Scrip
24 November 2017
No. 3881
scrip.pharmaintelligence.informa.com
Pharma intelligence | informa

Shutterstock: JenFoto

Amsterdam wins European Medicines Agency After Coin Toss

IAN SCHOFIELD ian.schofield@informa.com

Amsterdam is to be the new home of the European Medicines Agency after the Dutch capital beat the northern Italian city of Milan in a nailbiting voting process that was eventually decided by the drawing of lots.

Three cities – Amsterdam, Copenhagen and Milan – had made it through to the second round of voting, in which member state ministers gave Milan 12 votes, Amsterdam nine, and Copenhagen just five, putting the Danish capital out of the running.

The final result of the vote, which took place during the General Affairs Council in Brussels on Nov. 20, might have been different if Slovakia, which had put forward its capital Bratislava, had not abstained from voting after it failed to progress beyond round one. As it was, Amsterdam and Milan were tied in the final round and the winner was chosen by pulling the name out of a bowl.

Reaction to the result was predictably mixed, with many welcoming the choice of Amsterdam but others bemoaning the fact that a momentous decision such as the future location of a major EU agency should be taken on what amounted to a coin toss.

Italy was bitterly disappointed, given that up to that point Milan had been ahead in the voting. Massimo Scaccabarozzi, president of the Italian pharmaceutical industry association Farmindustria, said: "We won all the same. Italy showed that it could reach the highest level of the podium on an assessment of its merits. In the first voting rounds Italy in fact obtained more votes than the other candidates. This demonstrates that Milan best matched the quality characteristics that were requested. And it was defeated only because of the drawing of lots and bad luck."

Copenhagen will also have felt the pain, having invested a lot of effort in a lengthy, high-profile lobbying and publicity campaign. Lars Rebien Sørensen, who spearheaded Denmark's efforts to secure the EMA, was gracious in defeat, thanking all those who supported the bid and offering "big congratulations to Amsterdam… Good choice that will ensure business continuity of EMA to the benefit of all Europeans!"

LONDON THE REAL LOSER

But many would say that the real loser is London, which has hosted the EMA since its creation in 1995 and is now seeing it taken away as a direct result of the UK's decision to leave the EU. Moreover, the capital is also losing another EU agency: the European Banking Authority, which following a separate vote in Brussels will now move to the French capital Paris.

Following the EMA decision, Steve Bates, CEO of the BioIndustry Association, said: "London's loss is Amsterdam's gain. Today's decision on the location of the European Medicines Agency means 1000 high quality jobs leaving the UK, disrupting 1000 families as a direct result of Brexit, with implications for thousands more."

Winning the EMA is of course a real coup for Amsterdam, not only because of the prestige of hosting a very highly regarded agency but because of the practical benefits it brings, such as synergies with local regulators, the biopharmaceutical industry and

CONTINUED ON PAGE 7

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

First Digital Pill
Tracking adherence is now a reality p6-7

PD-1s Bring In The Money
See how the various products are performing p8-10

SITC Cancer Meeting
Novel immunotherapies come to the fore p18-19

from the editor

eleanor.malone@informa.com

You have to feel sorry for Milan, getting through two rounds of votes and actually winning most votes in the second round, only to see the coveted European Medicines Agency headquarters land in Amsterdam after a final round dead heat led to the decision being made by a game of pure chance.

Still, with the March 2019 Brexit deadline rapidly approaching, it is good for medicines regulation in Europe that a decision has been taken. For an agency of that size (around 900 people work in the current HQ in London) the move will still involve a fair bit of scrambling, but at least logistical planning can now begin.

Now, the political focus needs to be on establishing an orderly separation of medicines regulation in the EU and the UK, which for the benefit of patients and drug manufacturers across the continent would probably involve as much harmonization and collaboration as is feasible within the parameters of the UK's apparent commitment to separate decisively from its continental neighbours. With an area as complex as drug regulation, this would be no small task even without such a looming deadline; it is to be hoped that the departing member state does agree a transitional arrangement with the remaining 27-state bloc to extend the exit runway beyond 2019.

Back in London, there are other prizes to bestow. We have a cabinet bursting with beautiful trophies to award to the winners of the 13th annual Scrip Awards on November 29th. Check out www.scripawards.com to check out the shortlist and book your table.

Scrip

LEADERSHIP
Phil Jarvis, Mike Ward

SUBSCRIPTIONS
Daniel Frere

ADVERTISING
Christopher Keeling

DESIGN SUPERVISOR
Gayle Rembold Furbert

DESIGN
Paul Wilkinson

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@pharma.informa.com

TO SUBSCRIBE, VISIT
scrip.pharmaintelligence.informa.com

TO ADVERTISE, CONTACT
christopher.keeling@informa.com

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

exclusive online content

BMS Q&A: Hunting For Biomarkers To Improve Treatment Of Autoimmune Diseases
http://bit.ly/2jdpjOO
Bristol-Myers R&D leaders Brian Gavin and Sean Connolly offered insight into the company's immunology focus for autoimmune diseases, which increasingly is driven by a search for biomarkers that point to the best use of the big pharma's drugs.

Ultragenyx Gets Commercial Feet Wet With Mepsevii Launch In Sly Syndrome
http://bit.ly/2AiQt1N
Commercial opportunity for *Mepsevii* is small, but launch paves way for company's second product burosumab, following on its heels.

Redx Rises Out Of Administration With R&D Refocus
http://bit.ly/2mS0T2y
After a tough summer, the UK firm has exited insolvency with new management and programs in cancer and fibrosis, having decided to shut down its anti-infectives business.

AZ Sustains Strong China Growth Via Commercial Innovation
http://bit.ly/2hVqB4h
AstraZeneca's strong showing in China in the third quarter was driven by a combination of expanded coverage, investment in patient access efforts and an innovative commercial model. New introductions *Tagrisso* and *Farxiga* are also expected to add to the momentum.

ImmuneOncia: A PD-L1 Latecomer Hoping To Break Into The Market
http://bit.ly/2hRm17k
Emerging Company Profile: ImmuneOncia may be late entering the market for PD-L1 inhibitors, but the joint venture between Yuhan and Sorrento Therapeutics aims to develop best-in-class immuno-oncology drugs with differentiated products and strategy.

Deal Watch: Genentech Expands Upon Arvinas PROTAC Collaboration
http://bit.ly/2iBASzB
The Roche affiliate doubles the potential monetary value of partnership focused on PROTAC technology in a range of therapeutic areas. Cardinal sells off Chinese business for $1.2bn, while Novartis licenses Homology's gene-editing technology.

inside:

@PharmaScrip /scripintelligence
/scripintelligence /scripintelligence

Roche's Hemlibra Priced And Labeled To Beat Competition, Safety Concern

MANDY JACKSON mandy.jackson@informausa.com

Roche's **Genentech Inc.** won US FDA approval on Nov. 16 for its once-weekly injection *Hemlibra* as a prophylactic treatment for adult and pediatric patients who have hemophilia A with inhibitors, which could free patients from multiple weekly infusions.

And at a cost that's at least half of the current prophylaxis treatment with potentially better efficacy and a safety concern that now looks manageable, uptake among prescribers, patients and payers could be strong. Hemlibra (emicizumab-kxwh, ACE910) is expected to be a blockbuster product, though peak sales estimates range from $1.1bn to $5bn. But like the Genentech's product development leader and a clinical investigator who both spoke with *Scrip*, stock analysts believe thrombosis concerns that emerged during clinical trials won't significantly limit Hemlibra's use.

"Beyond its superior efficacy, Hemlibra's simple weekly subcutaneous injection will help transform the lives of patients that would otherwise require multiple infusions a week," Jefferies analyst Jeffrey Holford said in a Nov. 16 research note.

Holford predicted that the product "will generate [about] $5bn of peak sales across both inhibitor and non-inhibitor patients, more than double current consensus."

Genentech expects to report data before the end of this year from two Phase III trials: HAVEN 3 is testing once-weekly and every other week dosing in hemophilia A without inhibitors, while HAVEN 4 enrolled hemophilia A patients with and without inhibitors to test Hemlibra dosed every four weeks.

Holford wrote that Hemlibra for patients with inhibitors is "priced for rapid penetration" at the $482,000 first-year wholesale acquisition cost (WAC); the WAC drops to $448,000 in subsequent years (those prices are based on the average weight patient).

Genentech noted that the price of its product is less than half the cost of the WAC for the only other approved prophylactic treatment for hemophilia A with inhibitors, **Shire PLC**'s *Feiba* (anti-inhibitor coagulation complex). Prophylaxis with the current standard of care can cost more than $1m per year.

Deutsche Bank analyst Tim Race predicted strong Hemlibra uptake, but pegged its annual sales at a more modest $1.1bn by 2022. Race said the product's pricing "is very much in line with our published assumption of around $400,000 to $500,000."

Michael Callaghan, a clinical investigator involved in the HAVEN 1 and HAVEN 2 trials that supported Hemlibra's US approval, estimated that the therapy's price is actually about a quarter of Feiba's cost, which he said could be as much as $2m per year. Callaghan, a pediatric hematologist-oncologist in Detroit, Mich. who is affiliated with Children's Hospital of Michigan, said that based on the experience of his eight patients in Genentech's studies the drug is well worth its price.

"Usually we're weighing the balance between a new product that has more benefit and more cost, but here we have a dramatically better benefit and dramatically lower cost, so it should be a no-brainer," he said, in terms of whether payers decide to reimburse Hemlibra's cost.

Payers around the globe indicated in a report issued earlier this year by Datamonitor Healthcare, an Informa Pharma Intelligence service, that Hemlibra was a highly anticipated product due to its weekly subcutaneous self-injection. The therapy could result in better convenience and adherence to therapy as well as lower costs than infused clotting factors.

FROM ONE OPTION TO TWO

Hemophilia A patients lack or do not have enough of the clotting protein Factor VIII, which brings together Factors IXa and X to cause blood to clot. Patients are treated with Factor VIII replacement therapies, but some people develop inhibitors that make those treatments ineffective. About 20,000 people in the US have hemophilia and about 50% to 60% have hemophilia A; about 20% to 30% of those patients develop inhibitors.

While Feiba, also known as an activated prothrombin complex concentrate (aPCC), previously was the only therapy approved for prophylactic treatment of hemophilia A with inhibitors, both Feiba and another bypassing agent (BPA) – **Novo Nordisk AS**' *NovoSeven* [coagulation Factor VIIa (recombinant)] – are approved for on-demand use to treat breakthrough bleeding.

Hemlibra is a bispecific Factor IXa- and Factor X-directed antibody, which brings the two factors together to restore the body's clotting ability. It was approved three months ahead of its Feb. 23 PDUFA date, reflecting a particularly speedy FDA decision, since the biologic license application was granted priority review on top of a prior breakthrough therapy designation. The European Medicines Agency is reviewing Hemlibra under an accelerated assessment and reviews in other ex-US markets are ongoing.

FDA approval was based on the Phase III HAVEN 1 trial, which enrolled patients aged 12 and older who had hemophilia A with inhibitors, and an open-label study known as HAVEN 2 that enrolled patients under the age of 12. Injection site reactions, headaches and arthralgia were the most common side effects across both studies.

Individuals treated with Hemlibra prophylaxis had an 87% reduction in treated bleeds versus those who did not receive prophylaxis in the 109-patient HAVEN 1 trial; 62.9% of Hemlibra-treated patients had zero bleeds versus 5.6% who were not treated prophylactically. Also, 70.8% of patients who received prophylactic BPA treatment prior to the study and were given Hemlibra prophylaxis during the study had zero bleeds compared with 12.5% of patients treated with BPA prophylaxis in a non-interventional study (NIS) prior to HAVEN 1 enrollment.

Interim results of HAVEN 2 evaluating Hemlibra prophylaxis showed that 87% of the children had zero bleeding events at 38.1 weeks. Among the 13 patients who participated in the NIS, including 12 previously treated with BPA prophylactically and one who used BPA on demand, there was a 99% reduction in treated bleeds.

SAFETY FLAG RAISED

Safety is a key consideration for hemophilia patients when determining whether to switch treatments, so an adverse event that emerged during Genentech's Hemlibra clinical trial program raised some doubts. Incidences of thrombotic microangiopathy (TMA), including one deadly case in HAVEN 1, have been reported.

However, Genentech's clinical development lead for Hemlibra Gallia Levy noted that TMA was seen only in patients who were treated with Feiba due to a bleeding event. That's why the product's label has box warnings to make doctors and patients aware that TMA and thromboembolism has been observed in patients treated with aPCC for 24 hours or more.

The boxed warning advises physicians to "monitor for the development of thrombotic microangiopathy and thrombotic events if aPCC is administered. Discontinue aPCC and suspend dosing of Hemlibra if symptoms occur." There were 125 administrations of aPCC to 36 patients and thrombotic adverse events related to treatment with more than 100 U/kg over 24 hours occurred in five patients – three with TMA and two with thromboembolism.

"We really do feel that we have a good understanding of what the risk is," Levy said. "That's why the boxed warning is there and we're happy to have it there." She noted that limitations on Feiba use has been in Genentech's Hemlibra clinical trials for almost a year and there have been no new TMA cases since then.

