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AstraZeneca stays afloat in I-O after strong data for Imfinzi

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AZ Rides PACIFIC Wave To Be First In Early-Stage NSCLC

KEVIN GROGAN kevin.grogan@informa.com

Following positive results for its PD-L1 inhibitor *Imfinzi* (durvalumab) for stage III non-small cell lung cancer, **AstraZeneca PLC** believes that the major market opportunity for the drug will be its use even earlier on the treatment pathway.

Speaking to a small group of reporters at the weekend on the fringes of the European Society for Medical Oncology congress in Madrid, AstraZeneca chief executive Pascal Soriot noted that the company will be the only player in the earlier-stage lung cancer space for a couple of years. Trials of other anti-PD-1/L1 agents such as **Merck & Co. Inc.**'s *Keytruda* (pembrolizumab) and **Bristol-Myers Squibb Co.**'s *Opdivo* (nivolumab) are only just beginning.

Soriot said that there had been a somewhat myopic view of research in lung cancer which has resulted in the focus being firmly on the metastatic stage IV of the disease. The latter setting makes up about 50% of lung cancer patients, but this still leaves the other 50% with stages I, II and III, he stated, representing a sizeable opportunity.

The pool of early-stage patients is going to grow with better lung cancer screening campaigns, he noted, which will boost the prospects of earlier diagnosis. What a number of analysts have not paid much attention to in their sales forecasts for Imfinzi, Soriot said, is that when it comes to the earlier, non-metastatic settings, "we are going to be the first there."

He was speaking after the full results of the PACIFIC trial of Imfinzi in patients with unresectable stage III NSCLC after standard chemoradiation treatment were presented at ESMO. They showed that the drug improved progression-free survival by just over 11 months – 16.8 months in the Imfinzi arm compared to 5.6 months with placebo – with a hazard ratio of 0.52.

Presenting the data at ESMO, Luis Paz-Ares of the Hospital Universitario Doce de Octubre in Madrid said that the size of the PFS benefit suggested that Imfinzi could become the new standard of care for unresectable stage III NSCLC patients. With the drug decreasing the probability of disease progression by 48%, he pointed out that the improvement was consistent across all patient subgroups that were analyzed, not just those expressing PD-L1.

Overall survival data were immature and would be analyzed after a longer period of follow-up, Paz-Ares said, adding that Imfinzi was a reasonably well-tolerated treatment with a manageable safety profile. He stressed that it was the first medicine to show superior PFS in this setting, pointing out that standard treatment with platinum-based chemotherapy concurrent with radiation only gives a PFS of about eight months – only 15% of patients are alive at five years.

Stage III lung cancer represents about one-third of NSCLC incidence and AstraZeneca says it was estimated to affect around 105,000 patients in the G7 countries in 2016. More than half of these patients have tumors that are unresectable.

GAMBLE PAYS OFF

Soriot noted that with the PACIFIC trial, "we took a bit of a gamble frankly because many

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PARP Inhibitors
Rich prospects and more deals in store? (p10)

Scrip Awards Shortlist
See inside for the 2017 Scrip Awards finalists (p12)

from the editor

eleanor.malone@informa.com

After the longueurs of summer, pharma has gone back to school with a bang.

We've seen Novartis and Teva announce new leaders in recent days (more on the latter in next week's issue, or online now), Lilly's chief growth strategists unveil plans to cut 3,500 jobs and Merck KGaA put its consumer health business up for sale. The FDA has stirred excitement by approving the first CAR-T therapy, with Novartis winning kudos for its pay for performance plans and for not pricing Kymriah as highly as some expected (for more on the CAR-T field now Kymriah is approved and Gilead has bought Kite, see page 16). Over in the UK, the government has drawn up a strategy for life sciences that has provided a modicum of reassurance for businesses in the country in the face of Brexit.

Meanwhile, specialists in several medical fields have been assembling as the autumn congress calendar kicks in. We barely had chance to draw breath after the headline-grabbing European Society of Cardiology meeting in Barcelona before dashing back to Spain for the European Society of Medical Oncology meeting in Madrid (see cover story, in which PACIFIC results go some way to reversing the gloom that fell around AstraZeneca and its Imfinzi checkpoint inhibitor in lung cancer following the shock flop of MYSTIC in July).

Next week we'll be bringing you more detail from ESMO, where the presentations have been particularly noteworthy this year, along with highlights from the European Association for the Study of Diabetes that has been taking place in Lisbon.

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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
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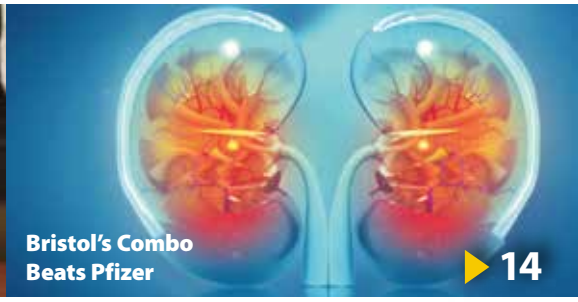

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ALIS In Wonderland: Insmed Reaches Fairy Tale Heights On Lung Disease Results
http://bit.ly/2fdc8w7
Insmed will commercialize ALIS, its inhaled amikacin formerly known as Arikayce, on its own for a rare, bacteria-driven lung disease if the company can win accelerated approval based on new Phase III results.

Bain and Cinven Bow To Elliott Pressure Over Stada Price
http://bit.ly/2gXlJqP
The private equity firms have agreed to pay more to Stada minority stockholders in a settlement that could add an extra €180-190m to their initial €5.4bn purchase price.

Manufacturing Snag May Stall Portola's Bevyxxa Launch
http://bit.ly/2eZaYaw
The company has priced its Factor Xa anticoagulant at $15 per capsule, on par with competitors, and is gearing up for a launch, but it first must resolve manufacturing issues with the FDA as it scales up to commercial capacity.

New Agents To Invade UC Market As Biosimilars Put Pressure On Stalwarts
http://bit.ly/2gXdej3
The ulcerative colitis pipeline is bustling with novel drugs, with new modes of action, that are ready to take on the market leading biologic therapies and their biosimilar counterparts; five launches are anticipated from four different drug classes before 2022.

Roche's Dry AMD Drug Lampalizumab Delivers Disappointment In Phase III
http://bit.ly/2wUWz3X
Analysts had already been doubtful about the prospects for success in the Spectri study. A second Phase III trial is ongoing, but the candidate is already being removed from revenue models.

The IO Switch: Making Tumor-Associated Macrophages Work In Our Favor
http://bit.ly/2gXNPSU
Emerging Company Profile: Macrophage Pharma is using novel chemistry to deliver therapies directly into tumor-associated macrophages, switching their activity from immunosuppressive to immuno-stimulatory to initiate anti-tumor immune responses.

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- Microbiome study

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- Hydrogenation
- Catalytic reaction
- Crystallization
- Chromatographic column

Big Pharma To Compete For Merck KGaA's Consumer Health Unit

LUCIE ELLIS lucie.ellis@informa.com

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After the divestment of its biosimilar business earlier this year, **Merck KGaA** is preparing to sell off or partner its consumer health unit in order to focus on branded pharmaceuticals – a deal potentially worth €3.5bn to the German group.

Merck is "considering strategic options" for its consumer health unit, including a potential full or partial sale of the business as well as strategic partnerships, the company announced on Sept. 5.

Analysts at Société Générale believe Merck could receive more than €3bn from the sale of the business. They said in a Sept. 5 note: "In a bid for 100% of the division we would value it at 4.0x sales, matching the **Merck & Co. Inc./Bayer AG** transaction multiple given a lack of plausible targets with meaningful scale. That would imply a total consideration of c. €3.5bn." US pharma giant Merck & Co. sold its over-the-counter business to Bayer in 2014 for or $14.2bn.

Companies that might show interest in Merck KGaA's consumer products include **GlaxoSmithKline PLC** and **Sanofi** in Europe, and **Johnson & Johnson** and **Pfizer Inc.** in the US, according to Société Générale. Although analysts noted that Pfizer might also envisage selling its consumer health division soon. **Bayer** has been ruled out by market spectators as a potential buyer this time around though due to its ongoing Monsanto deal. "As Bayer is currently involved in a big transaction with Monsanto and is facing some challenges in its consumer health division (US business sluggish), we don't see it as a credible candidate at this stage," Société Générale analysts said.

A STRATEGIC MOVE

Belén Garijo, a member of Merck's executive board and CEO of its healthcare business, said "increasing internal constraints" would prevent the company from fully funding its consumer health portfolio. As such the group is assessing its options now for this area of business. The consumer health unit achieved net sales of €860m in 2016, representing 13% of healthcare sales and 6% of total group sales. Its leading brands include: Bion, Femibion, Nasivin, Neurobion, and Seven Seas.

Proceeds from the divestment or partnering of Merck's consumer health portfolio will be used to "deliver on the company's overall financial targets," Merck noted in a statement.

The mid-sized pharma has taken other steps to narrow its focus within healthcare to concentrate on branded pharmaceuticals only. In April this year, the group sold its biosimilars portfolio to **Fresenius SE & Co. KGaA** for up to $670m. Of this, €170m was paid up front to Merck; the remaining €500m is linked to development milestones.

Société Générale analysts estimate that profitability of Merck's consumer health business "is slightly below the industry average" because of its "smaller scale and relatively fragmented portfolio with no US presence". But they also noted the business unit has six global brands and four regional brands, with a strong presence emerging markets.

A decision regarding the future of the consumer health unit will be made in early 2018 and completion of the project is flagged for the end of next year.

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Duaklir Moves Closer To US Filing

Circassia Pharmaceuticals PLC's plans to build up its respiratory franchise in the US appear to be on track, with its partner **AstraZeneca PLC** reporting positive top-line data from the Phase III AMPLIFY study of *Duaklir* (aclidinium bromide and formoterol fumarate 400 µg/12 µg twice daily) inhaler in patients with moderate to severe stable chronic obstructive pulmonary disease (COPD).

The UK biotech says it is looking forward to AstraZeneca filing a US NDA for Duaklir in the coming months – the submission is planned by AstraZeneca for the first half of 2018, and will include the AMPLIFY results and those from the recently completed ACHIEVE dose-ranging study. Duaklir is currently marketed by AstraZeneca in Europe.

Under a March 2017 agreement between the companies, AstraZeneca will complete the clinical development of Duaklir for the US market, with Circassia having exclusive US commercialization rights. In return, AstraZeneca has received an equity investment in Circassia, and the UK big pharma will also receive $100m from Circassia on June 30, 2019, or upon the FDA approval of Duaklir, whichever comes first, and royalties on sales.

The full results of AMPLIFY are expected to be presented at a medical meeting in the future, and will support making the long-acting muscarinic antagonist (LAMA)/long-acting beta-agonist (LMA/LABA) combination an option for the treatment of COPD, the companies said.

Duaklir has met its co-primary endpoints in AMPLIFY, showing a statistically significant and clinically meaningful improvement in lung function, measured by forced expiratory volume in one second (FEV_1) compared with the individual components, aclidinium and formoterol, AstraZeneca reported on Sept. 7.

john.davis@informa.com 7 Sept 2017

A Cellectis Trial Death Points To Challenges Ahead For CAR-T

JESSICA MERRILL jessica.merrill@informa.com

Cellectis SA is one of the companies that has benefited from investor enthusiasm over chimeric antigen receptor T cell (CAR-T) therapy in the last week, but its clinical-stage development program has been hit with a reality check. The company announced on Sept. 4 that the FDA placed a clinical hold on two Phase I studies testing its lead CAR-T candidate UCART 123 after a patient death was reported in one of the trials.

