed with payers and which falls below the cost of many biologics already on the market for the adjacent dermatology indication psoriasis.

The result is that some payers appear receptive to the new biologic, which could pave the way for faster uptake in the commercial market. Dupixent, approved by the US FDA under priority review on March 28, represents a paradigm change for patients with moderate-to-severe atopic dermatitis.

The first-in-class interleukin-4/IL-13 inhibitor is the first systemic treatment for a painful skin condition, which also is known as eczema and is characterized by red, cracked patches of skin and intense, persistent itching. The indication is for patients with moderate-to-severe atopic dermatitis whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable.

Physicians and patients have been eager for new treatments, since standard topical treatments have efficacy and safety limitations. But even ahead of the approval, some physicians were already expressing concern that payers might try to limit access to the drug, because of its potentially high cost. The anticipated launch of a high-priced biologic into the nascent category prompted The Institute for Clinical and Economic Review to develop an assessment report on the effectiveness and value of therapies for atopic dermatitis; a draft assessment was released March 24.

"RESPONSIBLE" PRICING

But Sanofi and Regeneron – whose CEO Leonard Schleifer has been an outspoken critic of some pharmaceutical industry pricing practices, notably price increases – appear to be trying to limit any blowback on pricing.

"In looking at the benefits this drug can provide to patients that really have no solution, we believe we have an innovative drug and we should charge for the innovation," executive vice president-commercial Robert Terifay said in an interview. "However, we didn't want to go outside of what is responsible."

The wholesale acquisition cost is lower than the price of other biologics on the market for psoriasis, drugs like AbbVie Inc.'s tumor necrosis factor inhibitor *Humira* (adalimumab) and Johnson & Johnson's *Stelara* (ustekinumab). Biologics on the market

CONTINUED ON PAGE 7

IN THIS ISSUE

from the editor

eleanor.malone@informa.com

Pharma spends a lot of money to develop products that not only help alleviate patients' suffering, but also reduce the overall costs to society of the diseases they address. Still, in a price-constrained world, the drug industry is often attacked for its contribution to the cost of treating disease, even though the cost of not doing so can be far higher.

So it is surprising to see not one but two US launch strategies pricing drugs below the value payers might accept, despite the fact that both are for innovative therapies addressing serious, unmet medical needs.

As Jess Merrill reports in our cover story, Sanofi and Regeneron's pricing of Dupixent has afforded them a warm reception from payers and the prospect of rapid uptake. (This is something of a contrast to the same partners' launch of Praluent, which caused alarm with its high cost and potentially large target population.) Roche is playing a similar game with Ocrevus, a breakthrough for progressive MS that is nonetheless being launched at a sizeable discount to older mainstay treatments for the better-served relapsing-remitting patient population (see p5).

exclusive online content

Finance Watch: Raising Cash Before A Trump Slump, La Jolla Nabs $125m, Akcea Eyes $100m IPO
La Jolla Pharmaceutical grossed $125m, Inspyr Therapeutics signs a deal to raise up to $100m, Ionis's Akcea makes $100m IPO plans, and $64m in cash for SutroVax tops recent venture capital rounds.
http://bit.ly/2ot34cS

Deal Watch: Merck, Incyte Double Down On Keytruda/ Epacadostat Collaboration
Expansion of 2015 development partnership adds lung and bladder cancer as well as renal and head-and-neck carcinoma to trials of the two immuno-oncology drugs. Jazz licenses Japanese rights to two of its commercial products to Nippon Shinyaku.
http://bit.ly/2oB9XoZ

@scripnews /scripintelligence
/scripintelligence /scripintelligence

© Informa UK Ltd 2017

Mylan's Generic Advair Delay Gives Leverage To Rivals

JESSICA MERRILL jessica.merrill@informa.com

Mylan received a "complete response" letter from the FDA on its application for a generic version of GSK's blockbuster Advair, offering scarce details on the reason why or possible length of the delay.

Shutterstock: Still Life Photography

Mylan NV's setback is GlaxoSmithKline PLC's advantage. Mylan announced March 29 that it received a "complete response" letter from the US FDA relating to its ANDA to market a generic version of GlaxoSmithKline PLC's asthma blockbuster *Advair Diskus* (fluticasone/salmeterol), likely delaying a launch by months and possibly longer.

The question of whether or not Mylan's generic would receive FDA approval has been a high-stakes game of will they or won't they. Advair is considered a complex generic drug, a combination of two active ingredients delivered to the lungs through a particular device, and the complexity is the reason GSK has been able to maintain market exclusivity in the US beyond Advair's patent expiration.

Still, in public presentations, Mylan executives have been bullish about a first-round approval. During an investor day in March, president Rajiv Malick said Mylan was preparing for a summer launch of the product and unveiled a new brand name, *Wixela Inhub*. Still, he acknowledged the company's timeline was ambitious.

Mylan announced the delay in a succinct press release that offered no details about the contents of the FDA's response or the potential length of a delay.

"Mylan is in the process of reviewing this response and will provide an update on its application as soon as practicable once it has completed its review and discussed the FDA's feedback with the agency," the company said.

Mylan's announcement came one day after the March 28 GDUFA date set for FDA action.

Being first to market with an interchangeable version of Advair would be a big win for Mylan. The drug, approved for asthma and chronic obstructive pulmonary disease, is one of the biggest generic opportunities in 2017. It is GSK's top-selling drug, generating £3.49bn (about $4.34bn) worldwide in 2016.

Now, a delay represents a temporary win for GSK; how long a reprieve the UK drug maker will get isn't clear. The news will at least be viewed as a positive start for incoming CEO Emma Walmsley, who officially takes over the helm of GSK from Andrew Witty on April 1. Witty, for many years, insisted the complexity of Advair would keep generic rivals out of the market and he worked to bring new respiratory drugs to market to reduce the company's reliance on its workhorse product in the interim.

He could yet be proven correct, although more recently even Witty began to prepare investors for the eventuality of a generic Advair. GSK worked an interchangeable generic into its 2017 forecasts, telling investors that a mid-year launch in the US would reduce Advair's sales to £1bn from £1.83bn in 2017.

Mylan's setback will also be viewed as positive news for generic rivals racing to launch their own interchangeable generics. Hikma Pharmaceuticals PLC has its own ANDA pending at FDA with an action date of May 10. Other drug makers including Novartis AG's Sandoz unit and Teva Pharmaceutical Industries Ltd. also are looking to bring generic rivals to market.

Teva's new competitor *AirDuo* also could benefit from the delay. AirDuo includes the two active ingredients in Advair – fluticasone and salmeterol – but isn't interchangeable because it is delivered through Teva's own *RespiClick* device and it was approved through a 505(b)2 regulatory pathway rather than the standard generic drug approval pathway.

A citizen petition filed by Sandoz sought to block the FDA from approving any ANDAs for generic Advair unless the sponsor met certain requirements in pharmacokinetic bioequivalence testing, which it said were lacking in FDA's 2013 draft guidance on generic Advair. FDA issued a somewhat cryptic response March 28 to Sandoz's petition, denying the petition but declining to comment on whether or not it would take action on the requests.

"Now the key questions are 1) timing of a potential Mylan generic Advair approval; and 2) what will the competitive landscape look like if/when Mylan gets approval for generic Advair," Leerink Partners analyst Jason Gerberry said in a same-day research note.

Gerberry speculated that Mylan's generic would be delayed until 2018, and recommended removing any revenues related to the drug from 2017 guidance. He had estimated $100m-$175m in 2017 sales.

"It is a stretch, in our view, to assume Mylan can resolve its CRL and get an FDA approval in the next eight to nine months," he said.

Mylan's stock fell 3% on the news to close the day at $40.35.

Published online 29 March 2017

Broad Label Gives Tesaro's Niraparib A Head Start In Ovarian Cancer

EMILY HAYES emily.hayes@informa.com

Tesaro takes opportunity of broad approval for Zejula (niraparib) in recurrent ovarian cancer to highlight franchise expansion opportunities in other tumor types, including PD-1 inhibitor combination studies.

Tesaro Inc.'s *Zejula* (niraparib) may be the third PARP inhibitor to the US market, but it is positioned to seize the first-mover advantage for maintenance treatment of ovarian cancer, following a broad FDA approval for this indication, regardless of mutation status and without the need for a companion diagnostic.

Approval for the poly ADP-ribose polymerase inhibitor was announced March 27, well ahead of the drug's June 30 user fee date. Niraparib had enjoyed breakthrough therapy, fast track and priority review designations with FDA; the agency granted approval for the drug as a maintenance treatment for adults with recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer, following a partial or complete response to platinum-based chemotherapy. The label covers patients with and without germline BRCA mutations.

Tesaro's filing was supported by the ENGOT-OV16/NOVA study of 553 ovarian cancer patients who had at least two prior therapies and who had a complete or partial response after their last chemotherapy.

Testing was done in the trial for germline BRCA (gBRCA) mutations. Efficacy results for both categories of patients are spelled out in the clinical trials section of Zejula's label. Those with gBRCA mutations on Zejula had median progression free survival (PFS) of 21 months versus 5.5 months for placebo, equivalent to a risk reduction of 74%, based on independent radiologic and central review. Median PFS in the non-gBRCA cohort for those on Zejula was 9.3 months compared to 3.9 months for placebo, a 55% reduction in risk. Both results were highly statistically significant ($p<0.0001$).

Richard Pazdur, FDA's acting director of the Office of Hematology and Oncology Products in the agency's Center for Drug Evaluation and Research, stressed the importance of maintenance therapy for ovarian cancer patients who respond to initial treatment in a statement from FDA.

Only 10%-15% of ovarian cancer patients have gBRCA mutations and a broad label including patients without mutations dramatically expands the market potential in this indication. Of 196,000 ovarian cancer patients in the US, 85% relapse.

Commercialization details – including pricing – are not clear yet. Tesaro CEO Lonnie Moulder declined to comment on Zejula's wholesale acquisition cost (WAC) during a March 27 investor call, but the company has done extensive market research with leading payers, covering 80% of lives in the US, to guide its decision.

"We have a sense of the value proposition here. And I think it will be a well-informed pricing decision," Moulder said.

A SIGNIFICANT EDGE

Zejula is now set to become the third PARP inhibitor on the US market after AstraZeneca PLC's *Lynparza* (olaparib), approved in December 2014 and Clovis Oncology Inc.'s *Rubraca* (rucaparib), which was cleared in December 2016, but Zejula has the best label by far.

Lynparza is approved after three prior treatments for ovarian cancer with gBRCA mutations detected by an FDA approved test. Rubraca is approved for use after two or more prior treatments in ovarian cancer patients positive for gBRCA mutations, per an FDA approved companion diagnostic.

Approval outside of the BRCA-mutated population gives Zejula a significant advantage over Lynparza and Rubraca, Datamonitor analyst Zachary McLellan said.

Lynparza, Rubraca and AbbVie Inc.'s Phase III PARP inhibitor veliparib are all being investigated beyond the BRCA-mutated population, but Zejula will have the first-mover advantage in the platinum-sensitive setting, McLellan noted.

Zejula is also the first PARP inhibitor approved as a maintenance treatment for ovarian cancer in the US. Lynparza has been approved in Europe as a maintenance treatment for gBRCA-mutated ovarian cancer patients since 2014.

It's unclear how long-lived Zejula's lead in the US maintenance setting will be. AstraZeneca is looking to expand labeling of Lynparza, with plans to submit a supplemental NDA by the end of the first quarter. In mid-March, the company presented impressive data from the Phase III SOLO-2 study to support an expansion into the maintenance setting.

That trial tested Lynparza in patients with platinum-sensitive relapsed or recurrent gBRCA-mutated ovarian cancer after two prior therapies. In the study, median PFS was 19.1 months versus 5.5 months for placebo, equivalent to a highly significant risk reduction of 70% for the primary endpoint, based on investigator review. A pre-specified analysis supporting the primary endpoint indicated median PFS of 30.2 months for the Lynparza arm versus 5.5 months for placebo based on blinded independent central review, a result that had a better hazard ratio of 0.25, or a 75% reduction in risk of progression.

AstraZeneca suggested at the time of the SOLO-2 release that including Phase II data, it might have enough evidence in totality to support a filing in all patients regardless of mutation status, even though the pivotal work was done in gBRCA-positive cases.

Asked about AstraZeneca's dataset during Tesaro's March 27 investor call, President and chief operating officer Mary Lynne Hedley noted that the PFS for gBRCA-positive patients in the pivotal study of niraparib was 21 months versus AstraZeneca's 19 months and that the hazard ratio for risk reduction in PFS was better at 0.26 for niraparib versus 0.30 for Lynparza.