"While a boxed warning is typically unhelpful for sales, this was expected given the serious adverse events observed when administering rescue medication," Deutsche Bank's Race wrote.

EFFICACY OUTWEIGHS RISK

Callaghan, the clinical investigator and hematologist in Detroit, said there's always caution with new hemophilia drugs, because this patient population has seen significant safety issues with new therapies in the past. He noted that even Feiba for prophylaxis, when tested in a smaller program than Genentech's studies for Hemlibra, had three deaths.

"It's helpful that [the TMA events associated with Hemlibra] were explainable and avoidable, because they were with concomitant use of aPCC," Callaghan said. He said the remarkable efficacy he's seen in Genentech's studies should outweigh the seemingly manageable safety concerns around co-administration of Feiba for breakthrough bleeding.

Levy said Genentech was particularly excited about Hemlibra's approval for all adults and children with no age limit, which means very young children under the age of 12 – who have difficulty sitting through an hour infusion – and their families have access to a less frequent injectable treatment.

Hemlibra will be available within the next two weeks. Genentech will offer services to help patients and their families access the drug, including assistance navigating their health plans and pharmacy benefits. Genentech Access Solutions, the company's patient assistance program providing financial help in paying out-of-pocket costs for its medicines, also will be available to individuals who qualify for Hemlibra therapy.

Published online 17 November 2017

Non-Inhibitor Data Secure Roche's Competitive Position in Hemophilia A: http://bit.ly/2zV102t

Samsung's Ontruzant Becomes First Trastuzumab Biosimilar Approved In EU

JUNG WON SHIN jungwon.shin@informa.com

Samsung Bioepis Co. Ltd. 's *Ontruzant*, a biosimilar version of **Roche** 's *Herceptin* (trastuzumab), has become the first trastuzumab biosimilar to get the green light from the European Commission, beating rival products also going through the regulatory approval process in Europe.

Celltrion Inc. also has a biosimilar trastuzumab, *Herzuma*, under review in the EU, and could be the next to secure a positive opinion the European Medicines Agency, having submitted its dossier at the same time as Samsung Bioepis. Other companies developing biosimilar versions include **Pfizer Inc.** (PF-05280014) and **Amgen Inc./ Allergan PLC** (ABP980); the latter product was filed with the EMA in March 2017.

With the latest approval, Samsung is in a favorable position to lead the European trastuzumab biosimilar market as the first mover. It already has EC approvals for three autoimmune disease drug biosimilars: *Benepali* (etanercept), *Flixabi* (infliximab) and *Imraldi* (adalimumab).

Ontruzant is approved for the treatment of early breast cancer, metastatic breast cancer and metastatic gastric cancer. The approval comes two months after the EMA's scientific committee, the CHMP, gave the biosimilar, formerly known as SB3, the thumbs up. Ontruzant is the first anticancer antibody biosimilar Samsung Bioepis has developed.

The EC approval of Ontruzant applies to all 28 EU member states and the European Economic Area (EEA) member states of Norway, Iceland and Liechtenstein. Ontruzant will be commercialized by Samsung Bioepis's marketing partner MSD, which is known as **Merck & Co. Inc.** in the US and Canada.

PATENT EXPIRED IN EU

"Herceptin's patent expired in Europe in 2014, therefore any potential stumbling blocks might come in the shape of market access issues in individual countries, and oncologists' cautiousness as Ontruzant would be the first MAb solely for use in oncology," said Datamonitor Healthcare analyst Hristina Ivanova.

Herceptin lost patent protection in the EU and Japan in 2014, with further patent expiries expected in the US in 2019. Biosimilar versions of Herceptin are anticipated to compete strongly with the branded drug for sales. Global sales of Herceptin totaled $6.78bn in 2016.

Samsung Bioepis plans to launch Ontruzant in Europe after discussions with MSD. *Published online 20 Nov 2017*

From the editors of PharmAsia News.

FDA Approves First Digital Pill: Otsuka/Proteus' Abilify MyCite

MANDY JACKSON mandy.jackson@informausa.com

Abilify MyCite (aripiprazole tablets with sensor) passed its first big test with US FDA approval of the digital atypical antipsychotic, but with a slow launch by **Otsuka Pharmaceutical Co. Ltd.** it may take a while for the product to receive passing grades from patients, doctors and payers.

Otsuka and partner **Proteus Digital Health Inc.** initially failed to win FDA approval in April 2016 for their digital pill – a system that includes an ingested sensor, wearable patch, smartphone application and online portal to track medication compliance. The agency endorsed the product on Nov. 13, but the FDA's announcement came with a few caveats about how the compliance benefits are unproven and the data may not be reliable in emergency situations. But while Abilify MyCite's approval represents the FDA's willingness to consider digital medicines, it remains to be seen whether patients with schizophrenia, bipolar I disorder and depression will embrace the technology or whether payers are willing to reimburse the costs for a high-tech version of a drug that's available as a generic.

"The FDA supports the development and use of new technology in prescription drugs and is committed to working with companies to understand how technology might benefit patients and prescribers," Mitchell Mathis, director of the Division of Psychiatry Products in the FDA's Center for Drug Evaluation and Research, said the in the agency's announcement about the approval.

For doctors, Abilify MyCite represents an opportunity to track adherence to prescribed drug therapy in a way that hasn't been available before, which could improve the overall coordination of care.

Otsuka Pharmaceutical Development & Commercialization, Inc. CEO William Carson, a psychiatrist by training, said in an interview that he would have loved to have had technology like this available when he was treating patients, because it's so important to keep them compliant with prescribed medicines. If the patient gives their consent to use the Abilify MyCite system as designed, he said, they can work with their doctor to monitor their medication compliance and the treatment progress.

"This system would help you to see if the patient is compliant. If so, and it's not working, then they may need a new medication choice. If not, you know they're not taking it on a regular basis," Carson said. "It might help you make better decisions about what patients really need to get better."

A PUSH TO PURSUE PSYCHIATRIC INDICATIONS

The World Health Organization (WHO) has pegged medication compliance at about 50% globally across all diseases, but Proteus Chief Medical Officer George Savage told *Scrip* that in his first interactions with the FDA in 2011, Proteus was encouraged to pursue psychiatric conditions – which have notoriously poor prescription drug compliance – as the initial indications for the company's technology.

Patients with those diseases, he added, have greater potential for decline if they aren't compliant and greater potential for improvement if they adhere to prescribed treatment regimens.

Abilify MyCite was approved for schizophrenia, acute and maintenance treatment of bipolar I disorder as a monotherapy or as an adjunct to lithium or valproate, and as an add-on therapy for adults with major depressive disorder. However, the label points out that the product's ability to improve patient compliance has not been proven – one of the caveats noted in the FDA's approval announcement.

The agency's other caveat was that the digital component of the drug cannot be relied on to track ingestion in real time or to provide ingestion information in an emergency situation, because the system's recognition that the pill has been swallowed could be delayed or it may not be recorded at all.

Abilify MyCite is designed to track the time when a patient swallows the medicine via a Proteus-developed sensor – about as big as a grain of sand – that's embedded in Otsuka's Abilify pills. The sensor sends a message to a patch worn on the patient's skin, recording the time that the drug lands in the individual's stomach.

The patch relays the data to an app on the patient's smartphone, where they can monitor when they took the drug and what their level of activity was at that time. They also can enter additional information, such as rest and mood. The patient may authorize doctors, family members and caregivers to view the data through an online portal.

The Proteus sensor and accompanying patch, app and online portal were approved as a medical device in the EU in 2010 and in the US in 2012. Embedded in a placebo, the product can be ingested at the same time as a traditional pill and similarly record and display tracking information. As for additional drugs formulated with the Proteus technology inside, the company is working on therapies for cardiometabolic indications, tuberculosis, hepatitis C and HIV. The technology also could be used in opioids to track use and potentially prevent addiction.

PERSEVERING AFTER INITIAL REJECTION

Otsuka and Proteus won the first-ever FDA approval for a digital pill only after failing the drug's first regulatory test about a year and a half ago. The agency issued a complete response letter in April 2016 requesting more information about human factors testing – information that showed how patients used and responded to the Abilify MyCite system.

FDA asked for simplification of some of the smartphone app and online portal content to make it easier for patients to use and understand, especially since some of those individuals may have some cognitive impairment, Proteus' Savage and Otsuka's Carson explained in a joint interview.

"The FDA looked at the system, which included two components that already were on the market independently," Savage said. "They were interested in what happens when you put this together. With people who have some cognitive impairment, they wanted something that they could use very easily."

Carson added that after the FDA's suggestions were incorporated the error rate for

Abilify MyCite dropped from about 12% to 1.5%. "It improved the ability of patients to use the entire system," he said.

When asked about whether it would be difficult to get patients with schizophrenia, which includes paranoia as one of its symptoms, to use technology that allows close surveillance of their treatment, Carson noted that many patients can separate their paranoid delusions from the practical matters of their treatment, such as the importance of taking prescribed medicines under close supervision, and that not all patients with schizophrenia are paranoid.

Savage said that in Proteus' study ending in 2011, patients with delusions were able to use the technology as designed. "It's not for everyone, but the general sense this isn't going to work for these [paranoid] patients is overdone," he said.

REAL WORLD USE WILL INFORM ONGOING PRODUCT DESIGN

Given the novelty of the Abilify MyCite system, Otsuka is planning for a slow, measured launch kicking off in early 2018. The product's initial rollout will start with just a few health care plans and providers, who will identify a limited number of adults with schizophrenia, bipolar I disorder or depression to use the treatment. That way doctors, payers, Otsuka and Proteus can learn from early patient experiences and the companies can update their digital medicine system as needed before a broader rollout.

"We have a limited number of people who have worked with it," Carson said. "People have really liked it, have continued to use it, and have been able to utilize their smartphones and the app. That all contributed to FDA approval."

Payers have been open to the idea that Abilify MyCite could improve medication compliance and potentially reduce overall health care costs for patients with schizophrenia, bipolar disorder and depression related to non-compliance.

"There are interested payers in this environment," Carson said. "They're looking at their population of these patients and see compliance is low. It impacts overall health care and increases the burdens on those systems."

Otsuka has not announced the wholesale acquisition cost of Abilify MyCite, which will compete with generic versions of the oral drug, but Carson said pricing information should be available closer to the product's launch in early 2018.

Suchira Ghosh, counsel at the law firm Axinn, Veltrop & Harkrider LLP, does not expect the Abilify MyCite approval to have much impact on generic distributors of the oral drug, because they are already competing against newer formulations of the drug, including the long-lasting injectable *Abilify Maintena*. She said they are not likely to jump on a generic of the new digital product, because they'd need to have access to relatively inexpensive versions of the sensor, wearable patch and app technologies.

"Generics manufacturers will pursue [digital medicines] if it looks like there's a market for it. If there is no market and insurers aren't going to pay for this type of digital product, they won't," said Ghosh, who has advised generic manufacturers in regulatory and patent litigation matters, including aripiprazole makers. "However, if this is the beginning of a digital pill revolution, which it could be, and generic manufacturers are interested in pursuing that market, there are some unique challenges associated with the sensor component and making sure there are available suppliers. They wouldn't partner with Proteus, since they're working with Otsuka."

But if digital medicines are cost-prohibitive for generics makers, she said Abilify MyCite would be one way for Otsuka to limit competition for its branded medicine.

"I really think it's going to depend on what insurers do and if there's a market for this," Ghosh said. "In the generic space, you have larger and smaller players, so it may just be a couple of manufacturers filing on it, which means they could have a bigger piece of the pie."

The good news, she noted, is that a regulatory pathway is coming into place for generic digital medicines, since the FDA issued draft guidance earlier this year on generic drug-device combinations.

Published online 14 November 2017

CONTINUED FROM COVER

the research community, and the fact that tens of thousands of experts visit the EMA every year, with obvious knock-on benefits for the local economy.

The EMA itself was clearly relieved by the decision, having feared that it might end up in a city where its staff might not want to live. Its executive director, Guido Rasi, said "Amsterdam ticks many of our boxes. It offers excellent connectivity and a building that can be shaped according to our needs. I am very grateful that the Member States took into account our requirements for business continuity and gave priority to the protection of public and animal health."

The relocation will result in some disruption to the EMA's activities. However, staff retention – which had been a key concern at the agency – is expected to be pretty high, at least according to the results of an EMA staff survey earlier this year which put Amsterdam among the employees' preferred host cities, alongside Barcelona, Copenhagen, Milan and Vienna.

"Our internal surveys have shown that a large majority of EMA staff would be willing to move with the Agency to Amsterdam," Rasi declared. "However, even in this case, our activities will be impacted and we need to plan for this now to avoid the creation of gaps in knowledge and expertise."

Ensuring business continuity and medicines supply as far as possible during and after the relocation has been a concern not only for the EMA but for the pharmaceutical industry and the wider life science sector, which also want to see some sort of collaborative arrangements between the UK and the EU regulatory network after Brexit.

"Businesses now need certainty," Bates declared. The best way to provide that certainty, he said, was "by an early agreement to a transition timeframe and continued close regulatory co-operation. We must now ensure Brexit does not disrupt the safe supply of vital medicines to tens of millions of families in the EU 27 and the UK."