"Cellectis is working closely with the investigators and the FDA in order to resume the trials with an amended protocol including a lowered dose of UCART 123," the company said in a statement.

Unfortunately for the French drug maker, the two clinical trials just kicked off this summer, with management positioning their initiation as a turning point for the early-stage company. The death occurred in the first patient treated in one of the studies, a trial in patients with blastic plasmacytoid dendritic cell neoplasm (BPDCN). In the other trial, in acute myloid leukemia (AML), the first patient dosed also experienced serious events, but they resolved.

The patient who died, a 78-year-old man with relapsed/refractory BPDCN, experienced Grade 5 cytokine release syndrome (CRS), together with Grade 4 capillary leak syndrome (CLS), and died despite treatment with corticosteroids and **Roche**'s *Actemra* (tocilizumab), in keeping with accepted CRS management strategies.

CRS is one of the serious risks associated with CAR-T therapies so the disappointment is not necessarily a surprise.

> The entire development of the CAR-T field has been a roller coaster ride – and it doesn't look like anyone will be getting off soon

Deaths related to CRS have been seen in trials for other CAR-T therapeutics, including **Novartis AG**'s *Kymriah* (tisagenlecleucel), which was approved by the FDA on Aug. 30 as the first CAR-T therapy to be cleared in the US. The swift approval of Kymriah by the FDA and the premium pricing strategy put in place by Novartis has contributed to investor enthusiasm around the space.

But CRS and other safety risks remain a challenge for CAR-T developers to manage. Almost all patients treated with CAR-T therapy experience some level of CRS, which can be life-threatening. CRS also is a sign the immuno-oncology approach is working as the immune system responds to elevated cytokines associated with T-cell engagement and proliferation.

Actemra, an interleukin-6 blocker, has been used to manage the immune response to CAR-T treatment. The FDA recently granted a new indication for the drug as a treatment for adult and pediatric patients two years and older with CAR-T cell-induced severe or life-threatening CRS, based on data from CAR-T trials.

THE PROMISE OF OFF-THE-SHELF

The question for Cellectis is if any other serious effects are the result of the specific CD123 target. UCART123 also is different from the first-generation individualized CAR-T therapies moving through development – including Kymriah and therapies under development by **Kite Pharma Inc.**, **Juno Therapeutics Inc.** and **bluebird bio Inc.** – in that it is an allogeneic treatment made using cells from healthy donors with the aim of an off-the-shelf treatment.

Off-the-shelf CAR-T therapy could be more convenient and less expensive than autologous CAR-T immunotherapies, which are made by reengineering individual patient cells. Cellectis's platform is based on the TALEN gene editing technology and relies on cells taken from healthy donors to develop a therapy that would be immediately available to patients. Cellectis has hoped the approach would also include some efficacy advantages, since it would not rely on the T-cells of patients who are already sick and have been treated with chemotherapy.

"CRS should be manageable with lower doses, but other [adverse events] could be CD123 specific," Jeffries analyst Biren Amin said in a Sept. 5 research note. "We think there is a chance that CRS events could be mitigated upon lowering the dose of UCART123 beyond the DSMB recommendation and treating CRS symptoms more aggressively, although ultimately we look to more information."

However, Amin added, the Grade 3 infection and Grade 4 CLS event have the potential to be target specific. Another analyst, Credit Suisse's Alethia Young also noted that "the safety issue that Cellectis is encountering with their technology could be to some degree related to the Cellectis platform."

STOCK MARKET'S LOVE/HATE WITH CAR-T

On the heels of the FDA approval of Kymriah and news Aug. 28 that **Gilead Sciences Inc.** will buy CAR-T developer Kite for $11.9bn, the stocks of most CAR-T developers, including Cellectis, soared. But the firm's share price took a hit on the latest news, opening 30% lower on Sept. 5 at $22.27, but regained some ground to close down 20.3% at $25.66. It recovered some of the lost ground during mid-day trading as the well understood reason for the death sunk in to trade at around the same level it was trading before the Gilead news and Novartis approval were announced.

The entire development of the CAR-T field has been a roller coaster ride – and it doesn't look like anyone will be getting off soon. Even for Novartis, there are still plenty of questions about whether or not Kymriah will be commercially successful – and profitable.

Investors have been continuously spooked and jazzed about the treatments, which have shown impressive efficacy in some very sick patients, despite the risks. Juno and its partner **Celgene Corp.** ended development of its lead candidate JCAR015 earlier this year in acute lymphoblastic leukemia due to safety, including severe neurotoxicity, including five deaths from cerebral edema.

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CONTINUED FROM COVER

people at the time thought it would not work but that's what you have to do when you are behind, you have to differentiate and that gamble worked."

He said that analysts' sales forecasts of about $2bn for Imfinzi in the stage III setting seemed reasonable. Soriot also claimed that AstraZeneca was well placed to be first in stages I and II, with ongoing trials of Imfinzi as adjuvant therapy in operable NSCLC, "where again we are two years ahead."

The PACIFIC results are certainly a boost for Imfinzi in lung cancer, especially given the bitter blow suffered in July with data from the large MYSTIC trial. A combination of Imfinzi and the company's CTLA-4 inhibitor tremelimumab failed to show a PFS benefit in patients with previously untreated stage IV metastatic NSCLC.

The MYSTIC trial will continue to assess OS for Imfinzi as monotherapy and Imfinzi plus tremelimumab combination. Final data are expected during the first half of 2018 and Soriot admitted that the prospects of the combo working were low.

However, if Imfinzi works as monotherapy in MYSTIC, it would be the only checkpoint inhibitor for stages III and IV, he pointed out, adding that "we don't need to be better than the others, we just have to be as good." Soriot said that AstraZeneca needed to offer doctors "a proposition" whereby they could use Imfinzi in stage III and carry on treatment in stage IV. Imfinzi, which got accelerated approval from the US Food and Drug Administration earlier this year for previously treated patients with advanced bladder cancer, received breakthrough therapy designation from the agency in July for locally advanced, unresectable NSCLC whose disease has not progressed following platinum-based chemoradiation therapy. AstraZeneca is in discussions with global health authorities regarding submissions for Imfinzi based on PACIFIC and timings will be provided with its quarterly results announcement.

When asked if the company was still in the lung cancer race with the rival PD-1/L1 inhibitors, Soriot concluded by saying it depended on which race - "in the early race, we are leading."

> Soriot also claimed that AstraZeneca was well placed to be first in stages I and II, with ongoing trials of Imfinzi as adjuvant therapy in operable NSCLC, 'where again we are two years ahead.'

Reaction to the data was largely positive at ESMO and among the investment community. Tim Anderson, an analyst at Bernstein, said "Imfinzi performed impressively" and noted that when anticipating where Imfinzi sales may end up relative to peers over the longer-term, "which extends well beyond the PACIFIC opportunity, we find it helpful to consider the number of clinical trials being run with each of the currently approved anti-PD-1/L1 therapies." He added that the breadth of AstraZeneca's program "substantially lags the two current market leaders (Merck & Co and BMS) in this regard. In oncology, being a first-mover is usually an imperative, and while AstraZeneca is clearly first in Stage III lung cancer, in many other settings it will very likely be a late entrant."

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Huahai Leaps Into IO Via Korean Startup

Chinese active pharmaceutical ingredients (API) manufacturer **Zhejiang Huahai Pharmaceuticals Co. Ltd.** has agreed to invest $30m for a significant stake in the Korean biotech startup **Eutilex**, plus an additional $8.5m to obtain exclusive rights to Eutilex's immuno-oncology asset EU101, currently in the preclinical stage.

In a regulatory filing with the Shanghai Stock Exchange, Huahai said it plans to invest $30m in cash and acquire an 18.75% stake in the two-year biotech venture, becoming the second largest shareholder, after Eutilex's founder Byoung S Kwon.

Additionally, Huahai will pay up to $8.5m in upfront and milestones-based payment to obtain the exclusive rights in China to EU101, a checkpoint inhibitor immuno-oncology asset. Eutilex will get sales-based royalties upon the product's commercialization. If Eutilex decides to use preclinical or clinical data from Huahai towards future licensing transactions, it will pay Huahai a certain percentage of the transaction proceeds.

EU101, a monoclonal antibody agonist that binds 4-1BB, is the Seoul-based venture's most advanced asset. 4-1BB is expressed in many immune cells including CD8+ and CD4+ T-cells, and binding to this stimulates and increases these cells, strengthening anti-tumor immunity. EU-101 is being studied alone and in combination with checkpoint inhibitors PD-1/PD-L1.

The company also has two other IBB4-CTL assets in preclinical stage. CTL is a form of autologous T-cell therapy in which the patient's own antitumor CD8+ T-cells are expanded and modified outside the body and then re-infused, where they can detect and efficiently kill tumor cells.

Founded in 2015 by Kwon, Eutilex has recently completed its round A financing, raising roughly $18.9m.

From the editors of PharmAsia News

brian.yang@informa.com 7 Sept 2017

Allergan Shifts Restasis Patents To Native American Tribe To Invoke Immunity From IPR

MANDY JACKSON mandy.jackson@informausa.com

Allergan PLC stumbled on to its latest intellectual property strategy by chance when a lawyer representing the Saint Regis Mohawk Tribe reached out to the company offering a solution for some of its *Restasis* (cyclosporine) patent woes. CEO Brent Saunders said it's a strategy that the company – and its peers – may pursue for other brand-name products.

The lawyer was from the Texas law firm Shore Chan DePumpo LLP, which helped a university claim sovereign status as a means of getting an inter partes review (IPR) proceeding dismissed by the US Patent and Trademark Office (USPTO) Patent Trial and Appeal Board (PTAB). He explained that if Allergan transferred ownership of its patents for the dry eye drug Restasis to the Saint Regis Mohawk Tribe in Akwesasne, NY, the tribe could get the IPR proceeding for Restasis dismissed, since Native American tribal governments have sovereign immunity that makes them exempt from IPR challenges.

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After its lawyers reviewed the proposal, Allergan agreed to shift ownership of all Orange Book-listed Restasis patents to the tribe. The company has an exclusive license to the patents and will pay the tribe $13.75m upon execution of the agreement and $15m in annual royalties.

The fees are a tiny fraction of Allergan's annual Restasis sales – $1.4bn in 2016 – but the deal could help preserve the company's blockbuster revenues from the drug through the life of its patents expiring in 2024. However, Restasis revenue already is under threat, since the drug is facing commercial competition from **Shire PLC**'s new dry eye drug *Xiidra* (lifitegrast), which has slowed the Allergan product's sales growth this year. *(Also see "Allergan Focuses On Aesthetics As Sales Dip For Dry Eye Leader Restasis" Scrip, 4 Aug, 2017.)*

"The actions we've taken today with the tribe really allows us to focus on the defense of the Restasis patents in the federal court system under the Hatch-Waxman regime and essentially avoid the double jeopardy created by the upcoming IPR process," Saunders said in an interview on Sept. 8, when the patent deal was announced.

"What we did today has no bearing on the Hatch-Waxman process, on the district court case that went to trial last week; closing arguments were on Friday. That will continue and that's where we believe the patents for Restasis should be adjudicated," he said. A hearing for the PTAB to consider the Restasis IPR is scheduled to take place on Sept. 15, during which the patents would be judged by a different set of standards than in federal court.