"So I think we are very comfortable with the data that we have and we have the broadest label at this point and the only evidence for activity in a non-germline BRCA setting," Hedley said.

© Informa UK Ltd 2017

A Phase III study of Clovis's Rubraca as a maintenance treatment in ovarian cancer is ongoing, with data expected in mid-2017.

PAIRING WITH PD-1

Tesaro also announced on March 27 that it is expanding development for the drug and will be pursuing approval in other lines of therapy for ovarian cancer, as well as in breast and lung cancer.

Hedley explained that now that it has approval in hand, it will be working on the franchise expansion opportunities for the drug.

Development in first-line metastatic ovarian cancer will now include a study (OvCa 3000-03-003) testing niraparib in combination with a PD-1 inhibitor as maintenance therapy, which has not been disclosed previously, the company said.

Tesaro also is planning to run a study (OvCa 3000-03-002) of niraparib with Roche's VEGF inhibitor *Avastin* (bevacizumab) in recurrent metastatic ovarian cancer.

The PARP/PD-1 combination also is being tested in metastatic triple-negative breast cancer. Tesaro had envisioned that the BRAVO study of niraparib in breast cancer with gBRCA mutations would support registration in this tumor type. However, the company said in its March 27 update that the study is "unlikely to produce data that is interpretable and therefore suitable for registration in this indication."

Tesaro believes that the commercial availability of a PARP inhibitor caused patients with gBRCA mutations in the placebo arm of the trial to drop out early. The company will be focusing now on the potential for combining PARP with PD-1 in this indication. Tesaro has a collaboration with Merck & Co. Inc. to test the PD-1 inhibitor *Keytruda* (pembrolizumab) with Zejula.

Tesaro also said that it foresees a role for niraparib in metastatic non-small cell lung cancer and plans to test a combination with an undisclosed PD-1 inhibitor in a Phase III study (Lung 3000-03-001) of first-line NSCLC with a high level of PD-L1 expression. A Phase II study (Lung 3000-02-001) of the same combination of first-line NSCLC in a general population, regardless of PD-L1 expression, also is planned.

Published online 28 March 2017

Roche's 'Brave' Ocrevus Pricing Strategy For Multiple Sclerosis

SUKAINA VIRJI sukaina.virji@informa.com

Shutterstock: Ralwel

Roche is taking no chances with its newly approved multiple sclerosis drug Ocrevus and has set a cost that ensures price is no barrier to treatment.

Roche's is embarking upon a brave pricing strategy for its new multiple sclerosis drug *Ocrevus* (ocrelizumab) now that it has finally been licensed by the US FDA, following a slight technical hitch over manufacturing. The drug has been approved to treat both relapsing-remitting MS (RRMS) patients and the underserved primary progressive MS (PPMS) population and has been priced competitively.

The wholesale acquisition cost (WAC) has been set at $65,000, a "25% discount to [Pfizer Inc./Merck KGAA's] *Rebif* [interferon beta-1a], 20% discount to other MS therapies on average", wrote Mizuho Securities USA Inc.'s senior biotech analyst Salim Syed in a March 29 note.

A high proportion of MS patients display a progressive disease course at some point in their lives, but they presently have very few therapeutic options, noted Datamonitor Healthcare analyst Daniel Chancellor. He estimates that PPMS and secondary progressive MS (SPMS) patients amount to more than 50% of the 2.3 million worldwide cases of MS. "This means that over 1 million MS patients worldwide have no effective therapy to slow down disease progression and the accumulation of disability," he noted.

Most analysts agree Ocrevus was set to claim a dominant position in the MS market owing to its impressive clinical data, but Roche is taking no chances and has employed a "brave" pricing strategy which sees it undercut the cost of currently available disease-modifying therapies (DMTs), noted Chancellor.

"Roche's decision to go in at this level is certainly interesting and very disruptive to the wider MS market," he added. "The company could certainly have been justified in charging as much as payers would have been prepared to bear, rather than cutting them some much-needed slack. It will be a trade-off between ensuring the maximum coverage for Ocrevus for eligible patients versus receiving the full value that their clinical data package merits."

Jefferies analyst Jeffrey Holford has forecast peak sales of Ocrevus at $5bn "given its strong efficacy and a relatively mild toxicity profile." He said in a March 29 note that "Ocrevus' future success will be important in helping to mitigate the anticipated competition from biosimilar threats to Roche's Herceptin and Rituxan."

The FDA has included a warning for progressive multifocal leukoencephalopathy (PML) even though there were no cases seen in any of the Ocrevus trials. "This should not come as a surprise given other drugs with the same anti CD20 mechanism carry such a warning," added Holford.

The "label is clean in our view," said Mizuho's Syed. "There is no black box and no REMS (risk evaluation and mitigation strategy) requirement."

COMPETITION

Meanwhile, Ocrevus may soon not be the only option for PPMS patients. The small French biotech MedDay Pharmaceuticals is currently having its highly concentrated pharmaceutical-grade biotin MD-1003 evaluated by the European regulator, which CEO Frédéric Sedel recently told *Scrip* was "synergistic" to Ocrevus rather than a competitor.

Novartis AG's *Gilenya* (fingolimod) follow-on drug, BAF312 (siponimod), met the primary endpoint in the Phase III EXPAND trial last year in SPMS patients.

Further back in development is GeNeuro SA with its "causal" approach to tackling MS which aims to reverse neuronal damage.

Published online 29 March 2017

BLA Accepted: Novartis Inches Ahead In CAR-T Race

Novartis may very well have the first CAR-T therapy approved in the US, beating its rival Kite Pharma to the finish line, since the FDA has accepted the Swiss big pharma's BLA for priority review. Kite says it will complete its rolling BLA submission in a different indication by the end of March.

MANDY JACKSON mandy.jackson@informausa.com

Novartis AG shot ahead of Kite Pharma Inc. in the race to get the first chimeric antigen receptor T cell (CAR-T) therapy approved in the US for hematological malignancies, announcing on March 29 that its biologic license application (BLA) for CTL019 (tisagenlecleucel-T) has been accepted by the FDA for priority review.

Kite, meanwhile, remains on track to complete its rolling BLA submission for axicabtagene ciloleucel (KTE-C19; axi-cel) by the end of the first quarter, or by March 31. But with an already accepted BLA and a priority review, CTL019 is likely to beat axi-cel to the finish line.

However, if approved by the FDA around the end of September, the Novartis CAR-T therapy would be available to a smaller patient population – relapsed and refractory pediatric and young adult patients with B-cell acute lymphoblastic leukemia (ALL) – than Kite is targeting initially with its product for aggressive non-Hodgkin lymphoma.

Both product candidates are designed to target cancer cells expressing CD19 and both are individualized therapies, which involve reengineering a patient's T cells to attack cancer cells and other B cells that express the chosen antigen. The individualized nature of the therapies is expected to require more expensive manufacturing and distribution than traditional small molecule or antibody therapeutics.

FEW PRICING CLUES

Novartis hasn't gotten into specifics yet about its pricing model or launch plans for CTL019, but the product's cost may reflect its novelty and its high efficacy in clinical trials to date. The company also may be ready to launch and manufacture the CAR-T therapy upon approval.

"While it is too early to talk about our commercial model or pricing, receiving priority review designation underscores CTL019's potential as a novel treatment innovation," Novartis spokesperson Eric Althoff told *Scrip*. "Findings from our pivotal study found that 82% of patients infused with CTL019 achieved complete remission or complete remission with incomplete blood count recovery within three months post CTL019 infusion. At six months, the overall survival rate was 89%."

"And, with our manufacturing facility in Morris Plains [New Jersey] we have a strong foundation for implementing the CTL019 manufacturing process and supporting clinical supply and approval timelines," Althoff added.

NECK-AND-NECK IN THE CAR-T RACE

Kite also has been building up its manufacturing facilities and entering into partnerships in anticipation of launches around the globe for axi-cel, so the company may be able to get its CAR-T therapy into the market close on the heels of Novartis's product.

In the US, both the Novartis and the Kite CAR-T therapies have breakthrough therapy designations from the FDA, which provides for a speedier review of drug candidates that meet unmet medical needs. That means Kite's BLA also is likely to be accepted for priority review – typically a six-month period – putting it only a month or so behind Novartis.

Novartis's BLA submission is based on the results of its Phase II ELIANA clinical trial, which were presented at the American Society for Hematology (ASH) annual meeting in early December, showing that 82% (41 of 50) of patients treated with CTL019 achieved complete remission or complete remission with incomplete blood count recovery three months after CAR-T cell infusions.

Data from other early and investigator-sponsored studies also were submitted to the FDA.

CAR-T therapies like CTL019 and axi-cel have shown impressive response rates in very sick leukemia and lymphoma patients, but not without safety concerns. Novartis reported that 48% of patients in ELIANA experienced grade 3 or 4 cytokine release syndrome (CRS) – a common side effect of CAR-T therapies – but each case was managed under a per protocol CRS treatment algorithm with no patient deaths.

CAR-T therapy developers generally have used Roche's interleukin-6 (IL-6) receptor antagonist *Actemra* (tocilizumab) to manage immune responses caused by CRS.

Neurological side effects also are a known response in some patients treated with CAR-T therapies and in ELIANA 15% experienced grade 3 neurological and psychiatric events, including confusion, delirium, encephalopathy, agitation and seizures. However, no cerebral edema was reported – a severe neurotoxicity that killed multiple patients for Juno Therapeutics Inc.'s now discontinued JCAR015 – and no grade 4 neurological and psychiatric events were observed for patients treated with CTL019.

ADCOMM POSSIBLE

The novelty of CAR-T therapies and the severe side effects associated with the new technology are issues that may cause the FDA to schedule advisory committee meetings ahead of any approval decisions, but Novartis could not say whether an AdComm is planned.

"As far as an advisory committee is concerned, we can't speculate, but we will continue to work closely with the FDA during the review process," Althoff said.

Kite spokesperson Christine Cassiano told *Scrip* that the company won't know whether axi-cel will be considered in an advisory committee until the company's BLA is accepted, but noted that: "As a new technology, it is feasible to believe that there could be an advisory committee, but the decision is made by the FDA."

Novartis has plans for rapid additional filings for CTL019, including an indication competitive with Kite's initial indication. The Swiss pharma expects to file a supplemental BLA for CTL019 to treat adults with relapsed or refractory diffuse large B cell lymphoma (DLBCL) with the FDA and submit a marketing authorization application (MAA) to the European Medicines Agency (EMA) for the treatment of relapsed or refractory B-cell ALL and DLBCL later this year.

While Novartis won't be far behind Kite in NHL, the US biopharma firm isn't terribly worried.

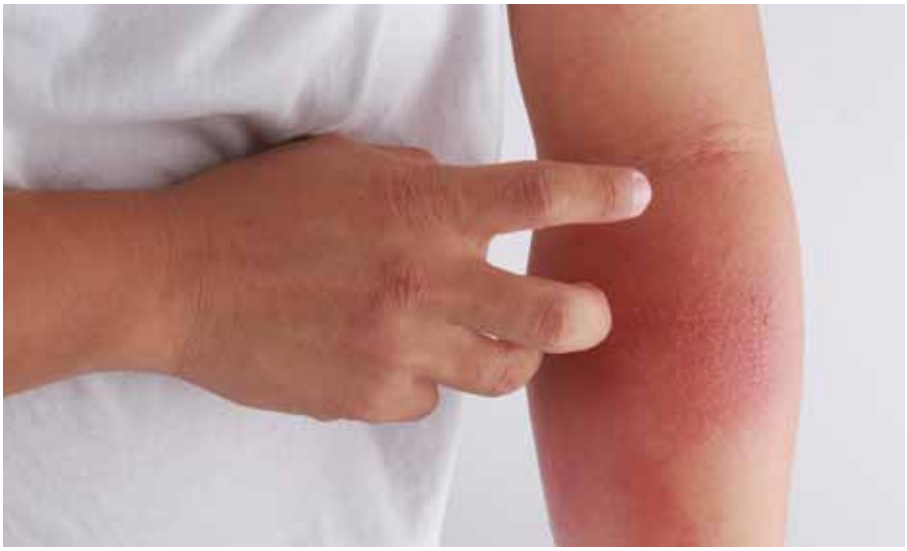
Published online 29 March 2017

© Informa UK Ltd 2017

CONTINUED FROM COVER

for psoriasis range in price from $41,000 to $83,000 per year, according to Terifay.