Now the decision on the EMA's future location has been taken, the agency, the EU institutions and the member states face a long drawn out process involving readying the new premises for the EMA to occupy before the Brexit date of March 29, 2019, moving the necessary equipment from London to Amsterdam, helping with staff relocation and settling in, and so on.

The EMA said the decision on the new location marked the "official start of a challenging joint relocation project that will have to be delivered within extremely tight timelines whereby the relocation has to be completed by 30 March 2019."

Published online 20 November 2017

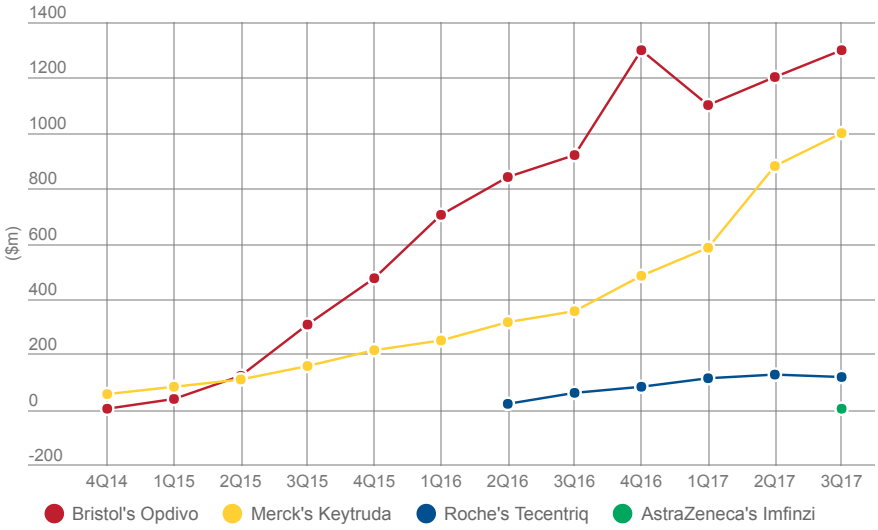
PD-1 Earnings Roundup: Buckle Up For A Bumpy Ride

EMILY HAYES emily.hayes@informa.com

The third quarter marked a turning point for **Merck & Co. Inc.**'s PD-1 inhibitor *Keytruda*, which hit the $1bn sales mark and finally started closing in on **Bristol-Myers Squibb Co.**'s market-leading competitor *Opdivo*, but with many catalysts around the corner for the most valuable indication of lung cancer, investors are bracing for shakeups.

Opdivo's performance in the third quarter was better than expected as nivolumab brought in $1.3bn in sales, up by 38% from the same period in 2016 (*see chart*). That compares to $1.2bn (up by 42% from 2016) in the second quarter. *(Also see "Post-MYSTIC, Bristol Renews CTLA-4 Vows, But Is "Not Wedded" In Lung Cancer" Scrip, 27 Jul, 2017.)* Consensus estimates expect Keytruda to overtake Opdivo in the next few quarters.

Sales Of PD-1/L1 Inhibitors



BRISTOL HOLDS ITS OWN

Chief Commercial Officer Murdo Gordon noted during Bristol's Oct. 26 earnings call that Opdivo's share in the second-line non-small cell lung cancer (NSCLC) in the US market has been stable, in the high 30s – and that there has been good growth in penetration and reimbursement of the same opportunity ex-US. *(Also see "Bristol's Opdivo Delivers, But CheckMate 227 Uncertainties Cloud Quarter" Scrip, 26 Oct, 2017.)*

There had been an expectation that Opdivo could suffer following the US FDA approval of Merck's Keytruda (pembrolizumab) in combination with chemotherapy for first-line NSCLC and **Roche**'s *Tecentriq* (atezolizumab) in second-line NSCLC. Keytruda is also the only PD-1 inhibitor approved as a monotherapy for first-line NSCLC, whereas Opdivo spectacularly failed in this indication in 2016. *(Also see "'Total Disaster' In First-Line Lung Cancer For BMS's Opdivo" Scrip, 10 Oct, 2016.)*

"We were surprised to learn the eligible pool of patients for 2L NSCLC has only shrunk by 5% as a result of 1L treatment with Merck's Keytruda, but we expect that to accelerate over the next couple quarters," Hilliard Lyons analyst Kurt Kemper said in an Oct. 27 note.

Opdivo also held its own in second-line renal cell carcinoma (RCC), with a 50% market share.

Bristol said that the combination of Opdivo with its CTLA-4 inhibitor *Yervoy* (ipilimumab) in first-line RCC will hopefully be reviewed quickly, following the release of positive overall survival results in this indication in the CheckMate 214 study, although the combination did not prove a benefit in progression-free survival (PFS). *(Also see "No Clear Winner in BMS, Exelixis/Ipsen First-line Renal Cancer Race" Scrip, 18 Sep, 2017.)* The company reported additional data from the study on Nov. 7 at the Society for Immunotherapy and Cancer (SITC) meeting, with an exploratory analysis showing the combination provided an overall survival benefit compared to **Pfizer Inc.**'s *Sutent* (sunitinib) across levels of PD-L1 expression in intermediate and poor-risk patients. *(Also see "Bristol's Strong SITC: IDO, 1L Kidney Cancer And New Mechanism Data Bode Well" Scrip, 13 Nov, 2017.)*

Opdivo was approved in September for liver cancer and is being positioned for a range other new indications.

Datamonitor Healthcare analyst Dustin Phan commented that he was impressed with Bristol's figures in the third quarter, specifically with Opdivo. "While some expected the drug to lose significant market share to Keytruda following its failure in 1L NSCLC last year, Bristol claims that it's still the leading brand in the 2L NSCLC setting, and a stream of approvals in new indications appear to have helped it maintain its leading position in the oncology market," Phan told *Scrip*.

While sales for Yervoy were up from the year-ago period in the third quarter to $323m, this was lower than the prior quarter and below analyst expectations. Yervoy had suffered from competition with PD-1 monotherapy, but was expected to still find a role through the approval of the combination with Opdivo in first-line metastatic melanoma. However, in the CheckMate 067 first-line melanoma study, the combination only showed a modest survival benefit over Opdivo monotherapy, with a large increase in toxicity. *(Also see "Bristol's CheckMate 067 Revives Debate On Rationing Yervoy/Opdivo Combo" Scrip, 3 Apr, 2017.)*

"Management noted the Opdivo/Yervoy combo has about 30% share of 1L melanoma while monotherapies (Opdivo or Keytruda) have about 40%, something for investors to consider as the combo looks to penetrate higher-risk 1L RCC down the road," Kemper said.

WIDE RANGE OF SCENARIOS FOR 2018

The biggest focus for the checkpoint inhibitors right now is the results for the pivotal first-line lung cancer studies of various PD-1

combinations; the leading PD-1/L1 sponsors fielded multiple questions during the third-quarter earnings calls on aspects of trial design and timing of readouts.

Following Opdivo's failure as a monotherapy in first-line lung cancer, Bristol's hopes are riding on the Opdivo/Yervoy combination in the CheckMate 227 first-line NSCLC study. Results for patients with high PD-L1 expression are due in the first half of 2018 but there may be an interim analysis by the end of the year, execs confirmed. The company declined to comment on whether its statistical analysis for the study would change to include tumor mutation burden, an emerging biomarker for response, in the primary analysis.

Bristol execs said that they were optimistic about immuno-oncology (IO) growth going forward, but also acknowledged that there are many new datasets coming from itself and competitors, so there are "a wide range of potential scenarios for 2018." These have been made more complicated by developments throughout 2017.

In January, Bristol had disappointed the market with an announcement that it would not be seeking accelerated approval of Yervoy/Opdivo in first-line lung cancer, as it preferred to wait for CheckMate 227 data. In addition to testing Opdivo with Yervoy, the trial evaluates Opdivo with chemotherapy.

Around the same time, **AstraZeneca PLC** announced changes to the Phase III MYSTIC study of its PD-L1 inhibitor *Imfinzi* (durvalumab) as a monotherapy with and without its investigational CTLA-4 inhibitor tremelimumab and chemo in first-line NSCLC. *(Also see "Bristol, AstraZeneca Changes To IO Strategy Could Ultimately Be Regulatory Gain" Pink Sheet, 20 Jan, 2017.)*

In July, AstraZeneca announced that Imfinzi failed to demonstrate a benefit for the PFS primary endpoint in the MYSTIC study, but it could still wind up proving an overall survival benefit. *(Also see "MYSTIC Misses: Devastation For AstraZeneca As Imfinzi Fails PFS Endpoint In NSCLC" Scrip, 27 Jul, 2017.)* The company has long thought that overall survival (OS) was the endpoint that better captured the benefit of IO therapies, Chief Medical Officer Sean Bohen said during the company's Nov. 9 earnings call.

AstraZeneca expects the full MYSTIC results in the first half of 2018, and "it is quite possible that that will be a positive result even though PFS was not a positive result," Bohen tried to reassure analysts.

TOUGH ROAD FOR NEWCOMERS IMFINZI, BAVENCIO

Imfinzi got its first US FDA approval in May for second-line bladder cancer, an indication where Opdivo, Keytruda and Tecentriq were already approved. AstraZeneca reported that the launch was going well and that the drug posted $1m in sales in the third quarter. Execs explained during the earnings call that the bladder cancer launch is mainly aimed at increasing awareness of the product and gaining formulary access ahead of approval in other indications.

"The US approval and launch in this setting has been strategically important for us, allowing us to raise awareness, open accounts, obtain formulary access and set important groundwork for the future potential launches in lung cancer," Bohen said. "Imfinzi was the fourth of now five PD-1/L1s to launch in the second-line bladder space. And in this competitive space, we have seen steady progress month over month with market share now in the mid-single digits in our first full quarter post approval."

> 'The biggest focus for the checkpoint inhibitors right now is the results for the pivotal first-line lung cancer studies of various PD-1 combinations'

The company is also looking forward to launching the drug in Europe in early NSCLC, a filing supported by the PACIFIC study, in the first half of 2018. The PACIFIC data, which support use in unresectable Stage III NSCLC, a setting not targeted by other IO sponsors, are also being used for regulatory filings in the US and Japan. The drug has a user fee date of February 2018 for an early NSCLC filing with the US FDA.

Third-quarter sales for another newcomer to the PD-1/L1 space – **Pfizer Inc./Merck KGAA**'s *Bavencio* (avelumab) were not reported, which is usually a sign of non-material levels. *(Also see "Pfizer Says Big Deals Create Value & 10 Other Notable Q3 Moments" Scrip, 31 Oct, 2017.)* Bavencio was approved in March for Merkel cell carcinoma, a rare kind of skin cancer. *(Also see "Pfizer's Avelumab Makes Its Debut, In Rare Form Of Skin Cancer" Scrip, 23 Mar, 2017.)* The German Merck said it expects €20m in sales for 2017.

MERCK INVESTORS GET THE JITTERS

Although Keytruda sales have trailed Opdivo and it has taken time to catch up, the US-based Merck & Co. has held a leading position in the space due to its success in the valuable NSCLC indication, as the drug snagged the first and only FDA approval for Keytruda as a monotherapy in first-line NSCLC in patients with high level of PD-L1 expression (at least 50%) and won the first combination approval in that setting, for use with chemotherapy. The filing for the combination in first-line NSCLC was supported on the KEYNOTE-021 Cohort G study; the accelerated approval covers use with **Eli Lilly & Co.**'s *Alimta* (pemetrexed) and carboplatin chemotherapy, a niche population but more than enough to give an important time advantage in a highly competitive race.

Keytruda's sales of $1bn in the third quarter represented an increase of almost 200% compared to the same period in 2016.

"Nearly one in three new lung cancer patients in the US are being started on Keytruda, making it the most prescribed treatment for new metastatic lung cancer patients," Adam Schechter, executive vice president and president of global human health, said during Merck's Oct. 27 earnings call.

However, Merck made two discomfiting announcements on the day of its earnings call. First, the company said it was amending the design of the KEYNOTE-189 study to include a co-primary endpoint of overall survival in addition to PFS. That decision pushes the trial's end date to February 2019.

The company also announced at the close of the business day that it was withdrawing a filing for approval in Europe based on the KEYNOTE-021G study. Datamonitor's Phan

CONTINUED ON PAGE 10

CONTINUED FROM PAGE 9

commented to *Scrip* that "while Merck's decision to promote OS to co-primary endpoint in KEYNOTE-189 does indeed delay the readout timeline to 2019, this may be necessary for Keytruda's regulatory and commercial success in 1L NSCLC."

The analyst added, "Ultimately, I don't think there's necessarily anything wrong with the study. Rather, I think they may simply be responding to the clinical and commercial environment."

If Bristol's CheckMate-227 does highlight a significant survival advantage over standard chemotherapies in the 1L NSCLC treatment setting, Opdivo should be able to gain the favor of physicians and payers alike over Keytruda as CheckMate 227 is a proper Phase III trial, Phan said.

"However, the Phase I/II KEYNOTE-021G does have an active comparator arm, so I imagine Keytruda + chemotherapy would still experience some uptake due to its first-to-market advantage," he said.

Bernstein Research analyst Tim Anderson saw the inclusion of overall survival as a co-primary endpoint as a good move in the context of the market – competitors have PFS and OS as co-primary endpoints – and commented in an Oct. 27 note that the withdrawal of the European filing is not surprising as it would have been unlikely for such an application to be approved.