Mylan Pharmaceuticals Inc. initiated the Restasis IPR in June 2016 and **Argentum Pharmaceuticals LLC** joined the challenge soon after, but Allergan eventually settled with Argentum. **Akorn Inc.**, **Famy Care Ltd.** and **Teva Pharmaceutical Industries Ltd.** later joined the IPR.

Before the IPR was initiated, Allergan sued Mylan, Akorn, Teva, **Apotex Inc.**, **InnoPharma Inc.** and **Pfizer Inc.** for patent infringement in the US District Court for the Eastern District of Texas in 2015; InnoPharma and Pfizer also were sued in the US District Court for the District of Delaware. All six companies plus Famy Care, **TWi Pharmaceuticals Inc.** and **Deva Holding AS** have filed abbreviated new drug applications (ANDAs) with the intention of selling generic versions of Restasis before its patents expire in August 2024.

Famy Care and TWi were added to the ongoing ANDA litigation in the Eastern District of Texas in 2016 and Deva was sued separately in that court as well as in Delaware. Allergan has since settled its disputes with Apotex and TWi, but the Deva matter in Texas is scheduled to go to trial in October 2018. The Eastern Texas lawsuit against Mylan, Akorn, Teva, Apotex InnoPharma and Pfizer went to trial on Aug. 28 and closing arguments were heard on Sept. 1. The judge's decision in that case is expected within the next month or two.

A DEAL ALLERGAN COULDN'T REFUSE

Allergan Chief Legal Officer Bob Bailey explained in the same interview with Saunders that in the eyes of the PTAB it doesn't matter if a sovereign entity bought or built the patents they own, only that the patents are owned by a sovereign, which has immunity. So when the Saint Regis Mohawk Tribe first presented its idea to Allergan, in an Aug. 14 call to Bailey, the company moved quickly to evaluate the opportunity.

The tribe had been working with Dallas, Tex.-based lawfirm Shore Chan DePumpo. "They had represented state universities in IPR proceedings and asserted the sovereign immunity of state universities to prevent the state university patents from being challenged," Bailey said.

"This is a viable and sound opportunity for the Saint Regis Mohawk Tribe to enter into the patent, technology and research sector as part of our overall economic diversification strategy," the tribal council said in a unified statement. "We realize that we cannot depend solely on casino revenues and, in order for us to be self-reliant, we must enter into diverse business sectors to address

the chronically unmet needs of the Akwesasne community; such as housing, employment, education, healthcare, cultural and language preservation."

The patents transferred to the tribe include the US patents numbered 8,629,111; 8,633,162; 8,642,556; 8,648,048; 8,685,930 and 9,248,191, which expire on Aug. 27, 2024. Bailey said those patents become more valuable under the ownership of a sovereign entity, because they are not subject to IPR proceedings.

"When they presented this to us, we thought it was a very good idea, something worth examining closely," he said. "We worked with leading experts in patent law and sovereign immunity law and determined that it was a sound strategy and something that we should pursue."

Bailey noted in Allergan's announcement about the agreement with the Saint Regis Mohawk Tribe that the company reviewed recent case law, such as *Covidien LP v. University of Florida Research Foundation Inc.* and *Neochord Inc. v. University of Maryland*, in which the PTAB dismissed IPR proceedings against the universities when they asserted their sovereign immunity.

"Allergan just made a legal move that is extremely important for the industry to track," Evercore ISI analyst Umer Raffat said in a Sept. 8 note, but he had some doubts about the company's strategy.

"Allergan cites two precedent cases involving IPRs against universities that were dismissed on similar grounds," Raffat wrote. "But, there is a difference: the precedent IPRs were originally started against sovereign entities to begin with … the Restasis IPR was started against Allergan, but the patents are now being transferred to a sovereign entity."

Douglas Hahn, a shareholder in the Newport Beach, Calif. office of the law firm Stradling Yocca Carlson & Rauth PC, said Allergan's strategy is both unprecedented and clever – and it may hold up in court, if challenged.

"There is support for this. It goes back to the Eleventh Amendment cases where states have been immune from certain actions of the government," Hahn said, noting that those actions would include PTAB decisions. The Eleventh Amendment says that states cannot be sued in federal court, because they have sovereign immunity. Tribal governments have the same sovereign immunity.

"I'm not aware of any restriction on sovereign immunity that a state can't acquire ownership of a patent at any given time," Hahn added. Even so, it's unlikely that Allergan's strategy will go unchallenged, he said, noting that "I do imagine this is bound for a higher court if the PTAB dismissal is granted."

IPR PROCEEDING DISMISSAL IS IMMINENT

The first step in the tribe's request to dismiss the Restasis IPR is that it must ask the PTAB for permission to make a motion. "We expect that [permission] to be granted sometime in the early part of next week," Bailey said.

Allergan's executives said the company is not pursuing this route because it was certain that the Restasis patents would be invalidated by the PTAB, but it certainly is a possibility given the fate of other biopharma patents at such hearings.

"They likely assessed the risk of the IPR and realized it was substantial. At one time, there was approximately an 80% chance of the PTAB invalidating a patent," Hahn said. "Certainly patent holders are looking for ways out and this is the most clever one I've found so far."

Bailey reinforced Saunders's assertion that "we made this move to avoid the double jeopardy of the court case and the IPR proceeding. Those patents which are not subject to this double jeopardy are stronger and more valuable than those which are."

Allergan does not expect the deal with the Saint Regis Mohawk Tribe to affect the ongoing court case in the Eastern District of Texas.

"Once this decision is made on the validity of our patents, that decision will have precedential value, so this is a key court case and the only one that matters," Bailey said.

A NEW, REPEATABLE PATENT STRATEGY?

Saunders said the arrangement with the Saint Regis Mohawk Tribe "could be a strategy that we deploy for other intellectual property," but he noted that such agreements may not be necessary in the future, because the IPR process at the PTAB is being challenged at the US Supreme Court.

The Supreme Court has agreed to hear a complaint that PTAB decisions in IPR proceedings – which frequently have led to decisions invalidating biopharma company patents – remove the patent holder's right to a jury trial under the Seventh Amendment of the Constitution.

But if IPR proceedings continue, Saunders said Allergan will consider using the strategy of engaging a sovereign entity to hold its patents and seek a dismissal of IPR proceedings "and importantly others will consider using it."

Hahn said the strategy may take years to play out in the courts if the IPR is dismissed, but noted that "if the PTAB grants the motion to dismiss, I would expect you're going to see a lot of patents moved to tribes or some kind of sovereign entity."

REPUTATIONAL RISK OF INVOKING IMMUNITY

Saunders said Allergan "absolutely" considered the impact on its reputation and the reputation of the biopharma industry before it engaged in a patent agreement with the Saint Regis Mohawk Tribe.

He also said the move is consistent with the "social contract" the company adopted last year, which outlined a renewed commitment to invest in innovative new medicines, provide access to its medicines via responsible pricing, ensure quality and safety for its products, and educate doctors so that they prescribe Allergan medicines appropriately. The initiative garnered attracted a lot of attention because of the company's pledge to limit drug price increases. *(Also see "Allergan's Price Reform Pledge: Will Others Follow?" Scrip, 6 Sep, 2016.)*

"I do believe this is entirely consistent with our social contract. Our social contract went into four specific areas, but most importantly into investing in innovation, which we did in Restasis. We were granted patents that go into 2024," Saunders said. "They are being challenged by the generic companies early and we are defending them in federal court. To have to then do that 10 days later in a controversial setting like the IPR setting has nothing to do with reputation – it has to do with innovation."

He added: "We continue to price Restasis responsibly. We continue to offer patient assistance for Restasis and we continue to abide by all aspects of our social contract. But we have a right to defend our inventions and intellectual property and make a return on our innovation. It's always a balance."

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PARP Inhibitors: Rich Prospects And More Deals In Store?

ANJU GHANGURDE anju.ghangurde@informa.com

Poly (ADP-ribose) polymerase (PARP) inhibitors are expected to bring about a paradigm shift in the treatment of solid tumors and M&A activity around this promising class of drugs may well be corollary, indicates a report by ProGrow Pharma Partners, an Indian life sciences advisory firm.

ProGrow notes how the PARP market opportunity in the approved indication of ovarian cancer is large but with certain firms pursuing label expansion in other cancers such as prostate, breast, lung, endometrial, pancreatic and glioblastoma multiforme as a monotherapy or in combination with other targeted drugs, the best is yet to come. ProGrow believes that PARP Inhibitors offer a multi-billion dollar opportunity akin to *Avastin* (bevacizumab), *Gleevec* (imatinib mesylate) and *Zytiga* (abiraterone acetate) through label expansion.

While immunotherapy could probably be viewed as the fourth pillar of cancer treatment, joining surgery, radiation, and chemotherapy, Subita Srimal, partner at ProGrow, believes that PARP Inhibitors may well emerge as first or second line therapy in place of chemotherapy, targeting specific mutations and pathways. PARP inhibitors and immunotherapy combinations could be the way forward in some cancers, though not necessarily all since these are targeted therapies.

COMBINATION THERAPIES

There's been significant enthusiasm following data from **Tesaro Inc.** unveiled earlier this year indicating the potential of its PARP inhibitor *Zejula* (niraparib) in multiple tumor types beyond ovarian cancer following combination testing with *Keytruda* (pembrolizumab). *(Also see "Tesaro's Zejula Expansion Includes Keytruda Combo, Lung Cancer" Scrip, 5 Jun, 2017.)*

On whether the potential of PARP Inhibitors could open up the market for those who may have missed the initial immuno-oncology rush, Srimal told *Scrip* that those who have not joined the biologics/immune therapies fray but have been mostly focused on small molecules may likely do so with some assets lying in their pipeline itself. "BMS already has collaborated with Clovis for a combination therapy and like GSK, has bromodomain and Extra-Terminal [BET] inhibitors in the pipeline which together may be useful in cancer beyond BRCA," Srimal, a PhD in biochemistry, maintained. Clovis Oncology earlier this year firmed up a non-exclusive agreement to test *Rubraca* (rucaparib) with **Bristol-Myers Squibb Co.**'s *Opdivo* (nivolumab) in ovarian, triple-negative breast and prostate cancers. Clovis is also testing Rubraca with **Roche** / **Genentech Inc.**'s *Tecentriq* (atezolizumab) in gynecological cancers, with a focus on ovarian cancer.

> PARP Inhibitors may well emerge as first or second line therapy in place of chemotherapy, targeting specific mutations and pathways

Informa's Datamonitor Healthcare forecasts that ovarian cancer drug sales across the US, Japan, and five major EU markets (France, Germany, Italy, Spain, and the UK) could rise from $553m in 2016 to almost $2.7bn by 2025. Primary drivers of this growth are expected to be the marketed PARP inhibitors *Lynparza* (olaparib; **AstraZeneca PLC**/**Merck & Co. Inc.**), Rubraca, and Zejula, as well as pipeline PARP inhibitor veliparib (**AbbVie Inc.**). Seven other late-phase pipeline candidates will also contribute to the expansion of the market.

Within the PARP inhibitor class, Zejula and Lynparza are forecast by Datamonitor Healthcare to achieve the highest revenues due to their comprehensive development programs, while Rubraca and veliparib are seen garnering lower sales.