Still, it's hard to know exactly how much a drug costs. In a mature, competitive category like psoriasis, drug makers presumably offer steep rebates and discounts in exchange for prime real estate on formularies. Whereas, in the case of Dupixent, the drug is a first-in-class agent in a category with few treatment options. Regeneron confirmed it will offer rebates and discounts, but wouldn't say how significant they would be. The pharmacy benefit manager Express Scripts Holding Co., however, said rebates for Dupixent would be limited to low single digits, given the first-in-class nature of the product.



Shutterstock: TY Lim

Nonetheless, Express Scripts, in an email, agreed Sanofi and Regeneron were "responsible" in how they priced the product and approached the launch.

"They engaged payers early and worked to get our input. This different tone and tenor is a result of actions we have taken to change the marketplace dynamic," Express Scripts added.

Terifay said the companies tried to be proactive about working with payers. "We wanted to make sure they understood the disease and that we talked through what the appropriate utilization-management approach should be," he said, "We were straightforward with the payers, and it still is very collaborative."

One focus has been on trying to limit utilization-management restrictions, he added. Thus far, utilization-management restrictions are largely in line with the labeling for the drug, moderate-to-severe atopic dermatitis that is poorly responsive to topical therapies.

Leerink Partners analyst Geoffrey Porges applauded the pricing decision in a same-day note. "We expect the decision to result in significantly higher demand, faster than if [the companies] had hewn to their traditional premium price strategy," Porges said.

> 'Amgen has a long history of aggressively enforcing its patents against competitors like Sanofi and Regeneron'

"Ultimately, there are hundreds of thousands of patients with moderate-to-severe atopic dermatitis, many of whom will want to try this medication," he added. "In this setting, we believe the most important element of the strategy is to ensure access, and this price goes as far as investors, payers and patients could reasonably expect towards securing that goal."

BLOCKBUSTER OPPORTUNITY

Dupixent will launch within a week and is expected to become a blockbuster, given the unmet need, but rivals also are clambering to get into the space. Consensus sales estimates predict Dupixent generating $3.7bn by 2025, according to Jeffries analyst Jeffrey Holford. Pfizer Inc.'s *Eucrisa* (crisaborole) was approved by FDA in December as the first new drug for atopic dermatitis in more than a decade. The topical non-steroidal phosphodiesterase-4 (PDE-4) inhibitor is positioned as a treatment for patients with mild-to-moderate disease. It costs considerably less than Dupixent at $580 for a 60g tube.

The current treatments for atopic dermatitis have been on the market for decades, namely Astellas Pharma Inc.'s *Protopic* (tacrolimus) and Valeant Pharmaceuticals International Inc.'s *Elidel* (pimecrolimus), both topical calcineurin inhibitors that carry black box warnings dating to 2006 related to long-term safety over rare cases of malignancy. Topical corticosteroids are widely used, but have limitations and aren't recommended for chronic use.

Dupixent, on the other hand, targets what are believed to be two drivers of the underlying inflammation that causes the disease. It comes in a pre-filled syringe and can be self-administered as a subcutaneous injection every other week after an initial loading dose. It also can be used with or without topical corticosteroids.

The approval was based on the results of three randomized Phase III trials called SOLO 1, SOLO 2 and CHRONOS, which enrolled 2,119 patients. The first two trials studied Dupixent alone, while CHRONOS studied the drug with topical corticosteroids. Dupixent demonstrated strong efficacy in all three studies in terms of skin-clearing primary and secondary endpoints.

Dupixent is under review in the EU, where the European Medicines Agency accepted a marketing authorization application for the drug in December.

Sanofi and Regeneron are already apparently bracing for a competitive intellectual property fight. The companies made a preemptive move against Amgen Inc., filing a complaint requesting declaratory judgment of non-infringement. Amgen owns an IL-4/IL-13 inhibitor called AMG-317 that it tried to develop for asthma, but dropped after Phase II. Nonetheless, Amgen still owns some patents on the technology.

"Amgen has a long history of aggressively enforcing its patents against competitors like Sanofi and Regeneron," the complaint says. Indeed, as mentioned in the complaint, the companies are currently in patent litigation concerning patents related to Sanofi/Regeneron's PCSK9 inhibitor Praluent.

Published online 28 March 2017

Bristol Teams Up With Billionaire-Backed Parker Institute

EMILY HAYES emily.hayes@informa.com

A key goal of Bristol's second major academic research collaboration is to get trials up-and-running more quickly.

Bristol-Myers Squibb Co. says it will take an open-minded, flexible approach to working with the Parker Institute of Cancer Immunotherapy in San Francisco to spur translational research and speed development of new drugs and technologies.

Sean Parker, co-founder of the music file-sharing service Napster and former president of Facebook, launched the institute in April 2016 with $250m of his own foundation's cash as a hub for top research centers and pharmaceutical companies.

Shutterstock: beeboys

The institute aimed to unify research programs, intellectual property licensing, data collection and clinical trials across six major medical sites – Memorial Sloan Kettering Cancer Center, Stanford University School of Medicine, the University of California, Los Angeles, the University of California, San Francisco (UCSF), the University of Pennsylvania and the University of Texas MD Anderson Cancer Center – when it launched nearly a year ago.

Now, the Parker Institute, Bristol and the Cancer Research Institute (CRI) said on March 28 that they have entered into a multi-year clinical research collaboration in immuno-oncology. The partners noted in a statement that the collaboration marks the Parker Institute's first major agreement with a biopharma partner and that other industry tie-ups are desired.

Julie Hambleton, Vice president and head of US medical at Bristol, said the goal is to accelerate discovery, development and treatment options – the collaboration will make it possible to get a trial up and running much more quickly.

Funding will derive partly from the Parker Institute, the CRI's Clinical Accelerator venture philanthropy program and Bristol.

Bristol declined to comment on the financial details of the deal; Hambleton said that terms will vary depending on the project. Investigators affiliated with the CRI and the Parker Institute will pitch ideas for research, including drugs and technologies, and the three partners will determine on a case-by-case basis if a proposal represents an area of mutual interest and, if so, how it will be funded.

A number of different scenarios are possible for Bristol, including direct funding for trials and other kinds of support.

"Our goal here is to be flexible," Hambleton said.

Hambleton also declined to comment on drug targets and goals for the collaboration. Bristol has not developed a platform for chimeric antigen receptor T-cell (CART) therapy, an area of research focus for the Parker Institute, but is open to partnering on combination trials involving this technology through the new collaboration.

The partners said in their statement that they will be looking to address key unanswered questions in immuno-oncology – an area where therapeutics have transformed some patients' lives, while still are not deriving as great a benefit as possible, Hambleton said. Bristol is focusing on areas of highest unmet medical need; in some tumor types, like lung cancer and melanoma, there is still room for improvement, and in others, like breast and prostate cancer, there is even more work to do.

"On top of that is the question of which patient should get which type of immuno-oncology agent," she said.

Research will involve development of single agents and combination regimens, and drugs developed in-house as well as by outside companies.

"If investigators bring another company with an agent to the table, that is something we would consider, absolutely," she said.

Bristol has been the pioneer in immuno-oncology, kicking off an enormous wave of development with the approval of the CTLA-4 inhibitor *Yervoy* (ipilimumab) in 2011 and the PD-1 inhibitor *Opdivo* (nivolumab) in 2014.

But as single agents, these drugs don't work in about two-thirds of patients; the combination of the two improves efficacy, but is laden with toxicities associated with Yervoy. In the last year, competitor Merck & Co. Inc. has gained enormous momentum and grabbed the IO limelight with the clinical trial success of its PD-1 inhibitor *Keytruda* (pembrolizumab) in the valuable first-line non-small cell lung cancer indication, whereas Opdivo has slipped behind in this setting.

> 'If investigators bring another company with an agent to the table, that is something we would consider'

Bristol has been developing a range of new mechanisms, including GITR and OX40, and has been experimenting with adaptive trial design to enable rapid testing of novel combinations.

The deal with the Parker Institute is Bristol's second major academic/industry research collaboration in immuno-oncology. The company launched the Immuno-oncology Network (II-ON) in 2012 and it now includes 15 sites and more than 250 investigators.

Published online 28 March 2017

© Informa UK Ltd 2017

Darzalex Setback Raises Stakes For Myeloma Approval

Genmab AS and development partner Janssen Pharmaceutical Cos. (a Johnson & Johnson company) have ended Phase II development for *Darzalex* (daratumumab) monotherapy in two non-Hodgkin's lymphoma indications after a mid-trial review revealed poor results for overall response rates. A third NHL indication has also been dismissed because of a lack of data due to slow patient recruitment. Critical eyes will now shift to upcoming data for the drug in first-line multiple myeloma, which are expected in the second half of 2017. The important interim data from the Phase III ALCYONE study (Darzalex/*Velcade*/melphalan/prednisone) will be the first for Genmab and Janssen's drug in first-line multiple myeloma. Genmab's share price (Copenhagen) dipped 5%, or DKK69, in morning trading on March 31 after the Phase II trial discontinuation was announced. The Phase II CARINA study, led by Janssen as the worldwide licensee of Darzalex, will not proceed to stage two, effectively ending development of the drug in three NHL indications. A data review showed that two cohorts of the study, investigating the use of daratumumab monotherapy in relapsed or refractory patients with follicular lymphoma (FL) and with diffuse large B-cell lymphoma (DLBCL), did not reach the predefined futility thresholds of overall response rates (ORR) of 50%, and 30%, respectively.

lucie.ellis@informa.com, 31 March 2017

Corbus Cystic Fibrosis Data May Justify Longer, Larger Study

Corbus Pharmaceuticals Holdings Inc. searched for efficacy in a Phase II cystic fibrosis study for its only clinical drug candidate, anabasum (JBT-101; resunab), but the signal highlighted by the company was found in a data point outside of the trial's pre-defined endpoints. The clinical trial's primary endpoint sought acceptable safety and tolerability for the endocannabinoid-mimetic drug, which preferentially binds to the cannabinoid-2 (CB2) receptor on activated immune cells and fibroblasts; it resolves inflammation without suppressing the immune system, which can be dangerous for CF patients as they battle severe lung infections. But while evaluating safety was the primary objective for Corbus' Phase II study, the trial included secondary efficacy endpoints – pulmonary function and patient-reported outcomes – on which anabasum showed little effect. Even so, Corbus and the Cystic Fibrosis Foundation (CFF), an important supporter of the company's clinical trial, were encouraged by other secondary measures showing effects on inflammatory biomarkers and an observation that the rate of pulmonary exacerbations at the drug's highest dose was 75% lower than in the study's placebo arm. "The results from this trial were encouraging in that they demonstrated reduction of inflammatory biomarkers and suggested a potential effect on exacerbations, although in a small and early trial. We feel the data support a larger, longer study to better determine potential clinical benefit," CFF senior vice president-therapeutics development Michael Boyle told *Scrip*.

mandy.jackson@informausa.com, 31 March 2017

Strong Topline Data With Erytech's Pancreatic Vaccine

French biotech Erytech Pharma SA is likely to pursue expedited regulatory submissions for its second-line pancreatic cancer therapy, eryaspase, on the back of strong topline Phase IIb data; as well as assess its options in other solid tumor indications now that the treatment has demonstrated positive effects in oncological and hematological cancers. Analysts at Jefferies are predicting peak worldwide sales of $500m for eryaspase and have given the therapy an 80% probability rating for a successful approval. Erytech's treatment, known as Graspa in the EU, met both co-primary endpoints in the Phase IIb second-line pancreatic cancer study, significantly improving progression-free survival (PFS) and overall survival (OS) in patients with low asparagine synthetase (ASNS) expression.

lucie.ellis@informa.com, 28 March 2017

Broad Efficacy Of Takeda's Dengue Vaccine

Newly published details of a pre-planned, six-month interim analysis of a Phase II trial with Takeda Pharmaceutical Co. Ltd.'s dengue candidate vaccine TAK-003 show the tetravalent product elicited a broad antibody response against all four viral serotypes, regardless of previous infection. The findings with the live-attenuated product in the ongoing DEN-204 trial, which recruited 1,794 participants aged 2-17 in dengue-endemic areas, were published online in *The Lancet Infectious Diseases*, and shed some further light on the potential differentiation versus Sanofi Pasteur's *Dengvaxia*, so far the only available vaccine for the mosquito-borne disease. Subjects received one or two doses of TAK-003 (in the latter case three months apart) or placebo, and geometric mean titers (GMTs) of neutralizing antibodies were assessed at one, three and six months after the first injection for the interim analysis. Seropositivity based on GMTs ranged between 87-100% by Month 1, and was a sustained 85-100% at Month 6 in groups receiving either one or two doses.

ian.haydock@informa.com, 30 March 2017

Genentech's Early Cancer Technology Scout On Partnering, Roche Setup & BD Challenges

There is still much more to be learnt about cancer immunology, particularly what drives cancer cell growth, proliferation and resistance mechanisms, says Kevin Sin, Genentech's VP of oncology business development. Speaking to Scrip at the recent BIO-Europe Spring partnering conference, Sin describes Genentech's partnering strategy in oncology and how, almost a decade after the merger, Roche and Genentech are still working collaboratively and competitively to find the best new science in cancer.