Still, the move spurred concerns with investors about prospects for the KEYNOTE-189 study, based on KEYNOTE-021G.

Anderson said in an Oct. 30 note these two items tied together present a reminder that "in the topsy-turvy world of IO, things can change suddenly and unexpectedly." Merck was the top pick in 2016 but starting in early 2017, we started to "temper our enthusiasm for the name," Anderson said.

"While Q3 performance was decent overall and despite 2017 guidance being raised, quarterly results lend support to the argument that MRK's longer-term growth struggles. The company has done very well in IO, but investors have wanted to see other drivers beyond IO, and those are not yet shining through," Anderson said. Anderson put out another research note Nov. 15, flagging the potential for Merck's KEYNOTE-042 to further "cement Keytruda's 1L monotherapy leadership position" in lung cancer. The trial is due to report Q1 2018, and Anderson said the primary efficacy analysis may have been amended to look at patients with any level of PD-L1 expression (>1%) – an expansion Merck did post-market in the 2L setting. "In a best-case scenario, positive results could triple the size of the population eligible for Keytruda monotherapy," the analyst pointed out. Currently the 50% threshold covers about 20% of the 1L market, but the KN-042 results could expand that reach to around 70%, according to Anderson.

TECENTRIQ SALES DOWN

The coming months will also be important for **Roche**'s PD-L1 inhibitor Tecentriq (atezolizumab), which yielded sales of CHF118m ($118m) for the quarter, down from the second quarter ($124m). Roche incurred a setback for the drug in May, when it reported that the Phase III IMVigor failed to confirm efficacy in second-line bladder cancer. About 60% of sales were for the second-line bladder cancer indication and 40% for NSCLC. With four competitors in bladder cancer, which has a relatively limited patient population, that split will change over time and the company expects a higher degree of sales from lung cancer compared to bladder cancer on a percentage basis, Pharmaceuticals CEO Daniel O'Day said during the Swiss pharma's Oct. 19 earnings call.

The company emphasized that it is looking forward to a number of releases, including data from the Phase III IMpower50 study in NSCLC, which is due to report PFS results by the end of the year. That study will provide the first look at the combination of Tecentriq with and without chemotherapy and with or without the company's VEGF inhibitor *Avastin* (bevacizumab). O'Day said that the full data from IMpower 150 study will read out three to six months after the release of PFS data. Roche will also be reporting out additional Phase III studies combining Tecentriq with chemotherapy in lung cancer – IMpower 110, IMpower 130, IMpower 131 and IMpower 132 – in the first half of 2018 with potential to further shake up the landscape.

O'Day said during the call that the company can't be more specific about the release dates but that it is committed to providing the outcomes as soon as it knows them.

Roche is also set to release Phase III studies of Tecentriq in triple-negative breast cancer, first-line renal cancer and second-line/third-line colorectal cancer during the second half of 2018. O'Day noted that the company has extended its Tecentriq program in hematology. The drug is now being tested in four indications: acute myeloid leukemia, non-Hodgkin lymphoma, multiple myeloma and myelodysplastic syndromes.

Bernstein's Anderson commented that there is a "still-uncertain pecking order" of competitors in the IO lung cancer market, contingent on other Phase III trial readouts.

"Because the IO lung cancer market is a zero-sum game, a setback with one competitor would seem to automatically benefit the others, but it is not as simple as this. This is because it remains unclear how competing IO combination trials will turn out," Anderson said.

Investors fear that the IMpower study may miss the mark because of signaling from the company in recent weeks, but it is also not clear whether the CTLA-4 combination arms of Bristol's CheckMate-227 and AstraZeneca's MYSTIC studies will succeed, Anderson noted.

Additionally, while all of the major IO companies are now running 'chemo combo' trials of their own, the timeframe of seeing 'final' results from these trials is uncertain. The companies may need to wait for mature overall survival results and this could impact the timing of their EU regulatory applications, the analyst advised.

Published online 15 November 2017

$1M For Luxturna? ICER Says Big Discount Needed

JESSICA MERRILL jessica.merrill@informa.com

The Institute for Clinical and Economic Review has weighed in on what is expected to be the most expensive drug yet to reach the US market – **Spark Therapeutics Inc.**'s gene therapy *Luxturna* (vortigene neparvovic, VN), a one-time treatment for an inherited form of blindness that could set the price bar for future gene therapies. ICER's draft conclusions could give payers leverage as they negotiate reimbursement for what is expected to be an ultra-pricey therapy for an ultra-orphan indication.

In a draft evidence report released Nov. 14 on Luxturna for biallelic RPE65-mediated retinal disease, ICER concluded that a $1m price for Luxturna would not likely be cost-effective based on traditional thresholds. ICER reports generally look at price in the context of $50,000, $100,000 and $150,000 cost per quality-adjusted life year (QALY) ratios, which attempt to quantify what society will pay for a treatment in a standardized way. ICER is accepting public comments on the draft through Dec. 13.

Spark has not yet established a price for Luxturna, as the drug has not yet been approved by FDA. But CEO Jeffrey Marrazzo has said the economics support valuing Luxturna in excess of $1m, given the therapy's life-altering benefit for patients, including direct medical expenses, indirect costs and employment.

The FDA is expected to clear Luxturna shortly, as FDA's Cellular, Tissue and Gene Therapies Advisory Committee unanimously recommended approval in October. The patient stories during the panel review about the life-changing benefit of the treatment for a debilitating condition for which there are no other options, drove home just how challenging it may be for payers to negotiate with Spark. Nevertheless, ICER's assessment could give payers some leverage.

Part of the challenge for payers is fronting the full cost of a treatment that works over a lifetime in a system that is not designed for it. Insurers are also scanning the horizon, thinking about how to handle the costs if and when more gene therapies reach the market, as is anticipated.

STEEP DISCOUNTS NEEDED, ICER SAYS

ICER used a placeholder price tag of $1m to complete its draft assessment and concluded that while Luxturna improves patient health outcomes compared to standard of care, the high cost would not make it cost effective, based on its thresholds. Nonetheless, ICER acknowledged the therapy's position as a drug for an ultra-rare disease could provide more flexibility when it comes to reimbursement.

"For ultra-rare diseases, decision makers in the US and in international settings often give special weighting to other benefits and to contextual considerations that lead to coverage and funding decisions at higher prices, and thus cost-effectiveness ratios, than applied to decisions about other treatments," the draft report says.

Spark estimates that REPE65-mutation-associated blindness affects only 1,000 to 2,000 patients in the US, and the company expects Luxturna will only be administered at three or four sites that specialize in eye diseases.

The case for cost-effectiveness is stronger when Luxturna is given to young patients, according to ICER. "We found that [vortigene neparvovic] provided more health benefits when given to a younger population, and was therefore more likely to be cost-effective for younger patient," the report says.

The report also took into account indirect and non-medical costs, which ICER said slightly decreased the total incremental costs for VN and slightly increased cost-effectiveness ratios.

"However, in all base case scenarios, VN would require large discounts to reach commonly used thresholds of cost-effectiveness," the report says. At a wholesale acquisition cost of $1m, a discount of at least 43% and up to 77% would be necessary to reach a cost-effectiveness threshold of $150,000 per quality-adjusted life year (QALY). Smaller discounts would be acceptable to achieve thresholds of $250,000 and $500,000 per QALY, ICER concluded.

WITHIN THE BUDGET

On the positive side for Spark, even with an assumed price of $1m, Luxturna wouldn't break the bank of US healthcare spending because of the small number of patients that would be treated a year and the relatively low healthcare costs incurred by patients following treatment, ICER says. The group uses a threshold of $915m annually to determine the potential impact of a drug on US healthcare spending. ICER considers the cost of treatment weighed against any medical cost savings; crossing the $915m threshold would be a warning that lower prices or access restrictions should be put in place.

Under ICER's analysis, the annual cost of Luxturna would be 38% of the $915m threshold, assuming 350 people are treated per year.

ICER highlighted several controversies or uncertainties surrounding its review, which incorporated data from four key studies, including Spark's pivotal Phase III trial, and patient interviews. Spark's Phase III trial involved a novel endpoint, change in score on the multi-luminance mobility test (MLMT), which the FDA advisory committee deemed clinically meaningful.

Uncertainties raised by ICER were the variability in treatment benefits seen in studies among patients and the durability of effect, which remains unknown, as the clinical trial data only extends to five years. Nonetheless, ICER concluded that Luxturna provided a small to substantial improvement for patients and ranked the evidence on the therapy a B+ (incremental or better).

The economic modeling used by ICER assumed a 10-year effect followed by a waning period in which the rate of change is slower than standard of care. ICER separately modeled a lifetime treatment effect duration as a scenario analysis. In that scenario, ICER found higher health gains and lower costs for Luxturna relative to the base case.

The base model assumed direct medical costs, including two vision-related doctor visits a year ($80) and costs like transportation, Braille equipment and supplies ($3,637). ICER also created a societal perspective analysis that included indirect costs for education, productivity losses, informal care and nursing home care.

Luxturna is one of several high-profile drugs ICER is reviewing in the next year. The group set an ambitious agenda for 2018, including the new CAR-T therapies from **Novartis AG** and **Gilead Sciences Inc.** (previously **Kite Pharma Inc.**) and the new class of CGRP inhibitors for migraine.

Published online 15 November 2017

What's Behind The Success Of Korean Biosimilars?

JUNG WON SHIN jungwon.shin@informa.com

Shutterstock: CJ Nattanai

South Korean biosimilar companies are entering their prime. One after another, **Celltrion Inc.** and **Samsung Bioepis Co. Ltd.** are making headlines and receiving approvals for their biosimilar products in major markets; the products they have launched are leading their markets, or have potential to do so.

This scenario was not expected by many industry players several years ago because, at that time, South Korea had a limited focus on innovation and R&D investment, and the country's pharma and biotech companies had not yielded notable outcomes in global markets.

"Celltrion focused on the high growth potential of the antibody biosimilars market, sought development of biosimilars earlier than others, and is now leading the market," said Dong Won Sung, senior analyst at the Export-Import Bank of Korea. "Samsung has entered the market late but it is quickly catching up with Celltrion based on the ample capital and strong drive frequently seen in large conglomerates."

Various factors, including savvy clinical trial and collaboration strategies, have played a part in the recent stellar performance of the two South Korean firms.

"One of the key factors contributing to the success of Samsung Bioepis and Celltrion in the MAb biosimilar space is the fact that they are conducting global clinical trials in key regions of interest such as the US and Europe, and the firms are tailoring their clinical development to the expectations of the regulatory authorities in those respective regions," Datamonitor Healthcare's analyst Hristina Ivanova told *Scrip*.

CELLTRION'S EARLY DAYS

Celltrion started out as a contract manufacturing organization (CMO) in South Korea, but it is now a pioneer in antibody biosimilars. When multinational pharma firms monopolized global markets with antibody drugs, many of them believed development of biosimilars would be difficult. But Celltrion had different thoughts and became the first mover in this field. Celltrion focused on the potential of the biotech industry and the value of biosimilar business, as patents of several blockbuster biologics were set to expire soon.

When Celltrion began global clinical trials of its first biosimilar product *Remsima/Inflectra*, a version of **Janssen Biotech Inc.**'s *Remicade* (infliximab), the concept of biosimilars was still unfamiliar and South Korea was little known in the global biotech industry. The company had to pioneer the process and pave the way for regulatory approval in Europe. "At that time, there were no global guidelines on biosimilars. We had to pioneer the process by persuading the EMA [European Medicines Agency], but our folks continuously challenged and succeeded. This has become the driving force of our first mover and first launch status," said Celltrion CEO Woo Sung Kee in an interview with *Scrip*.

Celltrion's Remsima now controls more than 40% of the European market. The biosimilar product launched in the US late last year and the company expects to repeat its success in the world's biggest market as it has accumulated prescription data and various clinical data needed to earn doctors' trust and boost recognition of its brand name.

Celltrion's biosimilar rituximab, known as *Truxima*, has also launched in various European countries. Truxima and *Herzuma*, its biosimilar version of *Herceptin* (trastuzumab), are undergoing regulatory approval review in the US.

Meanwhile, Celltrion received a US FDA Form 483 in early 2017 after the FDA's regular GMP inspection of the company's biomanufacturing site in South Korea. But by September the company had already completed improvements for the list of demands the US regulator made. It added that none of the issues directly impacted the company's drug quality; as a result, there were no disruptions in its drug production or global supply and there will be no changes in its products' approval schedules.

SAMSUNG CATCHES UP

Samsung Bioepis entered the biosimilar business several years later than Celltrion but it is quickly catching up. Backed by Samsung Group's ample capital and strong drive for the biotech business, Samsung Bioepis is swiftly progressing global clinical trials of its broad biosimilar candidates.

"When we started out five years ago, biosimilars were still new to many in the industry. We had the confidence that our development platform and scientists could capitalize on the level playing field, thereby allowing us to compete from the start and positively impact patients' lives sooner rather than later," Samsung Bioepis told *Scrip*. "Since then, we have relied on our agile biologics development platform to transform and enhance the way therapies are brought to patients from conception and development through regulatory approval by replacing legacy processes with new and innovative ones. In so doing, we have been able to develop arguably the industry's most expansive and rapidly advancing biosimilar pipeline."