DEAL-MAKING POTENTIAL FOR PARP INHIBITORS

Significantly, the market opportunity for PARP Inhibitors is estimated to be in excess of $5bn, which ProGrow believes should trigger M&A activity at "attractive terms".

"The take out of **Medivation Inc.** by **Pfizer Inc.** in 2016 for $14bn is an indicator for 'good times' as Medivation's portfolio included a PARP inhibitor besides the approved drug *Xtandi* (enzalutamide) for prostate cancer," Srimal said.

She underscored that while targeted biologic therapies have given "handsome returns" to innovator companies, the advantages and potential of a safe small molecule targeted therapy for cancer cannot be undermined and remains on the "wish list" of most pharma companies. It essentially translates into lower cost of therapy, ease of manufacturing, oral route of administration, stability etc, she explained. **AstraZeneca PLC**'s olaparib is a small molecule oral PARP1/2 and TNKS (tankyrase) inhibitor.

While the developmental history of PARP Inhibitors has been rocky, with the failure of late-stage molecules like **Sanofi**'s iniparib and the termination of certain other candidates adding to the early gloom, ProGrow says that big pharma may well, in hindsight, be regretting exit decisions made in haste. These large firms may be keen to grab emerging opportunities in the space either via acquiring marketing rights or outright buyouts.

ProGrow also expects the outcome of combination trials of approved blockbusters to pave the path for acquisition. "Pursuing firms could pay up for Tesaro which has higher valuations as it boasts of two approved drugs and a robust pipeline," the report observes. Clovis may be another potential target on the horizon.

Tesaro, at the time of its second quarter earnings on Aug. 8, said that Zejula had quickly became the most frequently prescribed PARP inhibitor in the US, following its introduction in late April.

TESARO, CLOVIS UNDER SPOTLIGHT

Srimal notes that Tesaro has two marketed drugs including niraparib [Zejula] and a "good pipeline" and thus was generally "pricey" till recently when some issues with its manufacturing site for its IV CINV [chemotherapy-induced nausea and vomiting] drug cropped up in the US. The FDA earlier this year issued a Complete

Response Letter (CRL) for Tesaro's *Varubi* [rolapitant] IV New Drug Application (NDA) for the prevention of delayed nausea and vomiting associated with initial and repeat courses of emetogenic cancer chemotherapy. The agency requested additional information regarding the in vitro method used to demonstrate comparability of drug product produced at the two proposed commercial manufacturers for rolapitant IV that were included in the NDA. At the time of its second-quarter results last month, Tesaro said that the NDA re-submission for the intravenous (IV) formulation of rolapitant is under review by the FDA, with a Prescription Drug User Fee Act (PDUFA) action date of Oct. 25.

There has been speculation in the past on **Gilead Sciences Inc.**'s potential interest in the oncology-focused Tesaro, though it's unclear if its recent acquisition of Kite Pharma Inc. for $11.9bn has dulled Gilead's appetite. *(Also see "Gilead Makes Cell Therapy The Base Of Its Oncology Platform With Kite Buy" Scrip, 29 Aug, 2017.)* Srimal notes that Gilead is known to pay a premium "if convinced" [of the asset potential] as in the case with the acquisition of Pharmasset, which was primarily driven by the strength of that firm's HCV candidate sofosbuvir.

On whether the Clovis-BMS deal could be viewed as a prelude to an eventual sale of Clovis depending perhaps on early data from the combination studies of Rubraca and Opdivo, Srimal maintained that BMS may be playing safe not to disappoint further on Opdivo - the drug has seen a string of disappointments over the recent past. *(Also see "Another Opdivo Disappointment For BMS, This Time In Kidney Cancer" Scrip, 15 Aug, 2017.)*

"If it works then it [BMS] may acquire [Clovis] as it has a nice pipeline too - though Clovis is currently focused on rucaparib," she said.

At the time of the Clovis-BMS alliance some analysts were reported by Scrip as suggesting that the deal structure may be aimed at setting up the best possible buy-out value for the biotech. "Some investors may have hoped for an outright acquisition of Clovis by Bristol in the near-term, but we think this deal doesn't preclude a future acquisition of the company and in our view, increase the competitiveness and value of Rubraca," Leerink's Michael Schmidt stated at the time.

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First In MS: Fingolimod Nears Pediatric Market

JOHN DAVIS john.davis@informa.com

In top-line results from the first ever Phase III study of a disease-modifying therapy (DMT) in children and adolescents aged 10 to 17 years with multiple sclerosis, the use of **Novartis AG**'s oral S1P modulator, *Gilenya* (fingolimod), has been associated with a significant reduction in the number of disease relapses over two years compared with weekly intramuscular injections of interferon beta-1a, the primary endpoint of the study.

The safety profile of fingolimod was consistent with that seen in other clinical trials, and more adverse events were reported in beta-interferon treated patients, Novartis reported on Sept. 5. Further details of the differences in actual relapse rates in the PARADIGMS study, that were also reported to be clinically meaningful, will be released at the joint ECTRIMS-ACTRIMS meeting that will be held in Paris, France, on Oct. 25-28.

Although MS usually starts when individuals are in their 20s or 30s, in a small proportion of patients it starts earlier – of the 400,000 diagnosed cases of MS in the US at any one time, 8,000 to 10,000 are in people younger than 18 years of age. Novartis's CEO-designate, Vas Narashimhan, is quoted in a Sept. 5 company statement as saying: "living with MS is a tremendous challenge at any age. However, its appearance in children and adolescents, when these young individuals should be developing and focusing on their future, can be devastating."

Novartis noted there is no specifically approved DMT for use in children and adolescents, even though pediatric MS, which starts usually during adolescence, is associated with more frequent and more severe relapses than adult MS. There have also been no randomized, controlled Phase III studies of DMTs in pediatric MS, the company pointed out.

The news follows a busy few months for breakthroughs in MS therapy. **Roche**'s *Ocrevus* (ocrelizumab) became the first drug to be approved for primary progressive MS in the US in March, 2017.

Merck KGAA's *Mavenclad* (cladribine) became the first oral short-course (20 days of oral therapy over two years) therapy for MS when it was approved in the EU in August. *(Also see "Merck KGaA's MS Drug Mavenclad May Defy Doubters" Scrip, 25 Aug, 2017.)*

TOP-SELLING PRODUCT

Gilenya is one of Novartis's top-selling products, with sales of $837m, up by 5%, in the second quarter of 2017, and the Swiss big pharma names it as one of six innovative medicines that are driving its growth. The addition of a pediatric indication for Gilenya should add to that product's sales potential and also to the breadth of the company's MS portfolio. Novartis said it planned to complete analysis of PARADIGMS before speaking to regulators about submitting the additional indication for approval.

Novartis is building up an industry-leading portfolio in MS: as well as the widely sold Gilenya, the company also markets the interferon beta-1b product, *Extavia*, for the treatment of MS in the US and Europe, and *Glatopa* (glatiramer acetate), a generic version of **Teva Pharmaceutical Industries Ltd.**'s *Copaxone*, in the US via its **Sandoz Inc.** generics subsidiary.

Its investigational products include siponimod (BAF312), which is expected to be ready for a marketing submission in 2018, and its anticancer product ofatumumab (OMB157) is being evaluated in two Phase III clinical studies in MS.

200 CHILDREN STUDIED

The 25-country PARADIGMS study enrolled 215 children and adolescents with MS, with expanded disability status scale (EDSS) scores between zero and five, and included a two-year double-blind phase followed by a five-year open-label extension. Secondary endpoints included the number of new or enlarged T2 lesions, gadolinium enhancing T1 lesions, safety and pharmacokinetics.

Published online 5 September 2017

Scrip Awards Finalists »

2017

www.scripawards.com

We are delighted to announce the shortlist for the 13th Annual Scrip Awards.

Over the summer, our panel of 16 respected judges has reviewed all the entries to produce a shortlist that displays the wealth of innovation, dedication and hard work that the pharmaceutical and biotech industries have shown over the past year.

The full range of industry activities from big pharma, biotech companies and CROs is represented: from novel deals, to new drug launches and finding technological breakthroughs in clinical trials. The Scrip Awards provides the industry with an opportunity to acknowledge its highest achievers across all parts of the value chain, and to recognize both corporate and individual achievement.

As in previous years, we will be announcing the winner of PPD's Pharma Company of the Year Award on the night, just as we do for the Lifetime Achievement Award (sponsored by Aptuit). We are thrilled that so many of you have taken the time to enter, and sorry that not everyone can make the shortlist.

This year's winners will be announced at a glittering black tie ceremony at the London Hilton on Park Lane on November 29.

Congratulations to all our finalists and good luck on the night!

BEST COMPANY IN AN EMERGIN
- ASLAN Pharmaceuticals (Singapore)
- Beximco Pharmaceuticals (Banglad
- CinnaGen Pharmaceutical (Iran)
- Hutchison China MediTech (Hong Ko
- Mundipharma (Singapore)
- WuXi Biologics (China)

BEST TECHNOLOGICAL DEVELOP CLINICAL TRIALS – PATIENT-FO
- Antidote's Antidote Match
- Aural Analytics' SpeechAssess and
- Exom Group's Genius Engage
- Janssen's Patient Voice in Trial Desi

BEST TECHNOLOGICAL DEVELOP CLINICAL TRIALS – SPONSOR-FO
- Algorics' Acuity analytics platform
- ERT's Centralized Clinical Trial Mana
- goBalto's goBalto Select
- Medidata's Medidata Synthetic Cont
- myClin's myClin Clinical Trial Knowle
- 4G Clinical's Prancer

COMMUNITY PARTNERSHIP OF T
- Antidote and Juvenile Diabetes Res Clinical Trials Connection
- AstraZeneca's Active Science progra
- Glenmark Foundation's Project mMi
- QuintilesIMS India's Race for 7
- Sandoz' Sandoz HACk – Healthcare
- Shire's Rare Count campaign

EXECUTIVE OF THE YEAR (COMP MARKET CAP >$1BN)
- Said Darwazah, chair and CEO of Hikma Pharmaceuticals
- David Meek, CEO of Ipsen
- Flemming Ornskov, CEO of Shire
- Jan van de Winkel, CEO of Genmab
- James Ward-Lilley, CEO of Vectura
- Elias Zerhouni, president of global R

BEST PARTNERSHIP ALLIANCE
- AstraZeneca and Pieris Pharmaceut for anticalin-based inhaled biologic respiratory diseases
- BioNTech and Genentech for mRNA- cancer immunotherapies
- Cancer Research UK and Bicycle The agreement to trial BT1718 for cance

Scrip Awards
Pharma intelligence | informa

EXECUTIVE OF THE YEAR (PRIVATE COMPANIES AND THOSE WITH A MARKET CAP OF <$1BN)

- Eliot Forster, CEO of Immunocore
- Kurt Graves, chair, president and CEO of Intarcia Therapeutics
- Elizabeth Iorns, CEO and co-founder of Science Exchange
- Kevin Lee, CEO of Bicycle Therapeutics
- Behshad Sheldon, president and CEO of Braeburn Pharmaceuticals
- Raman Singh, CEO of Mundipharma, Singapore