LUCIE ELLIS lucie.ellis@informa.com


Kevin Sin

Cancer therapy is changing too rapidly at present for it to make sense to have a strict partnering strategy listing specific areas to invest in, according to Genentech Inc.'s vice president of oncology business development Kevin Sin.

In an exclusive interview during the recent BIO-Europe Spring partnering event in Barcelona, March 20-22, Sin told *Scrip* that static partnering strategies were a danger for oncology firms seeking breakthrough technology. "Science is breaking open daily and new companies are being formed with great ideas," Sin said, adding that being too focused on a strict investment strategy could "close your eyes to other opportunities."

Genentech, a Roche company, is an active developer in the immuno-oncology space and Sin says the business is looking for new opportunities particularly in the earlier stages of development. "Some companies are focused only on one area in cancer – immunology – but we continue to invest in both, looking at what drives tumors and what drives the immune system to interact with the tumor," he noted. Genentech has 46 molecules in its clinical pipeline, the majority of which are targeting oncology indications.

As a group, Roche is set to lose patent protection for three of its market leading cancer therapies potentially as early as 2019. The products effected are *MabThera*, *Herceptin* and *Avastin*, which had combined sales of more than $20bn in 2016. But Sin said the loss of market value anticipated when these products face biosimilar erosion was having little impact on Genentech's early-stage partnering strategy. He said the organization was not driven by patent expiries. "You can always do better. If we can leverage what we do best – which is pursue pioneering science with strong and heavy investment in R&D, alongside hiring the best and brightest scientists and clinicians, and partnering with the best and brightest scientists in companies around the world – then we're going to find the next transformative breakthrough medicine," he said.

To get Sin's attention in the early-stage oncology drug development arena, potential partners need to bring to the table a certain level of evidence or data. "The level of evidence is different depending on the area of biology but in general it usually means that there is a reasonably well characterized selective and potent molecule, and some evidence *in vitro* and *in vivo* that it will do something to cancer," Sin said.

ROCHE VS GENENTECH

Sin's business unit is known as gRED, or Genentech Research and Early Development, one of the independent, autonomous R&D centers within the Roche group. This is separate from Roche's own early-stage pharma research arm, known as pRED or Pharma Research and Early Development. On top of these two groups is Chugai Pharma – another Roche business with its own R&D activities.

Unlike most mergers, Roche and Genentech have retained very separate identities since the big pharma acquired the latter company in 2009. Genentech has its own governance, budget, partnering teams and portfolio. Sin said Roche usually comes into play for a Genentech program at the later stage, "at the time when we're ready to take a drug into large multinational registration studies because there you need the scale, the reach and the speed of a global organization to ensure that you can develop, get approval, manufacture and launch in all the countries of the world," Sin said.

This individual R&D setup is designed to provide autonomy but it's not designed to be intentionally competitive, Sin said. However, there are no restrictions for one group to focused on specific therapeutic areas. "The groups are really composed of scientists and clinicians and each of them determines what's of interest to them, sometimes they overlap and there's opportunities potentially to collaborate or to keep them separate," Sin said. In many cases the companies keep R&D separate because they can offer different scientific approaches and more shots on goal. "Ultimately, we believe this diversity of ideas, diversity of cultures and diversity of approaches will bring benefit long-term," he told *Scrip*. If the groups were only able to develop products in different disease areas it would just be one company like all others, Sin said. Instead, he said, the Roche group is a diverse and layered collective of companies.

However, he likened management of these diverse companies to the challenges presented by globalization. While there are nationalities with unique differences (the different business cultures at Roche and Genentech) there are also values that are beneficial for all people (these being the Roche Group's global principles). Sin doesn't think it is a benefit to have one world, or one company, where every nationality, or unit, acts and thinks the same.

© Informa UK Ltd 2017

He said the group was focused on preserving one company with different cultures. "We take the best from both and allow them to thrive separately; but we also know that there are certain places where working together towards a common goal means you can achieve more."

He believes the Roche and Genentech merger has been successful because from the outset the intention to preserve both companies' identities was clear. Roche CEO Severin Schwan has kept to this plan and shown the commitment to both units by providing independent infrastructure, staff, portfolios and funding, Sin said.

CHALLENGES

Sin believes current political changes could pose barriers for people like himself who are scouting the world for groundbreaking science. "If we have a vibrant community of academic and industry startups then there will always be wonderful partnering opportunities," Sin said, noting that his concerns revolve around policy changes that could impede collaboration. The ability to exchange new ideas and the retention of a talent pool made up of experts from different regions are two things Sin highlighted as at risk currently, because of uncertainty around political changes in the US and Europe.

When it comes to economic challenges, Sin is less concerned. He believes that as long as collectively there is a continued desire for better healthcare there will always be investment in drug development. "One of the benefits of a large global organization like Roche is that you're able to weather cycles and stay focused on investing in new technologies at a time when others may perceive it as too risky or challenging," he said.

However, Sin is worried that the drug development sector is "data rich but knowledge poor."

He elaborated, "It doesn't mean we have no knowledge, but in relation to the amount of data we have we have an untapped resource. We have a large opportunity to really transfer that information into actionable knowledge that leads to new medicines."

In this area, Sin said Genentech continued to invest in biostatisticians and bioinformatics because the company needed "highly qualified scientists to not only interpret the data in a way that's meaningful but also look at ways of approaching interpretation of the data."

Published online 30 March 2017

PureTech Health: Applying Deep Thinking And Business Acumen

JOHN DAVIS john.davis@informa.com

Targeting the age-dependent decline in immune function is the aim of a new PureTech Health subsidiary, resTORbio, that has licensed two clinical-stage mTORC1 inhibitors from Novartis.

If you had a company board featuring a future-focused academic, a Nobel Prize winner and hard-headed ex-Big Pharma executives, where would you be investing your R&D efforts?

Chances are you would be applying their insights to some of the seemingly more intransigent issues in biology, such as immunosenescence, the age-related decline in immune function seen in animals and humans. And you might also be attempting to identify a therapeutic niche where there is great patient need and few potential competitors.

PureTech Health is satisfying all of those criteria in its collaboration announced last week with Novartis AG that has seen the Boston, MA-based but UK-listed biotech acquiring two of the Swiss company's Phase IIa investigational products and announcing it would evaluate them in a Phase IIb trial to see if they have potential in the treatment of certain aspects of immunosenescence.

That Phase IIb study is due to start this year, with the actual indication being kept under wraps for now – the decline in immune function is associated with a multitude of effects that could be studied, including a decreased ability to fight infections, an increase in cancer incidence and a decline in organ function.

The study follows reports in animals indicating that inhibition of the mTORC1 (mechanistic target of rapamycin complex-1) pathway with the two Novartis compounds leads to an improvement in age-related conditions. Novartis has already conducted two Phase IIa studies in hundreds of elderly patients, said to have been successful, and the results are set to be published shortly in a peer-reviewed publication.

mTORC is a protein serine/threonine kinase that regulates cell growth and metabolism, of which there are two types that have different effects when inhibited. mTORC1 inhibition appears to have beneficial effects on aging-related conditions, while mTORC2 inhibition causes adverse effects such as hyperglycaemia and hypercholesterolemia. In animal studies, inhibition of the mTORC1 pathway has been shown to extend the lifespan of various species; this caused some excitement in the popular media a decade ago, but that indication is not being pursued by PureTech Health.

Still, PureTech Health's focus on mTORC1 inhibitors is not accidental, it follows a period of intense evaluation. The company's usual working practice is for its advisors and the board to work together to identify an unmet clinical need and evaluate the potential of therapeutic approaches. These could include a variety of different modalities – PureTech Health already supports studying the use of music as a precision medicine, identifying vocal biomarkers for various disorders, and the use of priming, seeding and maintaining beneficial microbes in the body early in life.

What is different about the immunosenescence opportunity compared with other technologies that PureTech is working with is that the company is not starting from scratch to develop a new platform. "Usually we start by coming up with a specific unmet clinical need, and then we form a working group, including outside consultants, to brainstorm what would be the best technology to pursue," said Chen Schor, the leader of the immunosenescence program and a PureTech Health senior executive, in an interview.

With immunosenescence, "our team looked into every approach that has been tested or discovered, that would usually result in a new technology that we would develop from scratch, but in this case it was fortunate that the molecular profile we were interested in was in the hands of Novartis," Schor explained.

PureTech Health was also fortunate in that Novartis appeared to have no commercial priority to enter this therapeutic field, and apparently was happy to let the smaller company run with the idea. "We have a great relationship with Novartis," Schor noted.

Published online 28 March 2017

Payers Want Deep Discounts To Make Biosimilars Worth Their While

Interviews with US payers suggest that some expect discounts of 40%-50% off prices of branded drugs and that many insurers are more focused on promoting use of biosimilars in new starts, rather than switching stable patients.

EMILY HAYES emily.hayes@informa.com

US payers are expecting biosimilar manufacturers to offer significant discounts versus the originator price – as much as 40%-50% lower – to make covering knockoffs worth their while, and believe patients will vote with their pocketbooks, incentivized by low copays.

Four drugs have been approved through the dedicated biosimilars pathway in the US – Sandoz Pharmaceuticals Corp.'s *Zarxio* (filgrastim-sndz) in March 2015, Pfizer Inc./Celltrion Inc.'s *Inflectra* (infliximab-dyyb) in April 2016, Sandoz's *Erelzi* (etanercept-szzs) in August 2016 and Amgen Inc.'s *Amjevita* (adalimumab-atto) in September 2016. Amjevita and Erelzi have not launched yet, as they are entangled in patent litigation.

Two other products were cleared through the agency's 505(b)(2) follow on pathway – Novartis AG's *Omnitrope* (somatatropin) in May 2006 Boehringer Ingelheim GMBH/Eli Lilly & Co. *Basaglar* (insulin glargine) in March 2015. While not approved as biosimilars, these two products could be considered as a proxy for a biosimilar of the reference products, Pfizer Inc.'s *Genotropin* and Sanofi's *Lantus*, respectively.

As the US has trailed behind Europe in developing a system for approving biologic copies, not to mention lawsuits that have delayed rollouts, biosimilars pricing strategy is still unfolding and payers are still developing their policies, notes the Datamonitor Healthcare report Biosimilars Market Access in the US, published on March 13.

"It is widely anticipated that biosimilars will be priced at a discount of between 20% and 30% relative to the originator product," Datamonitor analyst Amanda Micklus said in the report.

However, in some cases the discount will be closer to 40%, with the level of discount likely to vary depending on the product class, she added.

One US payer interviewed for the report noted that price discount quotes for biologic copies have been "all over the place" – from 15% to 40%. "I think it will depend on the difficulty of manufacturing, the molecule, the level of competition for the biosimilars. But I think mid-20% range is probably a reasonable range for a discount," the payer said.

Shutterstock: funnyangel

It is reasonable to expect that discounts will rise, through contracting rather than list price, over time as more competing biologic copies launch – similar to multi-source generics, though not to the same level.

> 'It is widely anticipated that biosimilars will be priced at a discount of between 20% and 30% relative to the originator product'

The price discounts biosimilars manufacturers will have to offer through contracting are likely to vary depending on the disease. A 10%-15% discount is unlikely to cut it in diabetes because it would likely be matched by the manufacturer of the originator product, whereas 40%-50% would be harder to compete with.

"I think we are looking at that 40% as the magic number for any biosimilar, because if it is 10%–15% less, then the branded company just increases their discount, and it does not make a difference," one payer said.

Another payer told Datamonitor that expectation for supportive medications – white and red blood cell stimulants like filgrastim – is a discount in the 40% range, adding: "I think the [tumor necrosis factors (TNFs)] could eventually get very competitive and also in the 30%-40% range. I think those will probably be the most competitive."

Sandoz' Zarxio launched in September 2015 at a discount of 15% relative to Amgen Inc.'s *Neupogen* (filgrastim), but "this discount will be largely theoretical as Sandoz will need to offer deeper discounts in order to convince payers to change their policies and to compete with the discounts Amgen is likely to respond with," the Datamonitor report notes. Pfizer/Celltrion's Inflectra launched at a 15% discount to Johnson & Johnson's originator product *Remicade*

© Informa UK Ltd 2017

(infliximab). "But Johnson & Johnson has stated that Remicade itself has a 30% discount after rebates are included. In cases like these, the biosimilar would need to have an even larger discount to effectively compete," Micklus noted.