Samsung has launched its infliximab biosimilar *Renflexis* in the US, only a few months after Celltrion's Inflectra. With the latest EU approval for its adalimumab biosimilar *Imraldi*, Samsung has become the first company to receive EU approvals of three biosimilar anti-tumor necrosis factor products. Samsung is selling *Benepali*, its bio-

similar version of *Enbrel* (etanercept), and *Flixabi*, its biosimilar version of Remicade, in Europe, through its partner **Biogen Inc.** Samsung's biosimilar to Herceptin, *Ontruzant*, is also under regulatory review by the EMA. Ontruzant (formerly known as SB3) received a positive recommendation for approval in Europe from the EMA's scientific committee the CHMP in October 2017.

As a late comer, Samsung Bioepis, which is a joint venture between Samsung BioLogics and Biogen Inc., has largely benefited from the pioneering work of Celltrion. While Celltrion had to spend much time in the beginning creating approval guidelines in global markets, Samsung could receive approval in a shorter period. Renflexis could get FDA approval without review by an FDA advisory committee thanks to Inflectra, which had to earn the green light of the advisory committee as the first mover, NH Investment & Securities said.

As a late comer, Samsung Bioepis has largely benefited from the pioneering work of Celltrion

Unlike the EU market where Remsima had a significant head start and dominated the biosimilar infliximab market, some South Korean analysts predict it could be a closer match between Inflectra and Renflexis in the US where the launch time gap between the two is only several months. In addition, Renflexis's list price was 35% below its reference drug price, while Inflectra's list price was at a 15% discount to the innovator.

BUILDING ON PARTNERSHIPS

Another factor that contributed to the South Korean companies' success is their robust collaborations with global companies. Celltrion and Samsung Bioepis both have created a network of collaborations with a wide range of companies for the development and marketing of their biosimilar MAbs, said Datamonitor's Ivanova.

For example, Celltrion has a partnership with **Hospira Inc.**, now a subsidiary of **Pfizer Inc.**, for the marketing of Inflectra in the US, and has partnered with **Mundipharma International Corp. Ltd.** for the commercialization of Remsima and Truxima in Europe, benefitting from the local presence their partners have in US and Europe, Ivanova noted.

In addition, South Korean companies' ability to construct high quality manufacturing facilities required for manufacturing biosimilars and governmental policy support are likely to have made it easier for them to get a head start in the biosimilar business.

Helped by the South Korean government's policy support, Celltrion and Samsung Group were able to successfully build large-scale bioreactors in the beginning. From the early 2000s, the government has viewed the biotech industry, including biosimilars, as the country's next generation growth engine, while other countries had slightly different visions. For example, Japan focused much more on novel drug development, overlooking the biosimilars sector, while Singapore opted to attract the production facilities of multinational pharmas such as **Roche** and **Lonza Group Ltd.**, according to NH Investment & Securities.

INCREASING GLOBAL COMPETITION

As South Korea aims to develop global blockbuster drugs in the coming years, its success in biosimilars could serve as a basis for accumulating and building technology and knowhow to reach its goal.

Although the global biosimilars market is poised to grow sharply for now, EXIM Bank of Korea's Sung stressed the importance of novel drug development amid the toughening of competition in the biosimilar space.

Competition in the global biosimilar market is set to become fiercer as multinational pharmas such as **Pfizer Inc.** and **Merck & Co. Inc.** as well as leading generic companies **Teva Pharmaceutical Industries Ltd.** and **Sandoz Inc.** are actively pursuing the development of biosimilar businesses including through M&A. As a result, the global biosimilar market could turn into a "red ocean" with limitations in growth, Sung said.

According to the Informa Pharma's Trialtrove database, in 2017 there were more than 1,060 clinical trials of biosimilars ongoing worldwide and 158 trials in the US alone. By therapeutic area, there were 299 clinical trials of biosimilars in oncology and 291 trials of biosimilars in autoimmune and inflammation.

As part of its overall plans, Celltrion is already progressing a novel antibody drug pipeline including a new antibody influenza drug. It is targeting becoming a global top 10 biopharma after 2020 once it launches three biosimilar products in global markets, and after that plans to aggressively invest in the development of novel drugs.

Samsung is also stepping up efforts to diversify into new drug development. In August, Samsung Bioepis joined with **Takeda Pharmaceutical Co. Ltd.** to develop novel biologics, moving beyond its core focus on biosimilars. The partners will initially focus on acute pancreatitis and jointly develop Takeda's preclinical candidate in the segment.

Published online 15 November 2017

While The Money Flows, So Will Biopharma IPOs

MANDY JACKSON mandy.jackson@informausa.com

Public biopharmaceutical company valuations improved in 2017, prompting more initial public offerings in the US this year than last year. And with better stock performance for this industry than in other sectors of the economy, the market for drug developer IPOs may continue to strengthen in 2018.

The Nasdaq Biotechnology Index (NBI) was up 26% at the end of the third quarter versus the end of 2016 while the broader Nasdaq index increased only 20.7% and the Dow Jones Industrial Average was ahead by just 13.4%. With biopharma companies providing better returns than high-tech firms and industrial heavyweights, it's not surprising that 29 drug developers were able to go public in the US during the first three quarters of 2017 versus 30 for all of 2016.

"Companies that have strong development plans, that will have news flow, that have strong science, and where there's not competition that will not allow them to differentiate no matter how good their data is – and that have a supportive regulatory environment – will always be able to do an IPO," Back Bay Life Science Advisors Co-Founder, Managing Partner and CEO Jonathan Gertler told *Scrip*.

However, biopharma IPOs were expected to slow in 2017 after falling from 62 offerings in 2015 to just 30 in 2016, as valuations declined due in part to concerns about a crackdown on prescription drug pricing in the US.

While the NBI slumped 29.6% between its all-time high on July 12, 2015 and the start of 2017, valuations generally have increased this year despite President Donald Trump's promise to cut drug prices. Trump's comments in January that the pharmaceutical industry was "getting away with murder" rang hollow as his administration did not take immediate action on the issue. As a result, the average return for the 29 biopharma IPOs through the third quarter of this year was 35.2% versus 11.2% for last year's new offerings at the end of 2016.

"The hot IPO market cooled off and it's heating back up," Gertler said. "The general trend always is that when knowledgeable biotech investors feel the fundamentals are there to get good returns on their investments, then the generalists come in behind them. You can't have a good biotech financing environment without some general investors, but the decisions are driven by the biotech investors. Even the size of the deals is driven by the biotech investors."

The IPO-tracking firm Renaissance Capital has noted for the past few years that new biopharma offerings tend to have a high level of insider participation, meaning prior venture capital and crossover investors tend to buy a significant share of the stock offered in drug developer IPOs. Those investments help convince outsiders that a company is worthy of investment.

FINANCING FOR COMPANIES, NOT LIQUIDITY FOR INVESTORS

"I think that people still misinterpret what IPOs are about. They're still financing vehicles, not liquidity vehicles," Gertler said.

Pre-IPO investors typically hold on to their shares of newly public biopharma companies for a while, so the offering isn't necessarily an exit for venture capital firms. It just provides a means for therapeutics firms to occasionally tap the public market to fund drug development.

"You need to know there will be demand for your programs and for your future stock, whether your use of proceeds will be enough to carry you forward, and whether going public is going to be the right decision for you," Gertler said. He noted that those things should drive the decision to pursue an IPO rather than going public simply because the market will support the offering.

The 2017 biopharma IPO market is remarkable not only because it exceeded expectations based on the 2016 market's performance, but also because this year got off to a slow start. The first quarter total of just four IPOs represented a four-year low for therapeutics firms, Renaissance Capital noted in its review of the third quarter.

"After hitting a four-year low in the [first quarter], biotechs rebounded in the second quarter and remained active in the third," Renaissance reported. "In addition to promising clinical [trial] results and M&A interest, an important regulatory milestone was reached in August when the FDA approved a gene therapy for the first time."

GOOD NEWS DRIVES INVESTMENT

Advances in the field of chimeric antigen receptor T cell (CAR-T) therapies – both the FDA approval of **Novartis AG**'s *Kymriah* (tisagenlecleucel) and **Gilead Sciences Inc.**'s $11.9bn acquisition of **Kite Pharma Inc.** – contributed to rising cell and gene therapy company values and boosted the biopharma sector during the summer.

"As long as the market is going to be out there and warm for IPOs, [life science companies] are going to try it, because they're always going to explore IPOs for financing," Halloran Consulting Group President and CEO Laurie Halloran said in an interview with *Scrip*. "Acquisitions of companies make biotech seem like a bullish industry as compared to others."

Every company is different in terms of the type of funding they need and when they need to raise it, but Halloran said she tends to point biopharma firms in directions other than the stock market, because of the cost of being a public company and the pressure that trading publicly puts on drug developers – especially those that don't have any approved products to generate revenue.

"For a savvy executive in a company and their investment team, if they think an acquisition is going to move them forward without going public, I would go with that option," she said. "[Launching an IPO] is expensive and it also forces the company to be public with any news of an event that really is going to put them under financial pressure [and] events that don't look that bad are magnified in the public market."

However, rising biopharma company valuations, increased IPO activity and greater investor interest in the sector helps the industry overall.

"It makes for a whole lot of optimism within the industry as whole. People are willing to take a risk and start companies and continue to progress their development programs, because they don't feel constrained," Halloran said. "Being able to generate data and create even more value makes for a more optimistic industry."

Published online 17 November 2017

Scrip Awards Finalists 2017

www.scripawards.com

Scrip Awards
Pharma intelligence | informa

Licensing Deal of the Year
(Sponsored by Worldwide Clinical Trials)

Licensing is vital both in helping to keep pharma's pipelines replenished and for generating income for smaller firms.

AstraZeneca and Aspen for ex-US rights to AZ's global anesthetics portfolio

Aspen acquired the ex-US commercialization rights to AstraZeneca's global anesthetics portfolio for $520m upfront and will pay AZ up to $250m dependent on product sales, plus double-digit percentage trademark royalties, allowing AZ to retain a significant ongoing interest in the portfolio. The agreement aims to extend the reach of the mature portfolio.

AstraZeneca and Circassia for US rights to the aclidinium franchise

This novel deal has strategic importance to AstraZeneca, and a transformative impact for Circassia. It covered two of AZ's inhaled respiratory products, Tudorza and Duaklir, establishing terms for the promotion of Tudorza in the US, an option to gain the full US commercial rights to Tudorza in future and a license to Duaklir in the US.

Crescendo Biologics and Takeda Pharmaceuticals for Humabody-based therapeutics

In October 2016, Takeda Pharmaceuticals validated Crescendo Biologics' innovative approach when the two companies entered into a global, strategic, multi-target collaboration and license agreement for the discovery, development and commercialization of Humabody-based therapeutics for cancer indications with a high unmet medical need. The agreement is Crescendo's first major commercial deal.

EUSA Pharma and Apeiron Biologics for dinutuximab beta

This deal is a transformative one for EUSA, a young company founded in March 2015. Licensing the orphan-designated monoclonal antibody for the treatment of high-risk pediatric neuroblastoma from Apeiron Biologics has allowed EUSA to enter new European markets with an expanded direct infrastructure, and provides a route to expand their direct US operations and enter Asian markets.

MedImmune and Allergan for MEDI2070

For an upfront payment of $250m Allergan gains an exclusive, worldwide license to develop and commercialize the IL-23 monoclonal antibody MEDI2070 for inflammatory bowel diseases. The deal allowed MedImmune to sharpen its focus on its three main therapy areas while having the assurance of the continued advancement of MEDI2070 with Allergan's significant expertise in gastrointestinal and inflammatory disease.

Vertex Pharmaceuticals and Merck KGaA for Vertex's DNA damage response inhibitor portfolio

With this strategic transaction, Merck significantly strengthened its oncology pipeline in two attractive areas: DNA damage repair inhibition and immuno-oncology. Vertex found a strategic partner that will help fully realize the portfolio's value. Merck assumes full responsibility for the development and commercialization of all licensed programs and Vertex received an upfront payment of $230m.

PPD's Pharma Company of the Year Award

Scrip's Pharma Company of the Year Award honors outstanding achievement by pharmaceutical companies over the qualifying 12 months, June 1, 2016 to May 31, 2017.

This special award is chosen by Scrip's senior editorial team, based on a variety of key metrics:

- Financial performance in 2016 compared with the previous year.
- Strategic advances, looking at its most significant achievements over the year.
- Progress in emerging markets.
- New product launches including line-extensions and formulations.
- Advances in the drug pipeline, including major clinical trials.

Lifetime Achievement Award
(Sponsored by Aptuit)

The winner of this Award will be an exceptional individual with a consistent history of service, above and beyond the call of duty, throughout their career.

This prestigious international Award will go to someone who has had a distinguished career in the biotech or pharmaceutical arena, primarily within industry. Nominees may be retired or semi-retired but will still be active in the industry in some capacity.