BEST CONTRACT RESEARCH ORGANIZATION – FULL-SERVICE PROVIDERS

- Covance
- ICON
- INC Research
- Medpace
- PPD
- Worldwide Clinical Trials

BEST CONTRACT RESEARCH ORGANIZATION – SPECIALIST PROVIDERS

- Aptuit
- Cytel
- Orphan Reach
- Quanticate
- PHASTAR
- WuXi NextCODE

BUSINESS DEVELOPMENT TEAM OF THE YEAR

- AstraZeneca's Scientific Partnering & Alliances Team
- BioNTech's Business Development Team
- Clinigen's Multidisciplinary Team for lifting Cardioxane's Article 31
- EUSA Pharma Business Development Team
- F-star and Denali Therapeutics' Transaction Team
- Ipsen Group's Merrimack Transaction Team

FINANCING OF THE YEAR

- Abzena's public placing of £25m
- BiomX's series A financing of $24m
- Inventiva's €48m initial public offering
- Pharming's €104m financing
- Verona Pharma's $89m NASDAQ listing

- F-star with Denali Therapeutics for delivery of medicines across the blood-brain barrier
- Merck KGaA and Avillion for anti IL-17 A/F Nanobody in inflammatory diseases
- Takeda and Ovid Therapeutics for TAK-935 in rare epilepsies

WUXI APPTEC'S BIOTECH COMPANY OF THE YEAR AWARD

- AC Immune
- Avacta
- Bicycle Therapeutics
- BioNTech
- Genmab
- Tocagen

QUINTILESIMS' CLINICAL ADVANCE OF THE YEAR AWARD

- Amgen and Novartis' STRIVE study of erenumab in migraine
- Centrexion Therapeutics' TRIUMPH study of CNTX-4975 moderate-to-severe osteoarthritis knee pain
- Eli Lilly's EVOLVE-1 and 2, and REGAIN studies of galcanezumab in migraine
- Genmab and Janssen Biotech's CASTOR and POLLUX studies of daratumumab in multiple myeloma
- Immunocore's Phase I study of IMCgp100 in malignant melanoma
- Kite Pharma's ZUMA-1 study of axicabtagene ciloleucel in non-Hodgkin's lymphoma

INC RESEARCH'S BEST NEW DRUG AWARD

- Astex Therapeutics/Novartis's Kisqali (ribociclib)
- Merck KGaA/Pfizer's Bavencio (avelumab)
- Roche's Ocrevus (ocrelizumab)
- Sanofi/Regeneron Pharmaceuticals' Dupixent (dupilumab)
- Shire's Xiidra (lifitegrast)

LICENSING DEAL OF THE YEAR

- AstraZeneca and Aspen for ex-US rights to AZ's global anesthetics portfolio
- AstraZeneca and Circassia for US rights to the aclidinium franchise
- Crescendo Biologics and Takeda Pharmaceuticals for Humabody-based therapeutics
- EUSA Pharma and Apeiron Biologics for dinutuximab beta
- MedImmune and Allergan for MEDI2070
- Vertex Pharmaceuticals and Merck KGaA for Vertex's DNA damage response inhibitor portfolio

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T +44 (0) 203 377 3183 | **M** +44 (0) 7917 647 859 | christopher.keeling@informa.com

Bristol's Opdivo/Yervoy Combo Beats Sutent On Survival In Renal Cancer

JESSICA MERRILL jessica.merrill@informa.com

Immuno-oncology combinations have faced disappointing clinical trial data of late, but positive news from **Bristol-Myers Squibb Co.**'s Phase III trial testing its PD-1 inhibitor *Opdivo* (nivolumab) and CTLA-4 inhibitor *Yervoy* (ipilimumab) in advanced renal cell cancer could swing the pendulum back in their favor.

Bristol announced top-line data from an interim analysis of the Phase III CheckMate 214 study testing the combination in advanced renal cell carcinoma patients, showing improvements in overall survival (OS) versus the standard of care, **Pfizer Inc.**'s *Sutent* (sunitinib). The news is especially welcome after the company announced in August that the trial did not reach statistical significance on one of the other co-primary endpoints, progression-free survival (PFS), though a positive trend was seen.

The study's independent data monitoring committee (DMC) recommended that the trial be stopped early.

"The company looks forward to sharing the full results with regulatory authorities," Bristol said in a statement.

The overall survival data is a big score for Bristol as it looks for leverage in a crowded field. The opportunity in front-line RCC is big, possibly as much as $2bn for Opdivo in combination with Yervoy, according to some analysts. But the PD-1/CTLA-4 combination also is viewed as Bristol's last real chance to gain a foothold in frontline non-small cell lung cancer (NSCLC) – the most commercially valuable cancer indication – after Opdivo monotherapy notoriously failed to show a benefit in the CheckMate-026 trial.

"We believe the OS benefit likely confirms the durability of the signal seen on PFS, leading to a very high likelihood of approval," Leerink analyst Seamus Fernandez said in a same-day research note. "A win on OS is critically important to our bull thesis for the stock."

QUESTIONS

The benefit of the combination has been in question given the increased toxicity of adding Yervoy to Opdivo, especially after Bristol announced in January that it was scrapping plans to seek accelerated approval from the FDA for the combination in lung cancer and after the two drugs failed to significantly improve overall survival versus **Roche**'s *Avastin* (bevacizumab) in a glioblastoma multiforme trial earlier this year, though that is a notoriously challenging area.

It's also promising news for **AstraZeneca PLC**'s PD-L1/CTLA-4 inhibitor combination, after *Imfinzi* (durvalumab) and tremelimumab failed to meet a PFS endpoint versus chemotherapy in first-line NSCLC in the MYSTIC trial this summer, casting a further shadow over the combination. The overall survival analysis is still outstanding for MYSTIC.

The only indication the Opdivo/Yervoy combination has been approved for is unresectable or metastatic melanoma, an approval that came early in Opdivo's life cycle and under an accelerated approval.

Now the combination could be on track to add kidney cancer to its indications as well. Opdivo is already approved as a monotherapy for the treatment of advanced renal cell carcinoma after showing a survival advantage versus *Afinitor* (everolimus).

OS BESTS PFS AS AN IO ENDPOINT

The top-line PFS data Bristol released in August cast a pall over the trial, even though some immuno-oncology drugs have been known to fail PFS but hit OS, given the slower response to treatment. Nonetheless, investors were wary.

Shutterstock: crystal light

The Bristol results further add to the thinking around OS as the better endpoint for immuno-oncology drugs, which could be good news for AstraZeneca's ongoing MYSTIC trial.

"In other words, PFS is not destiny," Bernstein analyst Tim Anderson said in a Sept. 7 note.

Anderson said he will be waiting more details on the data in CheckMate-214. "In addition to clarity on [objective response rate (ORR)] and PFS in all patients and the nature of the PFS curve, we will be looking intently at tolerability (relative to Sutent, not a totally benign drug itself) and for association (or not) with PD-L1 status, or other biomarkers of sensitivity, such as tumor mutation burden," he wrote.

In Checkmate 214, patients treated with Opdivo 3 mg/kg plus Yervoy 1 mg/kg every three weeks for 4 doses followed by Opdivo 3 mg/kg every two weeks, experienced better overall survival versus patients in the comparator group, who received sunitinib 40 mg once daily for four weeks, followed by two weeks off before resuming treatment. The company did not provide details on the survival data, but said the trial met the co-primary endpoint of OS compared to sunitinib in intermediate- and poor-risk patients, as well as the secondary endpoint of OS in all randomized patients.

As previously reported, the combination yielded an overall response rate of 41.6% versus 26.5% for sunitinib in poor and intermediate-risk patients. PFS in the intermediate- and poor-risk patients improved 18% for those receiving the combination, but did not reach the pre-defined statistical significance threshold of 0.009 compared to sunitinib. The median PFS for the combination group was 11.6 months versus 8.4 months for the sunitinib group.

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Voyager's Parkinson's Gene Therapy Poised For Pivotal Trial Exploration

JESSICA MERRILL jessica.merrill@informa.com

Voyager Therapeutics Inc.'s gene therapy for Parkinson's disease, VY-AADC01, is poised to move into a pivotal trial later this year after the company reported positive results from a small ongoing Phase Ib trial on Sept. 6. The data showed dose-dependent improvements across multiple measures of motor function following a one-time administration of the treatment.

The positive early data are welcome news for the field of gene therapy, which continues to challenge drug developers despite advancements. **Spark Therapeutics Inc.**'s *Luxturna* (voretigene neparvovec) could be the first typical gene therapy approved by the FDA, though the agency declared **Novartis AG**'s newly approved CAR-T cancer therapy *Kymriah* one. An advisory committee review of Spark's treatment is scheduled for Oct. 12.

Voyager is partnered with **Sanofi**'s Genzyme unit, which has an option to acquire several programs after proof-of-concept under a 2015 agreement. Voyager retains US rights to VY-AADC01, its lead program.

"The finding speaks directly to our goal, to turn back the clock to when patients were more responsive to levodopa, required lower doses and had better, more consistent motor function," chief medical officer Bernard Ravina said during a same-day call. "AADC01 is peeling back years of levodopa dose increases in a matter of months. This pattern, to our knowledge, has not been seen in previous Parkinson's gene therapy trials and doesn't exist with current or emerging treatment."

AADC01 is not intended to be a cure for Parkinson's disease, but rather to help patients respond better to treatment with levodopa, the standard of care for treating motor symptoms associated with Parkinson's disease. Levodopa can improve motor symptoms because it helps the body produce dopamine, which patients with Parkinson's gradually stop making. Treatment with levodopa gradually becomes less effective for patients with more advanced disease.

The enzyme AACD is responsible for converting levodopa to dopamine, which is depleted in patients with Parkinson's disease. VY-AADC01 is a gene therapy vector that contains the gene that encodes the AADC enzyme, and Voyager's ambition is that one dose – administered surgically in the brain – could offer patients' improved motor function and reduce their need for oral levodopa and other dopaminergic medicines.

TARGETING ADVANCED PARKINSON'S DISEASE

Voyager hopes to position the treatment as an option for patients with advanced disease, particularly those who currently undergo deep brain stimulation (DBS), a surgical procedure to treat the most debilitating symptoms of Parkinson's disease: tremor, rigidity, stiffness, slow movement and walking problems. DBS uses a surgically implanted, battery-operated neuro-stimulator to deliver electrical stimulation to targeted areas in the brain to help control movement.

Voyager CEO Steven Paul pointed out during the conference call that the benefits seen in the Phase Ib trial with VY-AADC01 were similar to the range of benefits seen with brain stimulation in a similar patient population. The procedure is performed in 5,000 patients in the US and up to 20,000 patients globally each year.

"With no in-dwelling hardware or invasive catheters, meaningful effects and a well-tolerated safety profile, AADC01 could be a clear alternative to deep brain stimulation, but could also be a very attractive treatment option for the more than 100,000 advanced Parkinson's disease patients in the US alone who are eager to regain mobility in a productive stage of their lives," Paul said.

Voyager expects to initiate a Phase II/III pivotal trial later this year, with plans to dose the first patient in 2018. The company is still deciding which of two doses it will move forward, while it awaits data from one of three cohorts, cohort 3, out to 12 months.

"We have two really active doses here and time will tell," Paul said. "We will have that data well in advance of dosing any patients in the pivotal trial."

The company already released positive interim results from the Phase Ib trial in December 2016. The study has three cohorts, with the dose increasing in each cohort.

While the data are positive, the study is small, including only 15 patients with advanced Parkinson's disease and disabling motor functions. The company previously announced data showing improvement in motor symptoms in the first two cohorts. In the latest release, Voyager announced positive data from cohort 3 – the highest vector genome concentration – at six months, showing the same clinically meaningful improvements in motor symptoms observed in cohort 2 with even lower doses of oral Parkinson's medications, including levodopa.