As one payer said, if the pricing of biosimilars is not aggressive enough, "we will just stay with the brands… that is an automatic for us."

The launch of Lilly/Boehringer's Basaglar, the copy of Lantus, "will also provide an interesting test case for how discounts relative to the reference brand will play out," the report states.

Basaglar launched at a discount of 15% to 28% off the price of competing insulins but "in cases where Basaglar becomes the preferred brand over Lantus on the formulary, the discounts could be even steeper," according to the report.

One payer recounted: "Well [Basaglar's contracting terms] have got to be aggressive. I told the product manager he needed to be 50% below WAC [wholesale acquisition cost] … if they are giving me 15% off of WAC without a contract and let us say they give me 30% [on Lantus] … I do not need Basaglar. It is not likely I am going to get 50% off from Lantus, but I could, so if they give me 50% off that is going to be such a discount that I cannot avoid it, I would have to take it and then we would really aggressively try to move that market."

NEW STARTS

Datamonitor interviews suggest that payers are cognizant about avoiding disruptions in patient care where possible and appear to be leaning more toward driving use of biosimilars in treatment-naïve patients as opposed to switching them from branded drugs to biosimilars, to maintain continuity of care. Concerns about maintaining continuity of care are also likely to steer them toward biosimilar manufacturers in Western countries as opposed to emerging markets, to avoid any supply problems.

"There are two ways that the originator company can approach it; they can just ignore it and hope that they will get as much revenue as they can on whatever they can get, or they can actively compete and try to match discounts, which will make it easier for plans as it means that we do not have to deal with the disruption to our members and our patients. They could offer further discounts if we do not do a substitution with the biosimilar," one US payer told Datamonitor.

"We would be likely to stay with the branded company if they were competitive. We would not have to move anything," said another.

In cases where payers are happy with the discounts offered by biosimilar companies, a range of strategies may be used to steer use away from branded drugs, including formulary placement, step-therapy requirements and prior authorization.

Another important way they plan to drive use of biosimilars is by offering lower out-of-pocket costs – such as coinsurance and co-payments – compared to branded drugs to enrollees, incentivizing patients to "vote with their pocketbooks."

"Payers interviewed by Datamonitor Healthcare indicated that they will position biosimilars as preferred agents on their formularies. This means biosimilars will be included on a lower tier of the formularies compared to the brands with a lower co-pay. Co-pays can be a useful tool when driving lower-cost drug use. It is hoped that since the lower-cost products are associated with a lower level of co-payment, patients will be financially incentivized to take biosimilars, saving themselves, and the health plan, money in the process," the report says.

Manufacturers typically offer co-pay coupons, as well as other assistance, to shield patients from costs of new drugs, which presents a challenge for payers in driving use by lowering these costs.

"The discount biosimilars offer and the co-pay incentive payers put in place will be critical in ensuring that patients still have a financial incentive to switch, even when co-pay coupons are available. Alternatively, biosimilars manufacturers may also consider offering co-pay coupons to entice patients to switch onto their products," the report suggests.

Sandoz, for example, offered the One Source Co-Pay Program with Zarxio, it notes.

Published online 30 March 2017

[Editor's note: Datamonitor Healthcare's Biosimilars Market Access in the US report, available here, includes original research with anonymized key opinion leaders.]

Vertex To Triple Combos For CF

Top-line results from two Phase III studies indicate Vertex's potential new combination cystic fibrosis therapy, tezacaftor plus ivacaftor, is effective and well tolerated in certain cystic fibrosis patients, and could become the backbone of a triple combination therapy for a wider patient group.

Vertex Pharmaceuticals Inc. announced positive top-line results from two Phase III studies, EVOLVE and EXPAND, of its investigational cystic fibrosis therapy, tezacaftor (VX-661)/ivacaftor in the evening of March 28, in two patient subgroups, and suggested the double combination could become an important base therapy in the company's efforts to develop a triple combination that is clinically beneficial in a higher proportion of CF patients.

Tezacaftor/ivacaftor will be submitted for approval in the US and Europe in the third quarter of 2017, said Vertex's chief medical officer Jeff Chodakewitz. The company is likely to apply for accelerated approval status, and has already started studies in CF patients aged six to 11 years – the two Phase III studies were conducted in patients aged 12 years or over. "It is important that medicines that affect the underlying cause of CF are started early in patients," Chodakewitz noted.

The current results contrast with disappointment last year that the combination was found not to show a significant clinical benefit in a further Phase III study involving a subgroup of CF patients.

Leiden reported that four "next-generation" CFTR (cystic fibrosis transmembrane conductance regulator) gene correctors were in triple combination clinical trials, two in Phase I and two in Phase II.

john.davis@informa.com, 29 March 2017

View details of the EVOLVE study here: **http://bit.ly/2o1S9pt**

Astellas Offloads Japan Product Basket To Private Equity Group

IAN HAYDOCK ian.haydock@informa.com

Astellas has joined the growing ranks of research-based pharma firms offloading their older products in Japan, amid rising pricing and generic pressures and an increasing desire to focus on innovation.

Astellas Pharma Inc. is divesting a portfolio of 16 of its older drugs in Japan, in the latest in a string of similar moves by innovative pharma firms in the country to move out of low-margin products amid rising price pressures and generic competition.

Shutterstock: Julia Kuznetsova

In a deal due to close at the end of April, the Japanese firm will transfer to LTL Pharma Co., Ltd. for JPY20.1bn ($181m) the marketing authorizations in Japan for the basket of drugs, which comprises several former big sellers that are now well past their heyday.

These include various formulations of the H2-antagonist anti-ulcer *Gaster* (famotidine), the 5HT3 antagonist for chemotherapy-induced nausea and vomiting *Nasea* (ramosetron), the cephalosporin antibiotics *Cefzon* (cefdinir) and *Cefamezin* (cefazolin), and the calcium antagonist antihypertensive *Perdipine* (nicardipine). A number of antibiotics, blood pressure and other drugs are included in the transfer.

The asset divestment covers active pharmaceutical ingredients and any royalty streams related to the products, although any of the transferred products currently sold outside Japan by Astellas subsidiaries will continue to be sold through these channels. While Astellas will maintains commercial responsibility in this case, product supplies will come from LTL Pharma.

Combined sales of the portfolio - which will be transferred gradually by April 2020 - were around JPY29.0bn in the fiscal year ended March 31, 2016, and Astellas expects no financial impact in its current financial term ending this March 31.

PRIVATE EQUITY INTEREST

Tokyo-based LTL Pharma is a new wholly owned subsidiary of Japan Established Medicines Corp. (JEMCO), an entity specializing in older products formed by Unison Capital Partners IV, LPS and Unison Capital Partners IV(F), L.P., which are both funds under the Japanese private equity group Unison Capital.

This Tokyo-based company was co-founded in 1998 by three former senior employees of Goldman Sachs in Japan, and specializes in providing financial support for the growth of multi-sector, mid-cap companies formed from management buyouts or spun off from larger firms.

Unison Capital does have some prior pharma experience through the 2015 purchase of Santen Pharmaceutical Co. Ltd.'s rheumatism division to form a new venture, Ayumi Pharmaceutical Corp., which subsequently also acquired Showa Yakuhin Kako's medical business last year.

THE LLP CONUNDRUM

Branded so-called long-listed products (LLPs) in Japan have typically been on the national health insurance reimbursement tariff for 10 years or more and are usually subject to generic competition. Sales are often not significant but besides the price pressure, other costs are associated with continued promotion, administration, and production, and also if a regulatory delisting were to be pursued.

The price pressures and associated discounting, and Japan's pricing recalculation rules, also mean that LLPs are commonly subject to relatively large price cuts in the country's system of regular biennial price reductions.

Given all these factors, originators are increasingly preferring to focus on higher margin new drugs and to concentrate limited resources on novel products, for which Japan has for the past few years been offering an "innovation premium" that exempts these from price cuts for the duration of their patent life.

Against this background, several companies took similar steps to reduce their LLP exposure last year, with two Indian firms acquiring mature product portfolios in Japan - Sun Pharmaceutical Industries Ltd. from Novartis Pharma KK and Lupin Ltd. from Shionogi & Co. Ltd.

Sun subsequently entered into a local commercial partnership for the products with Mitsubishi Tanabe Pharma Corp.

TRAILBLAZER TAKEDA

But the trend to shift ageing drugs to a partner looking to expand its portfolio and more willing and able to maximize sales was really kicked off by Takeda Pharmaceutical Co. Ltd.'s 2015 deal to transfer a basket of product to a new Japanese joint venture with Teva Pharmaceutical Industries Ltd., which began operations in April 2016.

Astellas confirmed in a statement on the LTL Pharma deal that the move would aid in "reallocating internal resources to activities that drive our competitive advantage," while Unison Capital said that JEMCO is aiming for the stable, long-term supply of long-listed drugs.

The company will also be supporting the expansion of LTL's product portfolio "by actively seeking opportunities to acquire LLPs from various pharmaceutical companies," it added.

Published online 29 March 2017

From the editors of *PharmAsia News*.

© Informa UK Ltd 2017

Fosun On Course For Gland Buyout Clearance

China's Fosun group has inched closer to a final all-clear for its acquisition of the Indian injectables firm Gland Pharma Ltd. for around $1.26bn, after India's Foreign Investment Promotion Board (FIPB) approved the proposal. The FIPB approval comes after numerous deferrals over the past several months, which had raised some speculation that India may adopt a cautious approach when it comes to such foreign investment proposals in the pharmaceutical space, especially with an eye on issues around its own medicines security. A news agency report quoted a finance ministry official confirming that the Fosun-Gland deal had been cleared at a FIPB meeting on March 29, though no further specifics were provided. The transaction is now expected to require an approval from India's Cabinet Committee on Economic Affairs (CCEA). Fosun said that relevant approvals in China in relation to the acquisition have been obtained, and filings with the antitrust authorities of the US had been completed. "In addition, the acquisition was reviewed by the Indian FIPB and will be recommended to the Cabinet Committee on Economic Affairs of India for further review and approval," Fosun said in a statement. An industry expert told *Scrip* that the CCEA typically goes along with the FIPB's position, though the Fosun deal clearly offers a platform "on a platter" for a Chinese firm to access the US market via an Indian base.

anju.ghangurde@informa.com, 31 Mar 2017

First UK Debt Financing Fund For Life Sciences

A specialized investment fund, BioPharma Credit, started trading on the London Stock Exchange on March 30, following a substantial initial public offering (IPO) that raised double its initial target and answering those calling for the UK to build up its financial "ecosystem" for life science companies. BioPharma Credit is the first fund specializing in debt financing for the life sciences industry to be listed on the LSE, and its IPO raised gross proceeds of $762m, more than double its initial target of $300m. In a week characterized by the UK starting the process of Brexit and withdrawing from the EU, the IPO and stock exchange listing was said by the LSE to "highlight the global investor interest in UK life sciences and the strength of London's fund industry." BioPharma Credit is the fourth fund in various industrial sectors to list on the LSE in 2017, indicating its attractiveness to international fund managers, particularly those from the US, the LSE continued. This year, more than £2.5bn has been raised in initial and follow-on capital raising by London-listed funds, more than a 100% increase year-on-year, in areas such as property, renewables and now life sciences specific funds. The BioPharma Credit fund is listed on the LSE's Specialist Fund segment as an Investment Trust; the segment contains 31 funds and is accessed by the financial investment community. The investment manager for the fund is the New York-based company Pharmakon Advisors, and it is set up to invest in debt and royalty assets issued by biotech and life science companies.

john.davis@informa.com, 30 March 2017

Avillion Has Faith In Merck's Ablynx-Rejected Psoriasis Drug

In a move potentially revealing lack of confidence in a pipeline psoriasis drug, Merck KGAA is giving M1095 – a compound licensed from Ablynx NV – over to London-based biopharma Avillion LLP, which will be responsible for progressing the product from Phase II through to regulatory submissions. Merck appears to have made little effort with the compound, a trivalent nanobody that neutralizes both IL-17A and IL-17F, since acquiring worldwide rights to it in June 2013. M1095 has been listed as in Phase I development for several years. Financial terms of Merck's deal with Avillion, announced March 30, were not divulged but the latter firm believes it can make a go of developing the inflammation drug. Avillion's business model is based on partnering with pharma companies to accelerate clinical development of specific assets from proof-of-concept onwards. The company has previously partnered with Pfizer Inc. for late-stage development of the big pharma's cancer therapy, *Bosulif* (bosutinib). Bosulif underperformed for Pfizer when, despite winning conditional approval in Europe for second-line Philadelphia chromosome positive (Ph+) chronic myelogenous leukemia (CML), the product was rejected for reimbursement in Germany, Scotland and England and Wales. Under its deal with Pfizer, Avillion was tasked with developing the drug through late-stage trials as a first-line treatment for CML to expand the product's market reach and value. Avillion reported positive Phase III data for Bosulif, which is also approved as a second-line treatment in the US, in first-line CML in December last year. Different to a contract research organization or manufacturer, Avillion finances clinical development programs through to registration – taking on the full clinical and regulatory risk. Avillion CEO Allison Jeynes-Ellis told *Scrip* this setup works best with late-stage big pharma programs, as opposed to mid-stage products from biotechs, because of the financial backing needed.

lucie.ellis@informa.com, 30 March 2017

Microbiome 2.0: Leading BioSciences Focuses On The 'Gastrobiome'

Firms that label themselves as microbiome companies have mushroomed in the past couple of years. Leading BioSciences likes to think it's working on "microbiome 2.0" and has filed a trademark application for the term "gastrobiome" to express that differentiation.