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

Wider Than AZ's PACIFIC – Novartis Has Broad NSCLC Plans For Canakinumab

ALEX SHIMMINGS alex.shimmings@informa.com

Following its surprise effect on cancer in the CANTOS study, **Novartis AG** is set to take its anti-IL1β monoclonal canakinumab (ACZ885) on a path recently travelled so successfully by **AstraZeneca PLC**'s *Imfinzi* with a Phase III study planned in the earlier stage lung cancer.

It gave an outline of its confirmatory Phase III study plans during its recent third quarter financial results presentation and expanded on them during its R&D presentation on Nov. 13. The plans come on the back of analyses of the CANTOS data – which for its primary endpoint tested the drug's effect on major adverse cardiac events in 10,000 patients with previous myocardial infarction and a high-sensitivity C-reactive protein (hsCRP) level of ≥2 mg/L – that showed a 77% reduction in lung cancer mortality and 67% reduction in lung cancer cases in patients receiving the highest dose tested (300 mg).

While the Swiss company has been in discussions with regulators on how best to take canakinumab forward in the secondary prevention CV indication, it has, in parallel, been talking about what to do with the unexpected lung cancer benefit.

Its benefit in both indications lies in its anti-inflammatory effects. New analyses just reported at the American Heart Association meeting in Anaheim, California, on the MACE endpoint show that those patients whose CRP levels dropped to below 2 mg/dL at the three-month point had the best outcomes, and this seems to hold true for the cancer data too. "This responder group has a more profound effect for lung cancer than the non-responder group. So the overall analysis is consistent as well for the lung cancer finding," said Vas Narasimhan during the R&D update.

THREE STUDIES

Novartis has been working closely with FDA and EMA on getting agreement on the final Phase III designs of its three planned studies. It is on track to begin an adjuvant non-small cell lung cancer study (as a monotherapy) in the first quarter of 2018 as well as its first-line (in combination with a PD-1) and second-line (in patients who have relapsed after PD-1 therapy) NSCLC programs in the second quarter of 2018.

This would take canakinumab into the earlier stage NSCLC setting currently occupied by AstraZeneca's Imfinzi (durvalumab) after its successful PACIFIC study in Stage III NSCLC, which was reported at ESMO in September.

But Narasimhan said Novartis wanted to take canakinumab further, believing that getting it into patients who are Stage Ib or Stage II "would be attractive as well given the profile of the medicine".

In the adjuvant setting, the approach is to go purely with canakinumab versus current standard of care. "We believe that in an adjuvant setting, the efficacy that we've shown in *The Lancet* paper in August was quite substantial to the tolerability profile. Canakinumab was outstanding for this kind of therapy. It's a very well-tolerated drug. And so we think there'll be no reason to do a combination in the adjuvant setting."

In the metastatic first-line setting, the likely design to take is patients who had pembrolizumab for a period of one month, and then to add canakinumab on top of pembrolizumab versus pembrolizumab alone, Narasimhan said. "So we won't be supplanting PD-1 therapy, but actually supplementing PD-1 therapy in that setting."

In the second-line setting, it will look at PD-1 failures where the study will compare canakinumab versus placebo to see if canakinumab can provide salvage therapy for those patients. "With respect to additional details on biomarkers, patient segmentation, I'd prefer to wait until we have final feedback from the FDA signing off on our protocols before disclosing anything further," he said.

BACK UP

Novartis is also exploring canakinumab's use in other inflammatory cancers, Narasimhan said. Moreover, it has a back-up plan, in the form of an in-licensed anti-IL1β monoclonal antibody from **Xoma Corp.** (gevokizumab), which could be particularly valuable considering the fact that canakinumab's patent life is relatively limited (until 2024). It picked up the product in a deal announced in August just days before the CANTOS presentation at the ESC.

Narasimhan said Novartis was evaluating gevokizumab for use in oncology and autoimmune indications "so that we would have multiple shots on goal, particularly given that we might want to use the Xoma molecule in certain longer-lead-time indications given the expected LOE of canakinumab given that we believe we'll have additional extensions. Nonetheless, we'd prefer to have an additional molecule in hand."

While Novartis's NSCLC plans are ambitious, analysts point out that the CANTOS data in this respect are still exploratory as they were from a safety analysis. Analysts at Bernstein said the problem is how would an injectable monoclonal drug be best used in a healthy population. "The development challenge with this finding is that it showed a benefit in patients who did not have cancer at baseline, so how do you study a drug in healthy patients without disease?"

COST ISSUES

Another question, which has also been to the fore with the CV indication, is pricing. Canakinumab is marketed as *Ilaris* for rare diseases but Novartis has already conceded that its price would have to come down in heart attack patients dosed every three months.

The cost analysis in cancer is different once again. "I think in the oncology setting, it's important to note we will likely be dosing this medication on a monthly [basis] or perhaps every three weeks given that PD-1s are typically given every three weeks. So in combination, we're going to want to give it every three weeks as well. So there'll be a different total amount of doses given to those patients in a given year when you think about pricing."

Published online 15 November 2017

Novartis Has Blockbuster Targets For Cosentyx In New Autoimmune Indications: **http://bit.ly/2AZ5a6f**

Roche Causes Stir With Tecentriq/Avastin/Chemo Win

KEVIN GROGAN kevin.grogan@informa.com

Roche has received a major boost from a closely watched trial looking at a combination of its PD-L1 inhibitor *Tecentriq* (atezolizumab), the blockbuster *Avastin* (bevacizumab) and chemotherapy (paclitaxel and carboplatin) which shows that the cocktail shows promise as initial treatment for people with advanced non-squamous non-small cell lung cancer.

The Swiss major has revealed no actual data from the IMpower150 trial but noted that the combo provided a statistically significant and clinically meaningful reduction in the risk of disease worsening or death (progression-free survival) compared with Avastin plus chemotherapy in the first-line treatment of advanced non-squamous NSCLC. The company also said that "initial observations for the co-primary endpoint of overall survival (OS) are encouraging."

The OS data are not fully mature and the next analysis is expected in the first half of 2018, Roche said, adding that safety for the Tecentriq/Avastin/chemo combo "appeared consistent with the known safety profile of the individual medicines, and no new safety signals were identified." The data will be presented at the European Society for Medical Oncology Immuno-Oncology (IO) Congress in Geneva in December.

Sandra Horning, Roche's chief medical officer, said "We are extremely encouraged by these results and will submit these data to health authorities globally with the goal of bringing a potential new standard of care for the initial treatment of lung cancer."

Despite the absence of data, analysts have been weighing up the implications of IMpower150 for Roche, for first-line NSCLC treatment and the IO/chemo approach. Tim Anderson at Bernstein issued a Nov. 20 note saying that "this will come as a big relief for Roche investors, who had grown nervous about the outcome of IMpower150."

He states that "Roche was the first company to embrace chemo-combo, launching multiple trials filled with ambition if light on motivation, and IMpower was the least supported. This was a gamble and it paid off." Until the full results are disclosed, a number of questions remain, not least over the types of chemo used and the specific benefits of including Avastin. Also IMpower150 is a complicated trial and the initial analysis makes no reference to the Tecentriq/chemo versus Tecentriq/Avastin/chemo comparison in the study.

Evercore ISI analyst Umer Raffat said in a note to investors that despite the unknowns, the analysis showed that "Roche is now a real competitor in first-line lung." However, he added that "it's not clear if Avastin truly adds beyond just IO+chemo but even if it does, I don't think it's a competitive advantage for Roche, mostly because Avastin biosimilars are not far away."

The IMpower150 announcement indeed leaves several questions unanswered, according to Datamonitor Healthcare analyst Dustin Phan. He told *Scrip*: "I think it's hard to say whether IO/Avastin/chemo could really be a standard of care for first-line NSCLC right now since we don't have much data on what kind of changes in safety and efficacy additional Avastin provide over IO+chemo.

That being said, he concluded that "this data positions Roche as a real contender amongst the bigger PD-1s in first-line NSCLC."

So what does the IMpower150 news mean for the other players in the IO space? The competitor most affected would appear to be **Merck & Co. Inc.** which already has accelerated approval in the US for its PD-1 inhibitor *Keytruda* (pembrolizumab) in first-line NSCLC in combination with **Eli Lilly & Co.**'s *Alimta* (pemetrexed) and carboplatin chemo, based on the Phase II KEYNOTE-021G trial.

Bernstein's Anderson correctly predicted that "as the other manufacturer most immediately leveraged to chemo-combo, Merck shares may decline to some degree" as it will probably have to "face another entrant with a differentiated offering". Moreover the recent design change to Merck's Phase III KEYNOTE-189 trial to include a co-primary endpoint of OS in addition to PFS, pushing the study's end back to February 2019 "is likely to put Merck in the second position in ex-US markets, with IMpower150 now beating KEYNOTE-189 in timing," he added. The latter study will not complete before 2019 either and the company withdrew a European application for first-line lung cancer approval in October.

As for the two other licensed checkpoint inhibitors - **Bristol-Myers Squibb Co.**'s *Opdivo* (nivolumab) and **AstraZeneca PLC**'s *Imfinzi* (durvalumab), Anderson says "their fortunes are more proximately tied to CTLA4+PDx combinations," ie with *Yervoy* (ipilimumab) and tremelimumab respectively, but both are now pursuing Phase III chemo/combo studies of their own, "a testament to the uncertain risk/benefit profile with CTLA4," he says.

Anderson argues that the news further validates the chemo/combo approach, "which once garnered jeers from their 'CTLA4 combo' challengers. He believes that while a positive development has swung Roche's way, "high uncertainty remains around the future of the first-line lung cancer treatment landscape. Most proximately, the question is how will chemo/combo stack up against CTLA4 combo [and] another question that will arise is how will different chemo/combo regimens stack up against each other?"

The Bernstein analyst says that greater clarity will be gained as other important Phase III trials in first-line lung read out over the next 6-18 months. These include Bristol's CheckMate-227, (Opdivo/Yervoy and Opdivo/chemo), AstraZeneca's MYSTIC and NEPTUNE (Imfinzi/tremelimumab) and a host of Roche trials studying Tecentriq with different chemotherapies.

As for Roche, the analysis is a boost for Tecentriq which had sales of CHF118m for the third quarter, which was actually down from the second quarter (CHF124m). The decline was due to a clinical setback in bladder cancer with the failure of a key trial and more difficult reimbursement conditions in the US – about 60% of sales were for the second-line bladder cancer indication and 40% for NSCLC.

Tecentriq, the multiple sclerosis drug *Ocrevus* (ocrelizumab) and the recently approved hemophilia therapy *Hemlibra* (emicizumab) are key to Roche's efforts to combat patent expiries on its big earners such as *Mabthera/Rituxan* (rituximab), *Herceptin* (trastuzumab) and Avastin. Anderson concluded by saying that the Basel-headquartered group is probably the best R&D company, but biosimilar risk is the elephant in the room. As for IMpower150, he believes "consensus still won't likely view Roche as a dominant threat in IO because of its late entrant status, despite the company's legacy as an oncology powerhouse."

Investors were impressed however, and Roche's shares, helped by more positive Hemlibra data, closed Nov. 20 at CHF243.60, up 5.9%.

Published online 20 November 2017

Bristol's Strong SITC: IDO, 1L Kidney Cancer And New Mechanism Data Bode Well

EMILY HAYES emily.hayes@informa.com

Bristol-Myers Squibb Co. got a boost with promising data for its PD-1 inhibitor *Opdivo* in combination with drugs in a number of different classes, including the company's own assets – the CTLA-4 inhibitor *Yervoy* in first-line kidney cancer and its IDO inhibitor BMS 986205 in bladder cancer – plus **Five Prime Therapeutics Inc.**'s anti-CSF cabiralizumab in pancreatic cancer.

Bristol's highlights included an exploratory analysis of the Phase III CheckMate 214 study of Opdivo (nivolumab) with Yervoy (ipilimumab) in first-line renal cell carcinoma (RCC) that supports a filing in this indication, and early efficacy data for the once-daily IDO inhibitor BMS 986205 that a number of prominent analysts concluded look on par with **Incyte Corp.**'s twice-daily epacadostat, the most advanced IDO inhibitor in development by far.

The data were released at the Society for Immunotherapy and Cancer (SITC) meeting, held Nov. 8-12 in National Harbor, Md.

"The positive data BMY presented at SITC with their IDO inhibitor, as well as other pipeline assets, is encouraging as one thinks about the broader immuno-oncology market and the opportunity for various combinations to succeed in various indications. We see this as a reason to be bullish on BMY over the longer-term, but in the near term investors remain focused on the Opdivo+Yervoy combination, especially in 1st line non-small cell lung cancer (NSCLC)," Credit Suisse analyst Alethia Young commented in a Nov. 13 note.

The '214 study tested the combination of nivolumab at 3 mg/kg every two weeks with ipilimumab at 1 mg/kg every three weeks for four doses against **Pfizer Inc.**'s tyrosine kinase inhibitor *Sutent* (sunitinib) in first-line metastatic RCC. After treatment with the combination, participants received Opdivo until disease progression. The primary endpoints were overall survival (OS) and progression-free survival (PFS) in an intermediate- to poor-risk patient population, about 75% of the overall population.