POSITIVE DATA ACROSS ENDPOINTS

The data suggest higher doses of VY-AADC01 result in greater AADC activity, increasing the capacity for patients to produce dopamine and reduce their need for oral medications. The updated data also included results for patients in cohort 2 at 12 months, showing an average increase during the day of four hours of "on" time without dyskinesia, and data from cohort 1 at 24 months.

Patients enrolled in cohort 3 received similar infusion volumes of VY-AADC01 compared to cohort 2 (up to 900uL per putamen), but three-fold higher vector genome concentrations. The volume and concentration for cohort 3 represents up to a three-fold higher total dose of $4.5x10^{12}$ vector genomes compared to patients in Cohort 2 (up to $1.5x10^{12}$ vector genomes). Patients in cohort 1 received lower volumes and lower vector genome concentrations for a total dose of $7.5x10^{11}$ vector genomes.

The primary objective of the trial is to assess the safety and distribution of ascending doses of VY-AADC01 administered under magnetic resonance imaging (MRI) guidance to the putamen, a region of the brain associated with impaired motor function. Secondary objectives include assessment of AADC expression and activity in the putamen, measured by positron emission tomography (PET) using fluorodopa, which reflects the capacity to convert levodopa to dopamine.

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Rising Tide Lifts All CAR-T Ships After Gilead/Kite Deal, Kymriah Approval

MANDY JACKSON mandy.jackson@informausa.com

An outstanding week for chimeric antigen receptor T cell (CAR-T) therapy companies, between **Gilead Sciences Inc.**'s $11.9bn purchase of **Kite Pharma Inc.** and US FDA approval for **Novartis AG**'s *Kymriah* (tisagenlecleucel), could turn into a great run for cell therapy developers.

Gilead's Kite acquisition showed that big pharma and large biotech companies see significant commercial value in CAR-T therapies – enough to buy a whole portfolio rather than agreeing to partner on a handful of prospects. Meanwhile, the Kymriah approval and Novartis's pricing and reimbursement negotiations with the Centers for Medicare and Medicaid Services (CMS) confirmed that regulators and payers see these as important treatments that patients should be able to access. That pharma, regulator and payer validation should support increased investment in the growing cell therapy field.

"Other people are starting to see what we have had the benefit of seeing for some time, which is the incredible promise of this space," **Alliance for Regenerative Medicine** (ARM) CEO Janet Lambert said in an interview with *Scrip*. "This Novartis approval takes something with great potential and makes it a product. It's not coming – it's here, it's now."

Already, CAR-T stocks are rising. Novartis's US stock increased modestly during the past week, despite the approval of Kymriah, which the Swiss big pharma priced at $475,000 – below some very high expectations for the one-time treatment. The company also said it is talking with CMS and other payers about indication-based pricing and outcomes-based contracts under which there would be no charge for the CAR-T therapy if patients don't respond in the first month.

"We think the outcomes- and value-based pricing is a positive step for the CAR-T space broadly since we think it helps secure reimbursement for the likely very expensive therapies," Credit Suisse analyst Alethia Young wrote in an Aug. 30 note about Kymriah's approval.

While Kite is next in line for a FDA approval of a CAR-T therapy, the company's share value already was boosted by the Gilead deal news when the Novartis product was approved. Kite shares jumped nearly 30% after the transaction was revealed. Gilead's stock, which declined slightly following the deal announcement, climbed considerably after the Kymriah approval – an event that may have erased investors' doubts about the company's big investment in a novel treatment modality.

The earlier-than-expected approval for Kymriah for relapsed or refractory pediatric and young adult B-cell precursor acute lymphoblastic leukemia (ALL) also raised expectations that Kite's axicabtagene ciloleucel (KTE-C19) could be approved before its Nov. 29 PDUFA date. The first indication would be for relapsed or refractory non-Hodgkin lymphoma (NHL), including diffuse large B-cell lymphoma (DLBCL), transformed follicular lymphoma (TFL) and primary mediastinal B-cell lymphoma (PMBCL).

OTHER PUBLIC CAR-T COMPANIES BENEFIT TOO

Juno Therapeutics Inc., which could be the next company to seek the FDA's approval for a CAR-T therapy, shot up more than 36% during the past week, benefitting from the goodwill generated by the week's news and speculation that Juno could be the next big CAR-T acquisition. Of course, the company already has a pretty broad and high-value partnership agreement with **Celgene Corp.**, which paid $1bn up front – $150m in cash and $850m in equity – to collaborate with one of the CAR-T field's first business ventures.

"We would be surprised if Celgene felt compelled to fully acquire Juno," BTIG analyst Dana Leone wrote in an Aug. 28 report following the Gilead/Kite deal. Leone noted that Celgene recently acquired more Juno shares to keep its ownership stake at 10%, but a full acquisition was deemed unlikely, because the partners' lead program JCAR017 would be the third CD19-targeting CAR-T product on the market after Kymriah and axicabtagene ciloleucel. Also, Juno's BCMA-targeting therapy for multiple myeloma conflicts with Celgene's similar CAR-T partnership with **bluebird bio Inc.**

Bluebird and other smaller publicly traded CAR-T companies also rose by double digits following the Gilead/Kite deal news and Novartis's Kymriah approval. Bluebird already was flying high based on the 100% response rate reported for it and Celgene's BCMA-targeting therapy bb2121 in June. After the companies amended their 2013 agreement in 2015, bluebird and Celgene are working together only on CAR-T therapies that target BCMA, a protein on the surface of multiple myeloma cells.

The allogeneic CAR-T therapy developer **Cellectis SA**, which entered into a significant partnership agreement with **Pfizer Inc.** in 2014 for products addressing up to 19 different targets, also bounced higher on the past week's news. Pfizer paid $80m up front and bought a 10% stake in the French company in 2014. The partners also have an agreement related to Cellectis's gene-editing technology known as TALEN, which it uses in the development of CAR-T therapies.

Bellicum Pharmaceuticals Inc. was one of the biggest gainers from the Gilead/Kite deal and Kymriah approval news as well. Its pipeline includes CAR-T on/off switch technology to help moderate or stop severe side effects that occur frequently after treatment with the cell therapies.

DO DEALS, APPROVALS REMOVE RISK?

"On one side, I would say, yes, that the Gilead/Kite acquisition has signaled that CAR-T has been de-risked enough," Datamonitor analyst Amanda Micklus told *Scrip*. "Gilead was expected to do a big deal; was pushed by investors to do so. To make that deal Kite Pharma is definitely a note of confidence, especially for that price tag. Gilead didn't rush into the deal and probably had many other options in terms of other therapy areas to buy in, e.g. NASH, immunology/inflammation."

"But on the other side you have Novartis, which has already been involved in CAR-T for a while, and heavily invested, even after doing away with its cell and gene therapy research," Micklus continued. "So from a big pharma/big company perspective, CAR-T has already been validated by Novartis's involvement, and through bigger partnerships too, including Celgene/Juno. So from that end, it seems like Gilead is now just getting into the game with others already there."

Micklus said recent data suggest that CAR-T technology has become a central theme in drug development and deal-making. CAR-T represents 16% of the regenerative medicine pipeline, but it's the fourth-largest modality overall by share, behind gene therapy, stem cell therapy and other types of cell therapy beyond CAR-T, according to a recent Datamonitor report on deal trends in the regenerative medicine space. Within oncology, CAR-T is the dominant regenerative medicine modality, she said.

CAR-T also was the fourth-most active target for immuno-oncology deals, according to an earlier report on IO deal trends for the five-year period between 2012 and 2016. CAR-T fell behind deals for development programs targeting the immune checkpoints PD-1/PD-L1 (the top deals category) and CTLA4 (no. 3 on the list) and cancer vaccines (no. 2).

APPROVAL VALIDATES CAR-T

David Epstein – former CEO of Novartis Pharmaceuticals, a division of Novartis AG – said the approval of Kymriah provides validation of a big investment that was made at a time when the rest of big pharma were not backing CAR-T research. His team was responsible for partnering with the **University of Pennsylvania** in 2012 to develop Kymriah and other CAR-T therapies.

Now, Epstein is an executive partner at the venture capital firm Flagship Pioneering and executive chairman of the Flagship-backed company **Rubius Therapeutics Inc.**, which is developing next-generation cell therapies by creating engineered allogeneic red cells, or "super blood," as a new class of treatments for cancer, autoimmune and rare diseases. Rubius recently raised $120m in private financing after closing a $25m Series A round in 2015.

The Kymriah approval "tells us that if you have a medicine or intervention that works, the FDA will work with companies to make it available. It tells us we're not just working in a world of small molecules and biologics; there will be a whole variety of products," Epstein said.

Going forward, CAR-T and other cell therapies will be more like cell phones than small molecules or biologics, he said, because companies will rapidly develop and bring to market versions 2.0, 3.0 and so on to quickly improve on the first generation products. Such innovations will include allogeneic, off-the-shelf therapies to reduce or eliminate the three-week lag time between harvesting T cells and reengineering them to attack cancer cells, like the process involved in treating patients with Kymriah, axicabtagene ciloleucel and other autologous products.

"I think it's pretty cool that the door is opened, but there are better ways to do it," Epstein said. "Clearly there has been investment growing over time as more and more data came out from the Kite and Novartis products. Even to this day there are skeptics. But this approval [and] this deal, does bring more money to the table."

Pioneers like Novartis and major players like Kite – now Gilead – will continue to invest in improvements of their own technology, while some companies will try to leapfrog Kite and Novartis, and venture capital investors will put more money into emerging players.

Kite already has engaged **Cell Design Labs Inc.** to create an on/off switch for a CAR-T therapy to treat acute myeloid leukemia (AML). The agreement was announced in 2016 concurrent with the start-up's $28.4m Series A venture capital round. Cell Design Labs CEO and co-founder Brian Atwood said the company expects to initiate its first clinical trial in late 2018 or early 2019 for a precise and controllable CAR-T therapy. The company also is working on earlier-stage technology that adds a payload to a reengineered T cell to deliver a biologic directly to the tumor.

Atwood said Gilead's Kite acquisition and the first approval of a CAR-T therapy "is encouraging from the point of view of corporate partners that this is a validated and important way to treat patients." Cell Design Labs already has seen increased interest in its technology following the deal and Kymriah's approval.

Atwood expects investment and deals to increase across the cell therapy field based on those two major milestones, but he acknowledged that the biggest boost is likely to occur among companies developing CAR-T technology for the treatment of cancer.

ARM's Lambert pointed to the trade association's recent second quarter report, which showed "there had already been an uptick in investment and deal activity in 2017 as compared to 2016."

The quarterly report on cell and gene therapies, which was supported by Informa Pharma Intelligence, noted that global financings increased 88% year-over-year to $2.45bn in the second quarter, including $1.18bn in public and private fundraisings for gene and gene-modified cell therapy developers (up 56%) and $1.33bn for cell therapy companies (up 70%).

"I think that this [week's news] will change the trajectory of the line even more so – especially Gilead's acquisition of Kite," Lambert said. "But what was so exciting about Novartis was the positive AdComm, the positive FDA language around it, and the statement CMS put out that they want to support these game-changing technologies. You've got to get the science right, the regulatory framework right and the reimbursement right."

COMMERCIALIZATION NEXT KEY VALIDATOR

The true test for the CAR-T field will be the commercial success of companies in this sector, in terms of measuring the return on investment from deals and research in this space, Datamonitor's Micklus noted.