ELEANOR MALONE eleanor.malone@informa.com

Leading BioSciences has been around for more than a decade, targeting the microenvironment of the gut to address specific disease states associated with acute and chronic health issues, including the effects of surgery and of diabetes. With the recent surge in research and development focused on the gut and its microbiome, the firm, with freshly installed leadership, has adopted a new term to define its particular focus – gastrobiome – and has aligned its development activities around three core pillars.

The new term reflects the company's desire to distinguish its work from the increasingly fashionable idea of targeting the microbes in a given environment. Thus, the gastrobiome includes the bacteria in the gastrointestinal tract (the gut microbiome), but also includes food, digestive enzymes and the mucosal barrier that separates that environment from the rest of the body.

In fact, Leading BioSciences is focused on preserving the integrity of the gastrobiome by protecting the mucosal barrier and thus preventing a range of adverse health effects associated with mucosal barrier breakdown. "It's like microbiome 2.0: it's where the environment interacts with the body," says Thomas Hallam, the company's former VP of therapeutic development and SVP of clinical development and regulatory affairs, who recently was appointed CEO after a number of changes at the helm.

PILLAR NUMBER ONE

Hallam describes Leading BioSciences's lead drug LB1148 – which represents pillar number one – as "a sledgehammer." Under development initially to reduce patients' length of stay in the hospital following gastrointestinal procedures, it is intended to be administered to patients prior to surgery. It inhibits 17 digestive enzymes to "stop digestion cold within the body," he explains, and has applications "when a patient is in acute crisis or surgical condition where having no digestion at all is advantageous for the patient."

The foundational idea of the company is based on work done at the bioengineering department and in the medical school at the University of California, San Diego, where it was discovered that in certain conditions – for example, following an episode of shock – the mucosal barrier breaks down, and digestive enzymes normally confined to the intestine or pancreas can be found in other organs.

LB1148's key active ingredient is tranexamic acid, which itself is a generic medication with an established safety profile, commonly used intravenously to promote blood clotting in surgery. "It also inhibits digestive enzymes: trypsin, chymotrypsin, elastase and a number of other proteases that you find in the small intestine," says Hallam, but "one of our key learnings is that you have to get it into the small intestine where those digestive enzymes are in really high concentration: if you try stopping it systemically with an IV administration it just doesn't work."

The idea is for LB1148 to be administered to the GI tract in advance of surgery with the aim of reducing complications. The company initially is targeting GI/abdominal surgery, which offers a large patient population who must remain hospitalized until post-surgical return of bowel function is confirmed. GI surgery involves an incision into the GI tract – a key trigger for a breakdown in the mucosal barrier of the gut, which can delay return of bowel function and allow digestive enzymes to spill into the abdominal cavity. "Once you get the drug to stop the digestive enzymes in the small intestine, the mucosal barrier can heal itself," Hallam says.

"What we're focusing on in our GI surgery clinical trial is preventing damage to the GI tract so that the patient's bowel function returns faster and the patient is ultimately discharged from the hospital sooner," explains Hallam. With hospitals incentivized to drive costs down, he believes a product that is proven to reduce length of stay will be "put on formularies and mandated quickly."

A leakage of enzymes also can cause local tissue damage and inflammation leading to scarring and abdominal adhesions, with attendant complications: the current Phase II trial of LB1148 includes a second endpoint on a reduction in abdominal adhesions.

The first patient in the trial is expected to be enrolled in the second quarter of 2017 with the last patient enrolled by the end of the year, although it may go a quarter or two longer if the planned interim analysis leads to the study being repowered from

Leading BioSciences

Location: Solana Beach, California

R&D Focus: The "gastrobiome" – the ecology of the GI tract and the breakdown of the mucosal barrier in acute and chronic situations

Disease Areas: GI and cardiovascular surgery, shock/sepsis; diabetes

Founding Date: 2005 (as Leading Ventures; Inflammagen Therapeutics was subsequently formed as a subsidiary)

Founders: John Rodenrys (executive VP of R&D); Chip Parker (executive VP of Corporate Development); Chuck Gathers (then a steel industry executive who put up a significant portion of the founding capital)

Employees: 7

Financing To Date: $19m in private financing; $3m bridge note; $24m in NIH grants funded preclinical work

Investors: Private accredited investors: 3 institutional syndicates – two in San Diego, one in Denver, Colorado

© Informa UK Ltd 2017

120 patients to 200. Hallam acknowledges that LB1148 will have to compete with Merck's mu-opioid antagonist *Entereg* (alvimopan), which is FDA-approved to accelerate GI recovery following surgery, but he sees that drug more as a help than a hindrance to Leading BioSciences's potential offering. "Entereg has a lot of safety problems; its use involves a challenging process and it's not on the formularies of most US hospitals," he notes. "But its approval did set the vision that there really is a market. And it established a regulatory process for approval, meaning that we now know we have an approvable endpoint, and we know what the bar is on that endpoint to get an approval."

Meanwhile, the company also is conducting a Phase II study in complications of cardiovascular surgery and supporting a Phase II investigator-sponsored trial in shock.

PILLARS TWO AND THREE

While the acute care indications represent the first pillar, the second and third are represented by "leaky gut" diagnostics and therapeutic approaches in chronic conditions where an association between mucosal barrier breakdown and co-morbidities can be identified. The lead chronic care indication under investigation is diabetes, in which some patients are understood to have a chronic leak of digestive enzymes into the bloodstream, causing co-morbidities.

"What we realize strategically for chronic conditions is that it is absolutely important that I can take, for example, two diabetics and show that one has mucosal barrier breakdown and the other hasn't: the theory then is that I can treat the one with the breakdown and change the disease course." Hence the focus on the diagnostic. "Our pipeline diagnostic is ahead of our pipeline therapeutic, and that's strategically important, because we need a proven diagnostic to select the patient population for our proof of concept trial," says the CEO.

WHAT NEXT?

Leading BioSciences anticipates seeking a large pharma company to complete Phase III studies and eventually commercialize LB1148. In the meantime, it anticipates raising around $15 to $25m in one or two tranches with first closing in the next three to six months, to supplement the $19m it has raised in the private market to date.

Published online 30 March 2017

From the editors of *Start-Up*

AstraZeneca Adds Asia To Benralizumab Territories

IAN HAYDOCK ian.haydock@informa.com

In another vote of confidence in one of its newer respiratory assets, AstraZeneca is extending to Asia its already broad rights to benralizumab, adding to a deal it already has with Kyowa Hakko Kirin for Japan.

Following a recent biologics license application in the US, AstraZeneca PLC's confidence in the clinical and commercial prospects for its late-stage novel respiratory asset benralizumab remains high, as evidenced by a new extension of an existing alliance with Kyowa Hakko Kirin Co. Ltd.

The UK-based multinational has acquired exclusive rights in 13 Asian countries and regions to the interleukin-5 alpha receptor-targeting antibody in the indications of severe asthma and chronic obstructive pulmonary disease (COPD).

The deal builds on AstraZeneca's similar rights in Japan, where it exercised last year an exclusive option acquired in 2015 for a $45m upfront payment.

The new extension is worth $15m on signing to Kyowa Kirin, plus undisclosed regulatory and commercial milestones and "low double-digit" percentage sales royalties, and AstraZeneca will also cover all costs related to development, sales and marketing in the two indications in its additional territories.

The broader alliance goes back to a 2006 agreement between MedImmune LLC (acquired by AstraZeneca in 2007) and Kyowa Kirin's antibody technology subsidiary BioWa Inc., under which the UK firm gained global rights to benralizumab outside Japan and Asia, where Kyowa Kirin had initially retained these.

The IL-5 alpha receptor is highly expressed on, and involved in, the development of eosinophils, a type of effector cell that causes inflammation and airway hyper-responsiveness, which in turn occurs in around half of all asthma patients and causes exacerbations and impaired lung function.

Benralizumab, which uses BioWa's proprietary potency-enhancing technology, induces direct and almost total depletion of eosinophils by recruiting natural killer cells that knock out the cells, and has a rapid onset within 24 hours. AstraZeneca is already bullish on the therapy's prospects and differentiation given what is expected to be a once every eight weeks dosing schedule, and strong clinical data.

The company is hoping that Phase III data released last year will enable the drug to carve out convenience, lung function, and exacerbations benefits over other marketed, indirectly-acting antibodies for eosinophilic asthma, such as GlaxoSmithKline PLC's *Nucala* (mepolizumab), and Teva Pharmaceutical Industries Ltd.'s *Cinqaero/Cinqair* (reslizumab), which is administered every four weeks.

These IL-5 ligand-targeting therapies work in a biologically different way by blocking eosinophil progenitors, depleting eosinophils over a longer period.

Other novel therapies are coming through the pipeline however, including Chiesi Farmaceutici SPA acquisition target Atopix Therapeutics Ltd.'s oral small molecule CRTH2 antagonist, OC459, which is in Phase II for eosinophilic asthma.

Benralizumab was recently submitted in the US for severe uncontrolled asthma with an eosinophilic phenotype, and is in Phase III globally including Japan, where trials for both asthma and COPD are already underway.

A Phase II program is also underway in Japan for eosinophilic chronic rhinosinusitis.

The new deal with Kyowa Kirin builds on AstraZeneca's existing strong corporate presence in Asia and in the respiratory field, and the Japanese company pointed in particular to its partner's development and commercialization expertise.

Japan is already the second-largest asthma market globally, but Datamonitor Healthcare sees the value of the country's total asthma segment declining to $1.20bn by 2024, versus an expected $1.30bn this year.

Published online 27 March 2017

From the editors of *PharmAsia News*.

Editor's note: includes source data/analysis from Datamonitor Healthcare.

Alexion CEO Hantson Tasked With Kicking Growth Momentum Into Gear

The rare disease specialist's new CEO is former Baxalta CEO Ludwig Hantson, who takes over the helm immediately after a leadership shakeup coinciding with an audit investigation.

JESSICA MERRILL jessica.merrill@informa.com

Alexion Pharmaceuticals Inc.'s new CEO Ludwig Hantson will need to refocus the rare disease specialist onto a steady growth track after the company's recent missteps. Alexion announced the appointment of Hantson, formerly Baxalta Inc.'s CEO, on March 27.

Hantson succeeds David Brennan, who stepped in on an interim basis in December after former CEO David Hallal resigned for "personal reasons" amid an audit investigation related to sales of the company's blockbuster *Soliris* (eculizumab). Brennan will remain on the board of directors and will become chair of the board May 10, when Alexion founder and chair Leonard Bell will resign as previously announced.

The leadership changes come at an important time for Alexion as it tries to wring new growth out of Soliris while also attempting to reduce the company's dependence on the drug, which accounted for $2.84bn of Alexion's $3.08bn in revenues for 2016.

The appointment of a permanent replacement could dampen speculation over whether Alexion might be an M&A target, given its depressed share price, but Hantson does have experience executing on deals. Immediately after Baxalta was spun out of Baxter International Inc. in July 2015 as a blood products and rare disease specialist, the company was approached and eventually acquired by Shire PLC for $32bn.

"While the appointment of Hantson as a permanent CEO and a board member at Alexion may lessen the speculation of potential near-term takeout, it could also be viewed [that] his prior experience of selling Baxalta to Shire shortly after the spin-off from Baxter would not exclude such possibility," Jeffries analyst Eun Yang said in a same-day research note.

Hantson oversaw the spinout of Baxalta from Baxter, where he was president of Baxter BioScience, a $6bn global business unit within Baxter that was responsible for 13 product launches, according to Alexion. He previously worked at Novartis AG for a decade, including as CEO of Novartis Pharma, North America.