Bristol initially reported that the study missed the PFS endpoint, but went on to report positive OS results. A presentation at the recent European Society of Medical Oncology meeting proved controversial, because a subgroup analysis indicated that those with a favorable prognosis had better PFS on Sutent compared with the combination. *(Also see "No Clear Winner in BMS, Exelixis/Ipsen First-line Renal Cancer Race" Scrip, 18 Sep, 2017.)*

However, Bristol reported at SITC that in an exploratory analysis, the OS benefit over Sutent was seen regardless of expression of PD-L1. In those with less than 1% of PD-L1 expression, the hazard ratio was 0.73 and in those with over 1% it was 0.45, both statistically significant results, the company said. The OS breakdown was not available at the time that the company presented data at ESMO.

"We get a meaningful benefit in both populations of patients," Fouad Namouni, head of oncology development at Bristol, commented in an interview.

Median overall survival was not reached for those on the combination and was 19.6 months for the Sutent arm.

Safety was in line with prior reports; the rate of Grade 3/4 adverse events was 46% for those on the combination, versus 63% for Sutent. The dropout rate due to AEs was 22% for the combination versus 12% for Sutent.

Currently, Opdivo is approved as a monotherapy in second-line RCC.

During the third quarter, Opdivo maintained its US market share of 50% in second-line RCC and brought in a total of $1.3bn in sales across all indications. The company plans to file the Opdivo/Yervoy combination in first-line RCC rapidly and sees this is as a future catalyst for growth.

The combination of Opdivo and Yervoy is currently approved for first-line metastatic melanoma and is in development for multiple other tumor types.

"Overall, I think here one more time, we showed the combination of two agents really can beat the standard of care," Namouni said.

"We are going to study [the combination] tumor by tumor and understand what is the effect on every single major cancer we are exploring, but I think overall we believe continuing to push the immune system by combining multiple immunotherapy agents is probably the way to go," he added.

Credit Suisse's Young said, however, that while the CheckMate 214 RCC data are supportive of safety and efficacy of the combination, that doesn't mean that the data may be extrapolated to NSCLC. Furthermore, the number of safety-related discontinuations in the RCC study might be too high for first-line NSCLC, the analyst said.

But Young concluded that the risk/reward for the company is balanced ahead of the release of data from the CheckMate 227 study of Opdivo with Yervoy in first-line NSCLC. An interim release may come by the end of 2017 and final results are expected in the first half of 2018.

IDO COMBO ON FAST TRACK

Bristol also presented updated data for its BMS 986205, a selective, once-daily oral indoleamine 2,3-dioxygenase 1 (IDO1) inhibitor in CA017-003, in a Phase I/IIa dose escalation and expansion study of heavily pretreated cancer patients.

IDO inhibitors have a very high profile as an up-and-coming class in immunotherapy, with Incyte's epacadostat in the lead. Bristol is partnered with Incyte on combination studies of Opdivo and epacadostat, but is also developing BMS 986205 (F001287), acquired from **Flexus Biosciences Inc.**, on its own.

The company views IDO as an important IO mechanism – it recently started a registrational study in metastatic melanoma and is planning several other registrational studies in other tumor types.

Bristol is moving the candidate rapidly through development, moving from preclinical stage to Phase I in one year and launching registrational studies in less than two years, Namouni pointed out.

The company presented safety and tolerability data for BMS 986205 in eight tumor types at the AACR meeting in April. *(Also see "IDO Emerges As Clean Combo Partner, Rising Star At AACR" Scrip , 4 Apr, 2017.)*

At the SITC meeting, the company reported that in bladder (n=25) and cervical cancer (n=22) cohorts of the CA017-003 study, the combination of the IDO inhibitor with Opdivo demonstrated objective response rates of 32% and 14%, respectively. Response rates in those tumor types with at least 1% expression of PD-L1 were 46% and 25%.

Bristol also reported that there was an increase in proliferating cytotoxic T-cell count and lower production of serum kynurenine, a metabolite of the amino acid L-tryptophan produced by IDO1, which is associated with evasion of immune response.

"The preliminary response observed with BMS 986205 plus nivolumab in this study adds to our understanding of this combination, and together with the increases in tumor CD8 positive T-cells and decreases in kynurenine, suggests a potent effect, which warrants further investigation across advanced cancers," the company said.

Safety results were consistent with prior experience. The rate of Grade 3/4 toxicities was 11%, including increased aspartate aminotransferase (1.7%), increased alanine aminotransferase (1.4%) anemia (1.4%), autoimmune hepatitis (1.4%) and pneumonitis (0.7%). The rate of treatment-related dropouts was low at 1.4%.

HOW THE IDO INHIBITORS COMPARE

The company has said that there are pharmacokinetic and pharmacodynamic differences that could translate into advantages for its IDO inhibitor, but clinical data are needed to prove this hypothesis.

Bristol's data were well-received, but analysts saw the data on par with epacadostat based on cross-trial comparisons.

Looking at the objective response rate (ORR) data across subgroups of bladder cancer, both IDO inhibitors look generally comparable, though are some slight differences in subgroups. For example, Bristol's drug looks better in PD-L1 negative patients, while Incyte's looks better in PD-L1-positive cases, ISI Evercore analyst Umer Raffat said during a Nov. 13 webinar. But in addition to the limitations of cross-trial comparisons and single arm studies, the patient numbers for subgroups of trials are very small.

BMO Capital Markets Ian Somaiya said in a Nov. 13 note that the data for BMS 986205 was "similar at best vs. epacadostat."

There were no complete responses in Bristol's bladder cancer cohort whereas there was an 8% CR rate for epacadostat with **Merck & Co. Inc.**'sPD-1 inhibitor *Keytruda* (pembrolizumab) in bladder cancer patients in the ECHO-202 study. But this could be due to longer follow-up and treatment duration in Merck's study, Somaiya said.

Raffat noted that the ORR benefit from adding Bristol's IDO inhibitor to PD-1 compares well to PD-1 monotherapy studies in bladder cancer. Nivolumab monotherapy demonstrated a 26.2% ORR in PD-L1 positive bladder cancer patients in the CheckMate 275 study, for example, versus 46.2% in the new IDO/PD-1 combination study. The analyst pointed out that performance was better even though the patient population was more heavily pretreated compared with CheckMate 275.

MIXED RECEPTION FOR ANTI-CSF1R

Bristol and partner **Five Prime Therapeutics Inc.** also had data at the SITC meeting for the combination of cabiralizumab (FPA008) with Opdivo in a Phase I cohort of heavily pretreated, third-line+ pancreatic cancer patients. The combination demonstrated a response rate of 13% in 31 patients with this tumor type, per central review. The disease control rate was 16%. The partners are adding 30 patients to the trial and Bristol just started a new Phase II study of the combination in second-line advanced pancreatic cancer.

Five Prime's stock dropped by 9.95% to $25.96 on Nov. 13, following the presentation of full data at the SITC meeting. Upon release of a study abstract, it plummeted 34% to close at $25.86 on Nov. 7, but bounced back on Nov. 8 to close at $30.44.

BMO's Somaiya said in a Nov. 13 note that the Phase Ib data in third-line pancreatic cancer support expectations for a positive Phase III study and that investors are largely "unaware of how to define good data."

Jefferies analyst Eun Yang commented in a Nov. 12 note that although the cabiralizumab/Opdivo data in heavily pre-treated pancreatic cancer patients did not "excite the Street," the tumor type is associated with a very poor prognosis.

"We think additional positive data in other cancers in 2018 will further validate/strengthen utility of cabira/Opdivo, offering meaningful upside," the analyst said.

Array BioPharma Inc. presented data from a Phase I dose-escalation study of its anti-CSF1R candidate ARRY-382 with Merck's Keytruda at the SITC meeting. The study included 19 participants with pancreatic, colon, ovarian gastric, melanoma and triple negative breast cancers. Participants had a median of two prior therapies.

Array reported two partial responses for an ORR of 11% – one in pancreatic cancer and one in ovarian cancer with liver metastases. A dose of 300 mg daily was selected for a Phase II study, which initially included melanoma and NSCLC, but Array is planning to add a cohort of pancreatic cancer patients.

The company's stock price dropped by 2.55% to close at $10.61 on Nov. 13.

Leerink Swann analyst Michael Schmidt commented in a Nov. 13 note that "while it's difficult at times to discern a clear efficacy signal from background anti-PD1 activity," Five Prime's cabiralizumab and ARRY-384 both looked "very compelling in pancreatic cancer," Schmidt said.

However, BMO's Somaiya noted that Array Biopharma's data "comes with a few caveats."

"The PR (one of three pancreatic cancer patients) seen with ARRY's oral CSF1R, in our opinion, validates the mechanism, but we would caution against calling a 'winner' given the patient who achieved PR had stage 3 disease (all four cabira PRs had stage four disease) and microsatellite status was unknown," he said.

Other SITC releases include preliminary Phase I data for Bristol's OX40 agonist BMS 986178 and the combination of Opdivo with **Nektar Therapeutics**' IL-2 stimulating drug NKTR214 in melanoma, RCC and NSCLC in the PIVOT-02 Phase I/II study.

New mechanisms are coming together – they are in the early stages, but they are in the clinic now, Namouni said, adding that a year from now he thinks some triplet combinations will be in registrational development.

"This SITC shows we are making important progress with our diversified IO pipeline," the exec said.

Published online 20 November 2017

Nektar's IL-2 Impresses In Combination With Bristol's Opdivo: **http://bit.ly/2A0pQvs**

Executive Interview: Building Merck KGaA's Specialty Business In EMEA

JOHN DAVIS john.davis@informa.com

Chris Round, appointed executive vice president and head of the EMEA region at the Germany-headquartered multinational at the beginning of the year, describes **Merck KGAA**'s renaissance as a specialty biopharmaceutical business as an attractive opportunity, one that includes building an expanded European commercial operation while at the same maintaining a core business of marketed medicines.

"Merck KGaA is at a really interesting point, transitioning from a traditional business into an exciting biopharmaceutical business with real focus on breakthrough innovation," says Round. "I have also had the opportunity to bring together two business regions, Europe and the Intercontinental Region (comprising the Middle East, Africa and Russia/CIS states), into one expanded EMEA region, an interesting organizational challenge," Round told *Scrip* in a recent interview.

Merck now has four geographic heads, covering Europe, North America, Latin America, and Asia-Pacific, to drive the commercialization of its checkpoint inhibitor *Bavencio* (avelumab), in a global partnership with **Pfizer Inc.**, and the introduction of the short-course oral multiple sclerosis therapy *Mavenclad* (cladribine), that are being rolled-out to markets around the world.

But there were other reasons to join Merck apart from the organizational challenge of introducing significant new drugs: "I was excited about joining because of the science and the people leading the R&D effort, and the assets under development," Round explained.

The task is certainly different from Round's most recent previous position, as president of MSD China, a "fantastic experience," he says. But going back another step in his career, Round's new role follows a previous position at US big pharma **Merck & Co. Inc.**, when he was senior vice president and general manager of its oncology and immunology franchise, between 2011 and 2015.

"The whole area of immuno-oncology is extraordinary," Round remarked. "The opportunity is to produce targeted therapies that provide long-term durable responses in patients, some measured in years, when previously survival was measured in months," he noted.

Chris Round

Despite the lengthy period since the last new product launches at Merck KGaA, the company's preparations for its new product launches were well underway when Round joined. "Certainly it was a smaller organization than I am used to, but with that comes flexibility and speed. In addition, we have recruited from a variety of other organizations to add to our commercial experience at Merck," he said.

"We have built new capabilities from scratch, to make sure we are competitive from a 'share-of voice' perspective, and we have balanced medical, market access and commercial resourcing to equip the teams with capabilities to maximize launches."

"EMEA is a complex region, containing both highly sophisticated western countries but also young emerging markets, and we have organized ourselves to maximize the effectiveness of bringing new immunology products to the market, while maintaining sales growth in the core marketed products business," Round reported. There is a lot that employees in the smaller markets can learn from the more sophisticated markets, and vice versa. "The opportunity to share best practice and increase the effectiveness of the whole region is one of the exciting things I do," Round explained.

That said, Merck KGaA already has considerable commercial experience in the two sectors in which it is launching new products, in cancer and multiple sclerosis, having marketed the anticancer, *Erbitux* (cetuximab), and the injectable MS therapy, *Rebif* (interferon beta-1a), for many years. "It helps that we have an understanding of the therapeutic sectors and existing relationships with opinion leaders and key stakeholders," Round said.

Merck KGaA is also benefiting from its global partnership with Pfizer on the development and commercialization of Bavencio. "The alliance with Pfizer is only two years old, but it is really starting to pay off, with a significant number of regulatory successes, approvals in the US and Europe as first-line and second-line therapy in Merkel cell carcinoma, and US approval in advanced urothelial cancer. It is going to continue to roll out and we have a huge program evaluating it in different tumor types."

Other checkpoint inhibitors were being used off-label in Merkel cell carcinoma before avelumab was approved, but now physicians are switching patients to avelumab in Germany and the UK, where it is now launched. Merck and Pfizer are also evaluating the drug in lung, renal, ovarian and gastric cancer, and the partnership is working well at global, regional and individual country levels, with Pfizer taking the lead in some indications, and Merck in others.