"There has been some talk of pricing already, including potentially value/outcomes-based arrangements in oncology – and this itself is a shift, because to date payers don't really have many restrictions when it comes to covering oncology medications," she said. "These kinds of experiments will be important, I think, for CAR-T therapy success."

But first, CAR-T makers will have to show that their personalized therapies – using patients' own T cells – can be manufactured at a commercial scale or else oncologists will rule out the therapies as feasible options for patients with little time left. Manufacturing success as well as having enough doctors trained to administer the therapies and manage side effects are factors that Epstein noted may be more important than sales figures, especially in early small indications like relapsed or refractory pediatric ALL – about a 600-patient market for Kymriah.

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Alnylam Hopes To Resume Fitusiran Dosing Quickly, Despite Unclear Cause Of Trial Death

JOSEPH HAAS joseph.haas@informa.com

Less than a year after shuttering its amyloidosis candidate revusiran due to patient deaths in a Phase III trial, **Alnylam Pharmaceuticals Inc.** announced another setback Sept. 7, saying it was temporarily suspending dosing in ongoing studies of its hemophilia candidate fitusiran because of a patient death in a Phase II trial.

Alnylam said it hopes to restart dosing of fitusiran within three to six months by amending safety protocols in ongoing studies, including the just initiated Phase III trial ATLAS. Nonetheless, investors were dismayed, sending the company's stock down 15.7% to close at $72.53.

After the termination of revusiran last year, several analysts said it suggested little read-through to the rest of Alnylam's pipeline because the drug stemmed from an earlier technology than used in other Alnylam assets. There appear to be mitigating factors around the fitusiran patient death, as well.

During a Sept. 7 investor call, Alnylam executives explained that the patient who died presented symptoms, including severe headache and hip pain due to exercise. Physicians responded with the appropriate treatment for their diagnosis, subarachnoid hemorrhage, including administration of hemophilia A replacement Factor VIII two to three times a day, but the patient worsened over a 14-day hospital stay before dying. An investigator determined the death was not related to fitusiran.

The patient was enrolled in an open-label, Phase II study including patients with hemophilia A or B, with or without inhibitors to treatment with replacement factors. Prior to the fitusiran trials, the patient received Factor VIII on demand and had an annualized bleeding rate of 32 episodes. He first was dosed with fitusiran in a Phase I study in August 2015 and then joined the open-label extension after a treatment gap in March 2016, receiving 80 mg of study drug monthly, the higher of two doses being investigated. Alnylam said the patient demonstrated good hemostatic response and was bleed-free since August 2016.

Following the death, Alnylam asked three independent neuro-radiologists to review the patient's CT scans. On Sept. 1 those investigators determined that the adverse event had been a cerebral venous sinus thrombosis, not a subarachnoid hemorrhage. This conclusion re-opens the question of whether treatment with fitusiran played a role in the patient's death, Alnylam conceded.

The cerebral venous sinus thrombosis "may be related to the effects of fitusiran that the patient was receiving and positively may have been related to the antecedent administration of [replacement] factor for hip pain," Alnylam executive VP-R&D Akshay Vaishnaw told the call. He added that recommended treatment for subarachnoid hemorrhage and cerebral venous sinus thrombosis are "quite different."

MONTHLY DOSING

CEO John Maraganore said Alnylam still hopes to develop fitusiran, partnered with **Sanofi**, as a novel, monthly therapeutic alternative for both hemophilia A and B. He noted that treatment experience with the candidate so far includes 42 patients in Phase I or Phase II studies with a total of 31 patient years. The Phase III ATLAS trial has been initiated with active clinical sites, but dosing has not begun. The biotech's stated goal had been to file fitusiran for the FDA approval in 2018.

"The risk of thrombosis is a known and reported side effect of approved drugs and other investigational drugs in development, and safety monitoring is an important part of risk management in hemophilia," the CEO told the call. "We remain very committed to continuing the development of fitusiran as an investigational medicine that we believe has the potential to make a significant difference for patients with hemophilia and other rare bleeding disorders and we look forward to working with regulators to allow the resumption of dosing in the coming months."

Analysts said fitusiran's mechanism of targeting anti-thrombin always presented risks by affecting the balance between clotting and bleeding, but overall predicted that Alnylam would get the okay to resume dosing of the drug.

Do Kim of BMO Capital Markets wrote on Sept. 7 that "high levels of Factor VIII" used to treat the patient who died likely were a contributing factor to the outcome, "which suggests appropriate protocol changes could mitigate the risk of thrombosis." Kim predicted the Phase III study would be delayed between three and six months, the timeframe in which Maraganore said Alnylam hoped to resume dosing.

Paul Matteis of Leerink Partners noted the risk of blood clots has often been cited as a theoretical concern for fitusiran. He predicted on Sept. 7 that even if the fitusiran trials restart with revised safety protocols, the drug's commercial opportunity may be limited "given the risk-averse nature of the hemophilia patient population (especially patients without inhibitors)."

He conceded, however, that it remains uncertain if fitusiran will be implicated in the patient's death. "It seems that care for this patient was uniquely poor, and it's unclear if the event would have been fatal had it been caught earlier," Matteis said.

Credit Suisse analyst Alethia Young agreed, stating "in this case, it sounds like there were some other factors that may have led to the outcome." But targeting anti-thrombin to increase patients' thrombin levels always presented "a challenging target due to achieving the right dose to balance the cascade," she wrote in a Sept. 7 note.

Acknowledging last year's failure of revusiran, Young pointed out that it and fitusiran both derive from Alnylam's GalNAc technology, but that the latter candidate also employs next-generation enhanced stabilization chemistry to make it a more potent technology. BMO's Kim also contended that the thrombosis event seen with fitusiran seems unlikely to have any connection to problems related to revusiran treatment, because the two drugs address different targets as well as different indications.

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Novo Nordisk Settles US Federal Investigation Of Marketing Practices

STEN STOVALL sten.stovall@informa.com

Novo Nordisk AS has agreed to pay a total of $58.7m to end a US Justice Department investigation of allegedly illegal marketing of the Danish diabetes fighter's top-selling medication Victoza.

The settlement, announced on Sept 5, resolves claims the insulin maker's sales staff had played down the importance of warnings mandated by the FDA about the cancer risks associated with *Victoza* (liraglutide).

The deal resolves seven lawsuits filed under the whistleblower provision of the Federal False Claims Act which permits private parties to file suit on behalf of the United States for false claims and share in a portion of the government's recovery.

NO WRONGDOING ADMITTED

The legal resolution – in which Novo Nordisk did not admit wrongdoing – closes a probe launched in 2011.

The US Justice Department alleged in the complaint that some Novo Nordisk sales representatives gave information to physicians that created the false or misleading impression that the Victoza Risk Evaluation and Mitigation Strategy (REMS)-required message was erroneous, irrelevant, or unimportant.

The settlement "demonstrates the Department of Justice's continued commitment to ensuring that drug manufacturers comply with the law," acting assistant attorney general Chad A. Readler of the Justice Department's Civil Division said in a statement. "When a drug manufacturer fails to share accurate risk information with doctors and patients, it deprives physicians of information vital to medical decision-making."

FINANCIAL DETAILS

Under the settlement terms, Novo Nordisk will pay some $46.5m to the Federal government and to states that reimbursed for Victoza under their Medicaid programs. Novo Nordisk will also pay $12.15m to resolve a complaint filed by the US government on behalf of the FDA in Federal court. "While we do not agree with the US government's legal conclusions and deny any wrongdoing, we're pleased to have negotiated a resolution that allows the company to return its full attention to developing medicines that help improve the lives of patients." said Douglas Langa, Novo Nordisk Inc's president and senior vice president of the group's North America operations.

Asked why the settlement had been reached, a spokesperson for Novo Nordisk told *Scrip*: "Both sides felt this had been going on long enough, and each side wanted an end to the matter."

"For our part, we were looking at an investigation that had been running for six years and if we had not settled now it could have kept running for quite a time. There comes a point when one needs to decide what is the most appropriate form of action, and in this case both Novo Nordisk and the US government decided to end it and allow each to focus on more productive things," the spokesperson said.

FURTHER US LITIGATION

The newly settled litigation is not the only US legal action the Danish drug maker has been dealing with.

Along with peers **Sanofi** and **Eli Lilly**, the company has been the focus of congressional scrutiny on insulin prices. Novo Nordisk also faces a pair of class action lawsuits over insulin pricing.

The Danish insulin maker faces a class action lawsuit filed by a group of investors who say they were misled about the company's earnings forecasts. It's alleged the drug maker - which gets around half its revenue in the US - hid market trouble by colluding with other drug companies to keep the price of insulin artificially high. The lawsuit was filed by Bernstein Litowitz Berger & Grossmann LLP on behalf of the Lehigh County (PA) Employees' Retirement System, but it can include anyone who invested in Novo Nordisk between April 30, 2015 to October 27, 2016.

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Destiny Pharma Floats on UK AIM

The Brighton, UK-based biotech, **Destiny Pharma** listed on the UK junior stock market AIM with an IPO worth £15.3m ($19.8m) in gross proceeds on Sept. 4, and announced on the same day a development and commercialization deal for its investigational products covering China, underlining the significant progress being made by the company.

Destiny Pharma has a potential antibiotic, the dicationic porphyrin molecule, exeporfinium chloride (XF-73), in early clinical studies, and the company is hoping the compound will become the first drug to be specifically labeled in the US for the prevention of post-surgical infection, a market that Destiny estimates could be worth a billion dollars in the US alone.

The proceeds of the IPO will be used to move exeporfinium through a Phase IIb trial in the US over the next two years to prevent post-surgical *Staphylococcus aureus* infections, including methicillin-resistant *S. aureus* (MRSA), whereupon the drug will be Phase III-ready.

The excitement around exeporfinium revolves around the possibility that pathogenic bacteria may find it difficult to develop resistance to the compound, partly because of the way it kills bacteria so quickly.

In five Phase I/IIa clinical trials completed to date, exeporfinium has been shown to have a rapid antibacterial action combined with a no or a low resistance profile, Destiny noted.
The research has attracted interest from a wholly owned subsidiary of **China Medical System Holdings Ltd.** which has entered into a binding framework agreement to develop and commercialize Destiny Pharma's assets in China and certain other Asian countries, excluding Japan. **A&B (HK) Company Ltd.**, a company with a controlling shareholder in common with China Medical System Holdings, invested £3m in Destiny's shares.

john.davis@informa.com 4 Sept 2017

How Relevant Is Traditional Pharma In Sustainable Healthcare?

VIREN MEHTA mehta@mpglobal.com

An ageing society that is fortunate to benefit from an accelerating flow of innovative therapies must be prepared for an ever-increasing nominal healthcare spending. But can healthcare continue to take a larger share of the economy without starving other essential services for a healthy quality of life? This is an especially sensitive question in the 'new normal' average economic environment of low single digit percentage growth, when it is difficult to keep the healthcare cost growth rate at less than twice that. With the US healthcare budget already accounting for a high-teens percentage of GDP, and most other developed nations at least in double digits, it is no small matter.

The outlook is obvious. Unless we redouble our focus on efficiency at every step, the cost:benefit justification will not be sustainable for long. Some biopharma managers are taking the lead, promising to keep price increases of marketed drugs to around the GDP growth rate. This is a good beginning, but increasingly it is the flow of new drugs that is driving spending growth in the US, now accounting for up to half of tota lhealthcare inflation. And the pace of innovation is only accelerating.