Ludwig Hantson

"Ludwig is a results-oriented leader with a strong R&D and commercial track record based on his ability to implement sound business strategies grounded in scientific, commercial and financial analyses," Alexion's lead independent director R. Douglas Norby said in a statement.

STEADYING THE SHIP

A top priority for Hantson will be restoring investor confidence in the company's management team. Alexion's stock came under pressure last year after the company announced Nov. 9 it was conducting an independent investigation into an allegation that Soliris was sold inappropriately. Chief financial officer Vikas Sinha also was pushed out along with Hallal in the aftermath, but the company largely limited the damage. The company announced in January that its Audit and Finance Committee found "inappropriate" behavior, but nothing illegal related to the way management recorded sales of Soliris, and Alexion avoided having to restate any financials.

The company's stock jumped 8% on the news to open Jan. 5 at $133, but it has steadily declined since. Investors are concerned about the growth prospects for Soliris long-term and potential competition, as well as the underwhelming launch of *Kanuma* (sebelipase alfa) for lysosomal acid lipase deficiency (LAL-D), a drug Alexion paid handsomely to acquire with the $8.4bn buyout of Synageva BioPharma Corp. in 2015.

Alexion also announced in February that it decided to reduce investment in a pipeline drug, SBC-103, also acquired with Synageva. During an R&D briefing in December 2015, Alexion spoke enthusiastically about the opportunity for SBC-103 as an enzyme replacement therapy for patients with mucopolysachharidosis IIIB (MPS-IIIB), particularly about its potential to cross the blood brain barrier. However, the firm now has taken an $85m impairment charge related to SBC-103 and will reduce investment in the drug candidate after an evaluation determined it would require increases in development and commercial timelines.

Currently, Alexion is looking ahead to the expansion of Soliris in a new indication: refractory generalized myasthenia gravis (gMG), an ultra-rare disease that results in complications such as difficulty walking, talking swallowing and breathing normally. Alexion announced FDA accepted the sBLA for Soliris in gMG March 8, with an Oct. 23 PDUFA date. Soliris currently is approved for the rare diseases paroxysmal nocturnal hemoglobinuria (PNH) and atypical hemolytic uremic syndrome (aHUS).

The company also is focused on developing a next-generation anti-C5 antibody ALXN1210 for PNH and aHUS that could have the potential for monthly dosing.

Hantson most certainly will be evaluating new ways to diversify Alexion beyond those opportunities as well.

Published online 27 March 2017

© Informa UK Ltd 2017

Myelofibrosis Misery: Pacritinib Setbacks Boosts Jakafi

SUKAINA VIRJI sukaina.virji@informa.com

With the commercial opportunity in the myelofibrosis market expected to double to over $1bn in the next five years, competition to Jakafi seems further away than ever as CTI BioPharma pulls the European regulatory filing for pacritinib.

The European Medicines Agency has revealed that CTI BioPharma Corp. has withdrawn its application for marketing authorization for *Enpaxiq* (pacritinib) for treating patients with an enlarged spleen or other symptoms of myelofibrosis. With only Incyte Corp./Novartis AG's JAK1/JAK2 inhibitor *Jakafi/Jakavi* (ruxolitinib) approved specifically for the indication, this is a real setback for patients.

However, the news is not a big shock as drug development in the myelofibrosis space is notoriously fraught, and pacritinib in particular has had a tumultuous development history to date.

The US FDA issued a full clinical hold on pacritinib, an investigational oral JAK2/FLT3 inhibitor, in February 2016 because of concerns about excess mortality and other adverse events, including intracranial hemorrhage, cardiac failure and cardiac arrest, in the company's two Phase III studies, PERSIST-1 and PERSIST-2.

This hold was lifted in January this year after CTI provided, among other items, final clinical study reports for both the PERSIST trials and a dose-exploration clinical trial protocol that the FDA requested. The new trial, PAC203, plans to enroll up to around 105 patients with primary myelofibrosis who have failed prior ruxolitinib therapy to evaluate the safety and the dose response relationship for efficacy (spleen volume reduction at 24 weeks) of three doses: 100 mg once-daily, 100 mg twice-daily (BID) and 200 mg BID. The 200 mg BID dose regimen was used in PERSIST-2. The company expects to start the trial in the second quarter of 2017.

However, in its official communication with the EMA's CHMP committee, CTI does not mention conducting a new trial.

According to CTI, the European withdrawal is based on the fact that in order to answer the Day 120 questions put forward by the regulator, the company "will need to integrate into the dossier the data from the second pivotal Phase III study PERSIST-2 [and] there is insufficient time to complete this within the required CHMP timeframe."

The myelofibrosis space is marked with a series of high profile development setbacks, including Gilead Sciences Inc.'s JAK 1/2 inhibitor momelotinib, Geron Corp./Janssen's telomerase inhibitor imetelstat and Sanofi's JAK 2 inhibitor fedratinib, which failed in 2013.

Myelofibrosis, which is closely related to blood cancers, is a life-threatening bone marrow disorder caused by the accumulation of malignant bone marrow cells that triggers an inflammatory response and scars the bone marrow, limiting its ability to produce red blood cells and prompting the spleen and liver to take over this function.

Published online 28 March 2017

Scrip Awards Winner 2016

Lifetime Achievement Award

A world leader in nucleoside chemistry, Schinazi is best known for his pioneering work on HIV, HBV and HCV drugs. More than 94% of HIV-infected individuals in the US on combination therapy take at least one of the drugs he invented. He is the Frances Winship Walters Professor of Pediatrics and Director of the Laboratory of Biochemical Pharmacology at Emory University and co-Director of the HIV Cure Scientific Working Group for the NIH-sponsored Emory University Center for AIDS Research. Schinazi has authored over 500 peer-reviewed papers and seven books and holds over 100 issued US patents, which have resulted in 15 New Drug Applications.

Winner: **Dr. Raymond Schinazi**

"Receiving the lifetime achievement award for Scrip was an extraordinary experience. This is the first time I attended the event and the energy in the room was vibrant and exciting. The research we did on HIV, HBV and HCV impacts global health and has saved millions of lives. It's nice to give back to the community and to have enjoyed the gala evening with so many friends, colleagues and family. It was also great to see the diversity of awards given that evening for well-deserved pharmaceutical achievements that will impact the health of many people."

- Dr. Raymond Schinazi

Scrip Awards
Pharma intelligence | informa

Progenics On Way To The FDA With Second Product Offering Azedra

ALEX SHIMMINGS alex.shimmings@informa.com

Progenics looks set to expand its product portfolio with a mid-year filing expected for its novel radiopharmaceutical product in ultra-rare neuroendocrine tumors following success in a pivotal study conducted under an SPA.

Progenics Pharmaceuticals Inc.'s registrational Phase IIb study of its novel radiotherapeutic *Azedra* (iobenguane I 131) Injection, has hit its primary endpoint, setting the stage for an FDA filing in the next quarter and opening up a new ultra-orphan market.

The open-label, multi-center study was conducted under a special protocol assessment (SPA) and evaluated Azedra in patients with malignant and/or recurrent pheochromocytoma or paraganglioma, two related and very rare neuroendocrine tumors for which there are currently no approved treatments.

Azedra already has in the bag breakthrough therapy, orphan drug and fast track designations from the FDA which should help smooth its way to market. Progenics' first marketed product is the opioid-induced constipation therapy *Relistor* (methylnaltrexone bromide), partnered with Valeant Pharmaceuticals International Inc.

Analysts at BTIG think the new product has a peak sales potential of more than $300m by 2022, and that the company has sufficient cash on its balance sheet to commercialize Azedra in the US itself – at the end of 2016, it had about $139m of cash and, in November 2016, announced a $50m royalty-backed financing arrangement with HealthCare Royalty Partners, secured by royalties from future sales of Relistor.

CEO Mark Baker told a conference call that the company had already begun to leverage the benefits of these regulatory designations, recently submitting the nonclinical sections of the NDA. "With these positive data, we plan to move quickly to complete our NDA submission to the FDA by mid-year. Given our breakthrough therapy designation, we would expect to have an expedited review." Progenics says approval should come in Q1 2018, but analysts at Aegis Capital believe the company could receive approval before the end of 2017 given the breakthrough designation status.

Pheochromocytoma and paraganglioma are neuroendocrine tumors that arise from cells of the sympathetic nervous system (paragangliomas are pheochromocytomas that are located outside the adrenal glands). These tumors frequently secrete high levels of hormones that affect the cardiovascular system and can lead to life-threatening hypertension, heart failure, and stroke. Malignant and recurrent tumors may not be resectable, representing a significant management challenge with very limited treatment options to manage symptoms.

Azedra, an ultratrace version of I-131 metaiodobenzylguanidine (MIGB), is a theranostic consisting of a small-molecule ligand with a radioisotope attached to it. The ligand specifically targets the tumors and the radioisotopes act as an imaging agent at low dose and the cancer cell-killing therapy at high doses, explained Vivien Wong, Progenics' EVP of development. The company's proprietary manufacturing process uses a drug product that has very high specific activity, which it believes could translate to better efficacy and safety.

The study's lead investigator Dr. Daniel Pryma, of the Perelman School of Medicine at the University of Pennsylvania, noted that conventional I-131 MIBG has been used without FDA approval on a compassionate basis in the US but with limited success. "Azedra uses the same targeting molecules as conventional MIBG but with a much higher specific activity, avoiding the large amounts of unlabeled MIBG found in each conventional MIBG dose. As a result, Azedra may deliver higher levels of radioactivity to the tumor."

Published online 31 March 2017

CLICK
View study details here:
http://bit.ly/2nFxXX7

European Patent Decision Boosts CRISPR Therapeutics

CRISPR Therapeutics says its IP position has been reinforced by the European Patent Office's aim to grant the University of California patent recognition covering CRISPR gene-editing for non-cellular and cellular use.

The European Patent Office has indicated it favors the University of California's argument that its discovery covers CRISPR use in both prokaryotic and eukaryotic systems, boosting UC's legal position and that of the companies which have licensed its genome editing patents.

CRISPR Conflict Roots

UC and its commercial licensees have been fighting the Broad Institute of Cambridge, Massachusetts and its ally Editas Medicine Inc. over CRISPR patents. The EPO's new decision contrasts with the position taken in February by the US Patent and Trademark Office

The dispute's origins go back to 2012, when CRISPR technology was invented. The UC team first reported how to use CRISPR in pieces of circular DNA that can invade bacteria, but the Broad Institute was first to apply the method to human cells. The gene-editing approach has since become widely used and offers potential use in a wide array of therapies. The financial implications are consequently enormous.

The Germany-based European Patent Office announced its decision to grant UC a patent broadly covering CRISPR genome editing across all cell types despite a number of third-party observations filed by the Broad Institute and others which aimed to prevent or delay the move. The EPO decided that the technical evidence and associated legal arguments did not alter the patentability of UC's inventions.

sten.stovall@informa.com, Mar-29-2017

© Informa UK Ltd 2017

Sumagen's Killed Whole HIV Vaccine Set For Phase II

After a positive outcome from a US Phase I study, South Korea's Sumagen is stepping closer to the launch of the world's first killed-whole HIV vaccine with potential to both prevent and treat AIDS.

JUNG WON SHIN jungwon.shin@informa.com

Sumagen Co. Ltd. has confirmed the safety and anti-HIV immune response of its HIV-1 vaccine, SAV001, in an early clinical trial in the US, and is now gearing up to move to the next phase and hopefully eventually to market.

The product is the world's first killed whole-virus vaccine for HIV and could potentially be used to both prevent and treat HIV/AIDS infections, the South Korean firm says.

"At present, patients have to continue to take two or three types of marketed AIDS drugs. Sumagen's vaccine creates neutralizing antibodies that can effectively treat the disease...this has therapeutic effects for various types of HIV," Sumagen CEO Sang-Kyun Lee recently told local reporters.

Unlike existing HIV/AIDS drugs which suppress existing infection, Sumagen's vaccine may effectively treat the disease, the company believes.

PROMISING RESULTS

During the Phase I trial, SAV001 induced an antibody response sufficient to prevent AIDS but without serious toxicity or side effects, the venture said. Thirty-three HIV-1 positive volunteers receiving combination antiretroviral therapy were recruited for the blinded, placebo-controlled study.

According to the detailed Phase I results published in *Retrovirology* in November 2016, the vaccine was well tolerated, and HIV-1NL4-3-specific polymerase chain reaction showed neither evidence of vaccine virus replication in infected human T-lymphocytes in vitro nor in participating volunteers.