With Merck's other new drug, cladribine, the commercialization challenges are unique, with a dosing schedule that consists of a maximum of 20 days of oral treatment over two years and a sustained clinical efficacy for up to four years. "The way this drug is delivered is highly innovative and extraordinarily patient friendly, and reimbursement agencies have seen the value proposition of cladribine very quickly." NICE has just given a positive recommendation on cladribine in a final appraisal determination.

Cladribine has been launched in the UK and Germany, and is expected to be launched in France, Italy and Spain during 2018.

Published online 17 November 2017

Mehta Analysis: Data Will Revolutionize PBM System

VIREN MEHTA mehta@mpglobal.com

Google's Waymo self-driving car project just passed an important milestone, with the arrival of its fully autonomous modified Chrysler vans on the streets of Chandler, Arizona. Uber, GM and others will not be far behind. Society soon will need far fewer roads, parking garages, and of course cars—while hopefully the quality of our lives will see another step-change as it did with the smart phone revolution. And it is all about data and the resulting intelligence.

Healthcare systems globally are also affected by this new, data-driven reality. Necessarily, these healthcare systems, which account for 10-18% of the economy, adopt new technologies gingerly and often belatedly, but a dramatic shift is underway as vertical integration continues its march towards concentration of data and concentration of power. This puts patients' rights and benefits in the balance.

Our previous column pondered the mystery around the value that pharmacy benefit managers (PBMs) create and the beneficiaries of that value. From the perspective of patients, concerns include the fact that they only receive a meager share of the savings that the PBMs extract from the pharma companies, which now amount to a third of a total combined list price of over $400bn annually; accounting practices that are obfuscated to inflate the top line even when PBMs do not take title to the drugs they dispense or process, just so that they can show lower profit margins; and, above all, patient copays being based on list prices, not what they actually pay.

We also noted how the vast quantities of data the PBMs collect are a treasure trove, which can yield a wide range of potential benefits for patients from better outcomes to lower costs. But such valuable clinical benefits have proven difficult to realize. One explanation is that many disparate data sources need to be better integrated.

Enter the possible merger of CVS and Aetna even while CVS continues to grow the scale and power of its own Caremark PBM unit, and even as it prepares to manage the PBM benefits for the newly created Anthem PBM. Just as 90% of the US metropolitan areas now have only a handful of hospitals and provider organizations, the payer and retail pharmacy end of the healthcare system is about to reach a similar degree of concentration. Such vertical integration is needed to realize the potential of data analytics to yield actionable intelligence to enable patients to take responsibility for their care, though the parallel concerns about the concentration of power limiting patient choices while raising costs remain, especially in the present-day Washington environment.

CVS is already a diversified biopharma service provider with its now leading Caremark PBM unit, its specialty biopharma delivery unit, and its ubiquitous drugs stores that increasingly include a medical clinic. This vast network generates enormous data every moment, but still along just one or two dimensions, and not enough to generate intelligent recommendations that motivate the patient to do the right thing. As with the data held by PBMs, organization-wide data at CVS readily lends itself to identify ways to maximize cash flow, but evidence of impactful improvements in patient care or substantial savings is meager.

Prescription data without a broader perspective limits the pharmacist to offering mundane services, such as avoiding drug interactions or ensuring timely drug refills that can enhance compliance – all meaningful no doubt, but not really harnessing the power of integrated data analytics and resulting intelligence.

With Aetna's claims data, a whole new dimension should compound the value of data that joining hands with CVS ought to bring. From preventive care via timely vaccinations, to optimally matching drug selection to the diagnosis, to further leveraging their scale to ensure best drug prices, this combination can offer a step change in the way data can be translated to impactful patient care with better outcomes. It need not be just about the bottom line.

In fact, the profit potential of such healthcare behemoths is not assured. Regardless of whether the CVS – Aetna merger goes through, powerful outsiders are poised to pounce, promising truly effective data analytics that is already second nature to them.

GAME CHANGER: AMAZON

Amazon is the most direct and near-term threat. It is capable of disrupting the drug distribution and dispensing scene across the spectrum in multiple ways, from its free Prime delivery service anchored around its massive mail order eCommerce operations, to its recently acquired Whole Foods stores network that is bound to develop a national footprint. Imagine Amazon setting up its own PBM. It would probably prefer to build it organically to avoid many of the pitfalls of the current PBM model, rather than inheriting legacy burdens that acquiring, for example, Express Scripts would bring – as tempting as it may seem to get a running start. PBM business is a natural for Amazon; it would be well positioned to bring greater transparency and fairer sharing of greater savings that it should be able extract from biopharma companies as well as other participants in this chain.

More than any FTC edicts, such online marketing powerhouses are likely to bring and maintain some semblance of free market forces in our ineffective capitalist healthcare system.

However, the ongoing pharma-political debate in Washington and most other world capitals may further change the rules of the game. The US Senate HELP Committee has health legislation as a key part of its mandate, and has held two of the planned three hearings on the subject. A range of experts from across the political spectrum have put forth many policy ideas, not to mention the Idea Generator in Chief Mr. Trump, who periodically reiterates how biopharma gets away with murder. There seems to be a surprisingly uniform distaste for ever-increasing drug rebates, which drag biopharma companies further into the medicine pricing debate, along with several of the practices of PBMs. Can a CVS-Aetna type of alliance, with or without a full merger, address the fundamental need for fairer drug pricing and equitable sharing of profits from the therapeutics segment of the healthcare system?

Amazon, when it finally enters the fray – likely after the Washington drug pricing debate clears up – will only accelerate this journey towards all the players on the biopharma playing field losing the ability to exploit the regulatory veil in search of maximal profits just for shareholders, and instead truly focusing on all stakeholders.

Published online 17 November 2017

Viren Mehta founded and is managing member of Mehta Partners, LLC, a globally integrated boutique providing strategic insights to senior management teams in the biopharmaceutical sector for nearly 30 years.

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

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

Selected clinical trial developments for the week 10–16 November 2017

LEAD COMPANY/PARTNER	COMPOUND	INDICATION	COMMENTS
Phase III Results Published			
AstraZeneca PLC	*Imfinzi* (durvalumab)	NSCLC	PACIFIC; *NEJM*, Nov. 16, 2017.
Neurocrine Biosciences Inc.	*Ingrezza* (valbenazine)	tardive dyskinesia	KINECT3; *Journal of Clinical Psychiatry*, Nov. 14, 2017.
Roche	*Avastin* (bevacizumab) plus lomustine	glioblastoma	*NEJM*, Nov. 16, 2017.
Novartis AG	*Ilaris* (canakinumab)	atherosclerosis	CANTOS secondary analysis; The Lancet, Nov. 13, 2017.
Puma Biotechnology Inc.	*Nerlynx* (neratinib)	breast cancer	ExteNET; *The Lancet Oncology* online, Nov. 13, 2017.
Johnson & Johnson/Bayer AG	*Xarelto* (rivaroxaban)	peripheral or carotid artery disease	*The Lancet* online, Nov. 10, 2017.
Phase III Interim/Top-line Results			
Egalet Corp.	egalet-002 (oxycodone) abuse deterrent formulation	non-cancer pain	Positive clinical results, well tolerated.
Updated Phase III Results			
Spark Therapeutics Inc.	*Luxturna* (voretigene neparvovec)	Leber's congenital amaurosis	Three-year follow up, responses maintained.
Novartis AG	brolucizumab (RTH258)	wet-age related macular degeneration	HARRIER, HAWK; met primary endpoint.
Bristol-Myers Squibb Co./Pfizer Inc.	*Eliquis* (apixaban)	stroke prevention	ARISTOTLE; better outcomes with adherence.
Argos Therapeutics Inc.	rocapuldencel-T	renal cell cancer	ADAPT; T-cell responses seen.
Alimera Sciences Inc.	*Iluvien* (fluocinolone acetonide)	uveitis	Well tolerated in 12 month safety study.
Phase III Initiated			
bluebird bio Inc.	*LentiGlobin*	transfusion dependent beta thalassemia	Northstar-3; with a specific genotype.
Bristol-Myers Squibb Co.	BMS-986205 plus nivolumab	melanoma	In previously untreated metastatic or unresectable disease.
Phase III Announced			
PledPharma	*PledOx* (calmangafodipir)	chemotherapy induced peripheral neuropathy	POLAR-A; POLAR-M; in patients undergoing chemotherapy.
Bristol-Myers Squibb Co.	epacadostat plus nivolumab, chemo	head and neck cancer	CheckMate 9NA/ ECHO-310; in advanced disease.

Source: Biomedtracker

What's In Store For Roche's New India Boss?

ANJU GHANGURDE anju.ghangurde@informa.com

For someone who led Roche in Venezuela at a time when the South American nation grapples through one of its worst economic crises, Lara Bezerra's India posting may seem like a breeze. The Swiss multinational on Nov. 14 announced that Bezerra was taking over as managing director for **Roche Products (India) Pvt Ltd** from Maturin Tchoumi who has moved to Roche Finland in a new role.

But Bezerra may need to stay "resilient" and "lead by example" – attributes she refered to in her online posts during her stint in Venezuela – as she steers Roche through a maze of evolving regulations and potential policy shifts in the price-sensitive Indian market. India is also heading towards a general election in 2019, which usually means that vote-bank interests rank high on the agenda of political parties.

And then there is the Swiss multinational's high-profile and acrimonious legal battle against the Indian regulator and biosimilar players in India, where Roche has, in the past, been accused of attempting to distort competition and also disparage the reputation of biosimilars. Most of these cases are ongoing. Roche has all along maintained that it adheres to all applicable laws and regulations in countries where it operates and refuted the allegations regarding anti-competitive conduct.

On the business front, Roche, although ranked well below peers **Abbott**, **GlaxoSmithKline Pharmaceuticals Ltd.** and **Pfizer Ltd.** in India, reported growth of 27.6%, albeit on a relatively small base, as per September 2017 MAT (moving annual total) data from AIOCD AWACS, the market research agency that tracks retail sales.

NAVIGATING TURBULENCE

Bezerra, who comes with over 24 years of experience in the pharmaceutical industry, has held various positions of leadership across various geographies, including Europe and Latin America. Her LinkedIn profile indicates stints with **Bayer** as well, before her role as general manager of Roche Venezuela.

"Her tenure in Venezuela was among the most turbulent times in the country's history, and her leadership was critical in navigating that period," said a statement from Roche, which also noted that in 2016, Roche was named among the top 20 places to work in Venezuela. Bezerra expects to build on Roche's foundation in India by "bringing transformational medicines" to the country, being a "strong" healthcare partner and making a "meaningful difference" for patients in India.

In previous online posts, Bezerra has described herself as neither a "traditional" or "modern" person, but as someone with "lots of faith, in humanity, in countries", which is perhaps indicative of a strong sense of awareness around balancing the old with the new and acceptance of varied thinking. In a developing but upwardly mobile country like India, which is keen to balance traditional and modern medicine and also ensure affordable access to drugs alongside encouraging the development and launch of innovative therapies, such attributes may perhaps hold her in good stead.

Published online 14 November 2017

Asia Executives To Watch: Gilead, BMS, AZ in Japan, WuXi NextCode
http://bit.ly/2AjkGgS

APPOINTMENTS

Shire PLC has named ***Thomas Dittrich*** CFO and a member of the rare disease specialist's executive committee. Dittrich will assume his roles at Shire in early 2018 after a transition period from his current employer, global industrial engineering and manufacturing company Sulzer Ltd, where he is CFO. Dittrich joined Sulzer in August 2014, serving as interim CEO between August and December 2015.

Biogen Inc. appointed ***Jeffrey D. Capello*** CFO effective Dec. 11 where he will lead the group's business planning, tax, treasury, internal audit, accounting, and investor relations functions and report to Biogen CEO Michel Vounatsos. Capello brings 26 years of experience in finance and will be based in Cambridge, Massachusetts. Most recently, he was executive vice president and CFO at Beacon Health Options Inc. Before that he founded and ran his own company, Monomy Advisors, and served as CFO of Ortho Clinical Diagnostics, Boston Scientific Corp. and PerkinElmer Inc.

BTG PLC said ***Duncan Kennedy*** will succeed ***Rolf Soderstrom*** as CFO Jan. 1, 2018. Soderstrom will remain with BTG until the handover is finished, probably by end of March 2018. Duncan currently leads BTG's Interventional oncology business, a role he has held since May 2015. He joined BTG in December 2005 as group financial controller and became a member of its executive leadership team in April 2012 when he was appointed group director of finance, managing the global finance function and supporting the CFO.

Bayer AG's supervisory board appointed ***Heiko Schipper*** head of the German conglomerate's consumer health division, replacing Erica Mann who decided not to extend her contract which was scheduled to run until end of December 2018. Mann has now asked to be able to hand over leadership of the consumer health business and leave the company from end of March 2018. Currently, Schipper is deputy executive vice president of Nestle SA.

Gamida Cell named ***Julian Adams*** chairman and chief executive officer of the cellular and immune therapeutics group. Adams was previously president and chief scientific officer at Clal Biotechnology Industries (CBI) where he oversaw the Boston office, evaluating investment opportunities and supporting portfolio companies, including Gamida Cell. Before joining CBI, he headed Infinity Pharmaceuticals Inc.'s R&D efforts. Adams succeeds Dr. Yael Margolin, who will remain president of Gamida Cell, continuing to lead the team in Jerusalem.