Society's mandate for its healthcare system, and for the biopharma managers within it, is to deliver sustainable value that enhances quality of life, not to force repeated compromises and polarizing choices in allocating individual and collective resources.

Here, the entrenched systems and decision processes and the resulting cost structures create a dilemma for the established biopharma players, whose spending on the next generation of rational drug discovery is not much lower than the previous two generations of trial-and-error discovery. This is the opening for the non-industry R&D entrants who do not have the legacy cost structures, nor the mindset to rationalize pricing on inherently high legacy costs, nor the same regulatory burdens. We have talked about these non-industry players' gradual progress before, and are sure to return to new developments on this front.

These efforts by the non-industry entrants is just one facet of a multidimensional shift that is underway. A broad range of new collaborative initiatives seems poised to disrupt the industry structure even further. Consider these recent developments:

- KTH-Royal Institute of Technology in Sweden and three Swedish institutes analyzed the transcriptome of 17 major cancer types and identified 32 potential targets that could be inhibited to slow or kill tumor growth. These organizations bring a majority of skills needed to advance these programs through the clinic.
- IBM Corp. (NYSE:IBM) and diabetes research charity JDRF (New York, N.Y.) partnered to identify risk factors for Type I diabetes in children by applying IBM's machine learning algorithms to data from JDRF research programs. Both have many complementary relationships to take the resulting targets into advanced development.
- Patients For Affordable Drugs called on Novartis to set a "fair price" in advance of the US approval of its chimeric antigen receptor (CAR) T cell therapy to treat pediatric and young adult relapsed or refractory B cell ALL, noting that the US taxpayers "bore costs during the riskiest development phases" of CAR-T science, investing more than $200m "as far back as 1993 when there was no guarantee that the research would be successful." But what if the future breakthroughs reach the patients with minimal biopharma engagement?
- Dentacoin, an Ethereum-based token for the dental industry, seeks to improve dental care by providing a transparent platform for dental care that empowers patients. An increasing number of clinicians in the not too distant future will respond just as today's drivers from ride-hailing apps do by active online engagement and being first to tap and respond to a patient in search of healthcare.

INTERNET OF VALUE WILL FORCE RADICAL CHANGE

The Internet of Value (IoV), as the next frontier of blockchain is being coined, is poised to build on the foundation that Internet of Things (IoT) has wrought, and promises to further transform our lives. The central tenet of IoV is to take the power of transparent information flow beyond secure transactions to find a superior alternative to centralized authorities. Such concentration of power has been essential for responsible functioning of democratic institutions, from banking regulators to the FDA to doctors, and the healthcare industry players in between. Imagine how the above four data points may converge: As with the four Swedish research institutes and the JDRF-IBM collaborations, key resources of biopharma innovation from target identification to clinical development are evolving in settings beyond the biopharma monopoly –which are usually less encumbered by pharma's legacy decision making lethargy and cost structures. In these circumstances, associations such as Patients For Affordable Drugs would no longer need to plead with biopharma for fair pricing, as the interests of the developers would be aligned with those of patients.

If such a disruptive bypassing of entrenched interests seems farfetched, just consider how many industries have been displaced just within this decade, from retailing to transportation. And then fast forward to the Dentacoin model to imagine the regulatory shift ahead. The time is fast approaching when before clinicians provide their services the same way as the Uber and Lyft drivers do today.

The US is especially ripe for this disruption, thanks to the way industry participants successfully leverage market forces from behind their regulatory veil. Few such veils will exist as the internet and blockchain level the playing fields, especially for industries that depend on innovation.

Deeper and integrated therapeutic options are evolving rapidly, and the biopharma industry seems to be short of breath as companies struggle to catch up. Novartis just announced the appointment of a Chief Digital Officer who will report to the CEO; the company's newly announced CEO-designate Vas Narasimhan is a vocal supporter and active deployer of new tools. Most others have yet to elevate this role to the same extent. Given the potential for rapid and radical change across all aspects of healthcare, it is high time they did.

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

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Selected clinical trial developments for the week 1–7 September 2017

LEAD COMPANY/PARTNER	COMPOUND	INDICATION	COMMENTS
Phase III Results Published			
Merck & Co. Inc.	*Gardasil 9*	HPV vaccine	*The Lancet*, Sept. 1, 2017 online.
Merck KGAA	*Mavenclad* (cladribine)	multiple sclerosis	CLARITY Ext; *Multiple Sclerosis Journal*, online Sept. 5, 2017.
Boehringer Ingelheim GMBH	*Spiriva* (tiotropium)	early-stage COPD	NEJM, Sept. 7, 2017.
Symbiomix Therapeutics LLC	*Solosec* (secnidazole)	bacterial vaginosis	Study 301; *American Journal of Obstetrics & Gynecology* online, Sept. 1, 2017.
Updated Phase III Results			
Roche	*Alecensa* (alectinib)	non-small cell lung cancer, ALK-positive	ALEX, ALUR; reduced CNS progression.
Shionogi & Co. Ltd.i/Purdue Pharma LP	*Symproic* (naldemedine)	opioid-associated constipation	COMPOSE I, II, III; patients satisfied.
Bristol-Myers Squibb Co.	*Opdivo* (nivolumab) and *Yervoy* (ipilimumab)	renal cell carcinoma	CheckMate-214; overall survival benefit versus sunitinib.
Nektar Therapeutics	NKTR-181	chronic pain	SUMMIT-07; significant analgesia, few side effects.
Recro Pharma Inc.	iv meloxicam	pain following major surgery	Reduced opioid consumption.
Phase III Interim/Top-line Results			
Novartis AG	*Gilenya* (fingolimod)	pediatric multiple sclerosis	PARADIGMS; met primary endpoint of reduced annualized relapse rate.
Verastem Inc.	duvelisib	chronic lymphocytic leukemia	DUO; met PFS primary endpoint.
Chiesi Farmaceutici SPA	*Trimbow* (beclomethasone, formoterol, glycopyrronium) inhaler	COPD exacerbations	TRIBUTE; showed superiority to *Ultibro*(indacaterol/glycopyrronium) in reducing episodes.
Helsinn Group	NEPA (fosnetupitant/palonosetron) iv	chemotherapy induced nausea and vomiting	New iv formulation, well tolerated, oral already approved in EU and US.
Insmed Inc.	amikacin liposome inhalation suspension	non-tuberculosis mycobacterial lung disease	CONVERT; met primary endpoint.
Circassia Pharmaceuticals PLC/ AstraZeneca PLC	*Duaklir* (aclidinium bromide/formoterol fumarate) inhaler	COPD	AMPLIFY; met co-primary efficacy endpoints.
Intra-Cellular Therapies Inc.	lumateperone	schizophrenia	Switch study; favourable side effect profile.
Phase III Announced			
Roche/Exelixis Inc.	*Cotellic* (cobimetinib) plus atezolizumab	melanoma	IMspire 170; in BRAF V600 wild type disease.

Source: Biomedtracker

Bicycle Partners With Biogen Spinout Against Rare Blood Disorders

LUCIE ELLIS lucie.ellis@informa.com

Bicycle Therapeutics Ltd. has signed a deal with US biotech **Bioverativ Inc.**, a spinout from **Biogen Inc.**, worth more than $420m in upfront and milestone payments; the pair will develop and commercialize innovative therapies for hemophilia and sickle cell disease.

Through the collaboration the companies will identify and develop so-called "Bicycles" to treat rare blood disorders. Bicycles are a new therapeutic modality that combine attributes of antibodies, small molecules and peptides within one molecule, enabling high selectivity and affinity while also being able to penetrate and bind to the targets of interest within the body.

Bicycle Therapeutics will be responsible for leading initial discovery activities through lead optimization to candidate selection for two programs. The UK-based biotech will receive an upfront payment worth $10m and near-term R&D funding of $4.2m from Bioverativ. Bicycle is also eligible to receive up to $410m related to development, regulatory and commercialization milestones for products planned under the two programs, as well as tiered single to low double-digit royalties related to product sales.

Bioverativ, a publicly traded biotech formed by Biogen to house its hemophilia portfolio, will lead preclinical and clinical development for the drug candidates, as well as subsequent marketing and commercialization activities.

'This collaboration offers a unique opportunity to identify an entirely new therapeutic modality'

"This collaboration offers a unique opportunity to identify an entirely new therapeutic modality that may lead to meaningful new treatments and outcomes for people living with hemophilia and sickle cell disease," Tim Harris, Bioverativ's executive vice president of R&D, said in a statement.

BIOGEN BLOOD DISEASE LEGACY

Bioverativ is focused on the development of new treatments for patients with hemophilia and other rare blood disorders. The company already has several preclinical assets in its pipeline for blood and coagulation conditions, including genome editing treatments for beta thalassemia and sickle disease, and gene therapies for hemophilia A and B.

The Waltham, Massachusetts-based biotech's most advanced clinical candidate, BIVV009, is a biological therapy for cold agglutinin disease, an autoimmune disease characterized by the presence of high concentrations of circulating antibodies, usually IgM, directed against red blood cells. BIVV009, formally known as TNT009, was acquired by Bioverativ when the company bought out True North Therapeutics in May 2017. The therapy, a humanized antibody and the only product in development for cold agglutinin disease, is currently in Phase I studies.

Meanwhile, Bioverativ's marketed therapies are the former Biogen drugs *Aprolix* (recombinant Factor IX), which is approved for hemophilia B, and *Eloctate* (recombinant Factor VIII), which is used for the treatment of hemophilia A.

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APPOINTMENTS

Oxeia Biopharmaceuticals Inc. has appointed ***Michael Wyand*** CEO and to its board of directors. Most recently, Wyand was president and chief operating officer of Epirus Biopharmaceuticals Inc. and before this, he was head of R&D at Percivia, a joint venture between Johnson & Johnson and DSM.

biOasis Technologies Inc. has appointed ***John H. Krystal***, ***Jeffrey L. Cummings***, and ***John P. Wikswo, Jr.***, to its newly established scientific advisory board. Krystal is the professor of translational research, chair of the department of psychiatry, and professor of neuroscience at the Yale University School of Medicine and chief of psychiatry at Yale-New Haven Hospital. Cummings is director of the Cleveland Clinic Lou Ruvo Center for brain health in Las Vegas and Cleveland, the Camille and Larry Ruvo chair of the Neurological Institute of Cleveland Clinic and professor of medicine (neurology) at the Cleveland Clinic Lerner College of Medicine of Case Western Reserve University. Wikswo is the Gordon A. Cain University professor at Vanderbilt University and founding director of the Vanderbilt Institute for Integrative Biosystems Research and Education.

Galderma SA, a company focused on skin health, has appointed ***Chris Chapman*** vice president and general manager of its prescription business in the US. Chapman joined Galderma in 2015; previously, he was vice president of strategic access for the company's prescription business unit.

John Fowler has been named **Piramal Pharma Solutions**' chief operating officer. Most recently, Fowler was divisional CEO of the global fine chemicals business at Johnson Matthey and before this, he held senior leadership roles in various other business verticals at Johnson Matthey.

Horizon Pharma Plc. has named ***Irina Konstantinovsky*** executive vice president, chief human resources officer. Konstantinovsky joins Horizon from Baxter International Inc. and before this, she spent 15 years in senior partner and director roles at a human resources consulting firm, Towers Watson (now Willis Towers Watson).

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