Furthermore, SAV001 with adjuvant significantly increased pre-existing antibody response to HIV-1 proteins. Antibodies in the plasma of recipients were also found to recognize HIV-1 envelope protein on the surface of infected cells, as well as showing an enhancement of broadly neutralizing antibodies inhibiting tier I and II of HIV-1 B, D, and A subtypes.

Vaccination with inactivated (killed) whole-virus particles has been used to prevent a wide range of viral diseases, but in HIV this approach has been largely negated due to inherent safety concerns, despite the ability of killed whole-virus vaccines to generate a strong, predominantly antibody-mediated, immune response in vivo.

Sumagen's product is different from other HIV vaccine candidates as it uses a genetically re-engineered whole virus genome to eliminate its pathogenicity, with its activity then inactivated through chemical and irradiation methods.

HIV-1 Clade B NL4-3 is genetically modified by deleting the nef and vpu genes and substituting the coding sequence for the Env signal peptide with that of honeybee melittin signal peptide, to produce a less virulent and more replication-efficient virus. This genetically modified virus (gmHIV-1NL4-3) was inactivated and then formulated as a killed whole-HIV vaccine.

The gmHIV-1NL4-3 virus itself was propagated in an A3.01 human T cell line followed by purification and inactivation with aldrithiol-2 and γ-irradiation.

HUGE NEED

"In short, the level of unmet need [in HIV] is huge," Michael Haydock, lead analyst at Datamonitor Healthcare, told *Scrip*. "While current antiretroviral [ARV] therapy can reduce HIV transmission by lowering the viral load in infected individuals, it can only act to slow the epidemic - especially as undiagnosed individuals are most likely to transmit the virus - and so there is great need for agents capable of preventing initial infection."

Within the US and five major EU markets (including the UK), an effective vaccine would be able to command a high price not only because it would help to reduce transmission of the virus, but would be a substantial cost saver for payers, Haydock predicted. "Bear in mind that once infected, patients have to take antiretroviral therapy for life, so for each case prevented there is a large cumulative cost-saving over the lifetime of the patient," the analyst observed.

CHALLENGES, MARKET

HIV treatment also currently poses a considerable clinical and economic burden on private insurers and social healthcare institutions, because highly active ARV therapy must be taken indefinitely to maintain virologic suppression and prevent progression to AIDS.

Patients must also be frequently monitored to evaluate treatment responses and toxicity, which further adds to treatment costs, Datamonitor notes. Its analysis shows that decreased cost of treatment and therapies that offer superior long-term safety are the major unmet needs in HIV treatment.

As for market size, Datamonitor forecasts that US HIV sales will increase from $11.7bn in 2015 to $18.4bn in 2024 (+5% CAGR). The US is currently the biggest market, comprising 76% of total sales, due to having the largest diagnosed HIV prevalence and the highest drug prices of all the forecast markets.

Sales are predicted to rise rapidly between 2015 and 2022, driven by continued uptake of new therapies such as ViiV Healthcare's *Triumeq* (dolutegravir/abacavir/lamivudine) and *Tivicay* (dolutegravir), and the launches of novel tenofovir alafenamide (TAF)-based regimens.

Covance Inc. as its external partner for the trial in the US. "We plan to file for an IND for the Phase II in the US this year and begin the study in 2018," said a company official. R&D costs for SAV001 are also being supported by an HIV/AIDS vaccine development fund jointly launched by the Bill and Melinda Gates Foundation and the government of Canada.

Published online 27 March 2017

From the editors of *PharmAsia News*.

(Editor's note: includes source data/analysis from Datamonitor Healthcare.)

Scrip's weekly **Pipeline Watch** tabulates the most recently reported late-stage, Phase III clinical trial developments for the more than 10,000 drug candidates under active research worldwide. To see changes to the progress of product candidates further back in the development pipeline, and a table of the week's product approvals, please visit our Pipeline Watch webpage at scrip.pharmamedtechbi.com.

CLICK

Visit the Pipeline Watch webpage at scrip.pharmamedtechbi.com for all the week's changes to the industry's R&D pipeline

Selected clinical trial developments for the week 24–30 March 2017

LEAD COMPANY/PARTNER	COMPOUND	INDICATION	COMMENTS
Phase III Suspended			
ArQule Inc./Kyowa Hakko Kirin Co. Ltd.	tivantinib	hepatocellular cancer	JET-HCC; no effect on PFS in Japanese patients.
Updated Phase III Results			
Anthera Pharmaceuticals Inc.	*Sollpura* (liprotamase)	exocrine pancreatic insufficiency in cystic fibrosis	SOLUTION; positive effects on body weight, height.
Adamas Pharmaceuticals Inc.	*Nurelin* (amantadine) extended-release	levodopa-induced dyskinesia	EASE LID; reduced dyskinesia.
Phase III Interim/Top-line Results			
Acorda Therapeutics Inc.	CVT-301 (inhaled levodopa)	Parkinson's disease	Study 004, 005; no effect on pulmonary function in long-term safety studies.
Vertex Pharmaceuticals Inc.	tezacaftor (VX-661) plus ivacaftor	cystic fibrosis	EVOLVE, EXPAND; met primary endpoints .
Allergan PLC/Paratek Pharmaceuticals Inc.	sarecycline (narrow spectrum tetracycline)	moderate to severe acne	SC1401, SC1402; met primary endpoints.
Foamix Pharmaceuticals Ltd.	FMX101	moderate to severe acne	FX2014-04, -05; well tolerated, mixed efficacy results.
Paion AG/Cosmo Pharmaceuticals NV	remimazolam	anesthesia during colonscopy	Positive data in safety study in high-risk patients.
Phase III Initiated			
Armo BioSciences Inc.	AM0010 (pegylated interleukin-10)	advanced pancreatic cancer	Combined with FOLFOX.
Eisai Co. Ltd./Biogen	elenbecestat (a BACE inhibitor)	Alzheimer's disease	MissionAD1; started in Japan.
Tonix Pharmaceuticals Holding Corp.	TNX-102 SL (cyclobenzaprine) rapidly disintegrating sublingual tablet	post-traumatic stress disorder	HONOR; in military-related symptoms.
Phase II Suspended			
Xenon Pharmaceuticals Inc.	XEN801	moderate to severe acne	Missed efficacy endpoints of changes in lesion counts .
Updated Phase II Results			
Omeros Corp.	OMS721	IgA nephropathies	Improved renal survival, no safety concerns.
Progenics Pharmaceuticals Inc.	*Azedra* (iobenguane I-131)	neuroendocrine tumors	Reduced high blood pressure, well tolerated.
Diamyd Therapeutics AB	*Diamyd* diabetes vaccine	type 1 diabetes	DIABGAD-1; mixed results, some positive effects.
ILJIN group	*Luveniq* (voclosporin)	lupus nephritis	AURION; Early biomarker responses.
Axovant Sciences Ltd.	intepirdine	Alzheimer's disease	Positive effects on symptoms, including patient independence.
Newron Pharmaceuticals SPA	evenamide	schizophrenia	Initial evidence of efficacy.

Source: Biomedtracker

© Informa UK Ltd 2017

Crescendo Biologics has appointed ***Philip Bland-Ward*** chief scientific officer (CSO) – effective May, 2017. Bland-Ward has over 20 years of experience in the biopharma industry and joins Crescendo from Kymab, where he was responsible for leading its most advanced development program. He has previously held senior positions at Cambridge Antibody Technology, PanGenetics, and was CSO at Navion, as well as a co-founder of Nascient.

Shield Therapeutics Plc. has named ***Joanne Estell*** chief financial officer (CFO) and a board member – effective May 1, 2017. Estell will join the company with more than 20 years' experience in senior finance, strategy and merger and acquisition positions. Most recently she was CFO and company secretary of Stadium Group Plc. Before this, Estell was head of M&A at Survitec Group Ltd., a manufacturing company.

Catherine Stehman-Breen has joined **Sarepta Therapeutics Inc.**, a company focused on the treatment of rare neuromuscular diseases, as chief medical officer. Prior to Sarepta, Stehman-Breen was vice president, clinical development and regulatory affairs at Regeneron Pharmaceuticals. She previously held senior leadership roles at Amgen, including vice president, global development leading the neuroscience, nephrology and bone therapeutic areas. In addition to the appointment of its chief medical officer, Sarepta has also named ***Kenneth Fischbeck*** and ***Matthew Wood*** to the company's strategic and scientific advisory board.

Verona Pharma Plc., a company focused on respiratory diseases, has appointed ***Richard Hennings*** to the company's senior management team as commercial director. With more than 15 years of experience, Hennings has held roles with increasing responsibility in various companies including AstraZeneca PLC, Gilead Sciences Inc. and Novartis AG. Verona has also announced that ***Patrick Humphrey*** will be retiring from his role as a non-executive director on the company's board – effective April 15, 2017.

Hansa Medical has appointed ***Sam Agus***, a board-certified neurologist, chief medical officer. Most recently, Agus was chief specialist, medical affairs neurology at H. Lundbeck A/S and has previously held leading positions at Shire PLC, Solvay Pharmaceuticals and Abbott Laboratories.

Paul Sekhri, CEO and president of Lycera Corporation, has been named **Topas Therapeutics GmbH**'s chair of the board. He has previously held various leading management positions in companies including Sanofi, Teva Pharmaceutical Industries Ltd., Novartis AG, Ariad Pharmaceuticals Inc. and TPG Capital group (TPG Biotech).

Astellas Pharma Inc. has appointed ***John DeMay*** president, **Astellas US Technologies Inc. (AUST)**, and will act as the site manager for AUST based in Northbrook. DeMay will also continue in his role as head of the project and product management group. He joined Astellas in 2002 as an associate director of technical services and previously, he was executive director, pharmaceutical technology management for AUST.

HIV focused company, **Aelix Therapeutics**, has named ***Ian McGowan*** chief medical officer. McGowan will continue to hold a part-time appointment as professor of medicine, division of gastroenterology, hepatology and nutrition at the University of Pittsburgh School of Medicine. Previously, he was principal investigator of the Microbicide Trials Network (MTN) and currently leads MTN's rectal microbicide program. Before this, he was a consultant with WHO and the Centers for Disease Control and Prevention (CDC).

Scrip

LEADERSHIP
Philip Jarvis, Mike Ward

SUBSCRIPTIONS
Daniel Frere

ADVERTISING
Christopher Keeling

DESIGN
Paul Wilkinson

EDITORS IN CHIEF
Eleanor Malone (Europe)
Denise Peterson (US)
Ian Haydock (Asia)

EXECUTIVE EDITORS – COMMERCIAL
Alexandra Shimmings (Europe)
Mary Jo Laffler (US)

EXECUTIVE EDITORS – POLICY AND REGULATORY
Maureen Kenny (Europe)
Nielsen Hobbs (US)

EUROPE
Lubna Ahmed
Neena Brizmohun
Francesca Bruce
John Davis
Lucie Ellis
John Hodgson
Ian Schofield
Vibha Sharma
Joanne Shorthouse
Sten Stovall
Sukaina Virji

US
Michael Cipriano
Derrick Gingery
Joseph Haas
Emily Hayes
Mandy Jackson
Cathy Kelly
Jessica Merrill
Brenda Sandburg
Bridget Silverman
Sue Sutter

ASIA
Ying Huang
Anju Ghangurde
Jung Won Shin
Brian Yang

EDITORIAL OFFICE
Christchurch Court,
10-15 Newgate Street
London, EC1A 7AZ

CUSTOMER SERVICES
Tel: +44 (0)20 7017 5540
or (US) Toll Free: 1 800 997 3892
Email: clientservices@pharmamedtechbi.com

TO SUBSCRIBE,
scrip.pharmamedtechbi.com

TO ADVERTISE, CONTACT
christopher.keeling@informa.com

All stock images in this publication courtesy of www.shutterstock.com unless otherwise stated

Scrip Awards 2017

Pharma intelligence | informa

Open for Entries

The 13th Annual Scrip Awards

2017

www.scripawards.com

29 November 2017 | London Hilton on Park Lane

General Enquiries:

Natalia Kay | Tel: +44 (0) 20 7017 5173 | Email: natalia.kay@informa.com

Sponsorship and Table Booking Enquiries:

Chris Keeling | Tel: +44 (20) 337 73183 | Mobile: +44 (0) 7917 647 859

Email: christopher.keeling@informa.com

Event Sponsors

HUYA bioscience international

inc Research

ICON A Symbol of Excellence

Lachman CONSULTANTS

PPD

WORLDWIDE CLINICAL TRIALS

药明康德 WuXi AppTec

Headline Sponsor

QuintilesIMS