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Novartis Goes Big On Gene Therapy With $8.7bn AveXis Acquisition

KEVIN GROGAN kevin.grogan@informa.com

Novartis AG has already started spending the $13bn proceeds from the sale of its stake in the **GlaxoSmithKline PLC** consumer joint venture, splashing $8.7bn on **AveXis Inc.** and making a huge stride into expanding its presence in gene therapy.

The Swiss major is paying $218 per share for US-based Nasdaq-listed AveXis, which represents a whopping 88% premium on the latter's closing stock price on April 6 and up 72% on its average price over the last 30 days. The initial driver behind the deal is AveXis' lead gene therapy candidate AVXS-101, which has already generated highly compelling clinical data in treating spinal muscular atrophy (SMA) type 1, according to Novartis CEO Vas Narasimhan.

Speaking on a conference call to unveil the acquisition, Narasimhan noted that SMA type 1 was the number one genetic cause of death in infants, and nine out of ten do not live to their second birthday or are permanently dependent on ventilators. He stated that the proposed acquisition of AveXis "offers an extraordinary opportunity to transform the care of SMA," thanks to AVXS-101 and its potential to be a first-in-class one-time therapy that addresses the root genetic cause of SMA, replacing the defective SMN1 gene.

His enthusiasm is based on a study where all 15 infants treated with AVXS-101 were event-free at 20 months compared with an event-free survival rate of 8% in an historical cohort. AveXis will present two-year data to the American Academy of Neurology meeting in Los Angeles later this month.

Novartis believes that AVXS-101 is a potential cure and Vincent Meunier, an analyst at Morgan Stanley, issued a note saying it represents "a multi-billion dollar opportunity." The FDA has granted the candidate both orphan drug and breakthrough therapy designation for SMA type 1 (it also has PRIME status in Europe and Sakigake designation in Japan), and the "impressive early data explain the ability of AveXis to file on the back of a small 15-patient, Phase I trial," Meunier wrote. A US filing is planned for the second half of 2018 with a European submission scheduled for the first half of next year. AVXS-101 is also being investigated for SMA type 2 in the STRONG trial.

The cost and burden to the US healthcare system of AVXS-101 represent the main obstacles to its success in the future, Meunier said in the investor note. The wholesale price tag of **Spark Therapeutics Inc.**'s gene therapy *Luxturna* (voretigene neparvovec) for a rare eye disorder (to which Novartis has the commercial rights outside the US) is $850,000 per patient and "we would expect a similar or higher price for AVXS-101."

He added that SMA (all types) affects one in 6,000-10,000 newborns, of which around 60% are type 1 and 27% are type 2. This represent an incidence of 250-400 new patients with SMA type 1 in the US every year, "a very small population suggesting the need for a very high price. While rare disease have usually commanded high prices and relatively low pushbacks from payors, this situation could evolve over time as gene therapies become increasingly available."

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from the executive editor

maryjo.laffler@informa.com

Is faster better? Companies can try to speed everything from modeling to manufacturing and review, but clinical trials take time.

Sometimes going too fast can backfire. Just a year ago, the IDO1 class was looking like an ideal partner for PD-1/L1 inhibitors. Sponsors moved fast and furious to accelerate development – Merck & Co. and BMS both jumped from Phase I into a wide range of Phase III trials with Incyte's epacadostat. Then, on April 6, Merck and Incyte announced that Keytruda plus epacadostat failed against Keytruda monotherapy in the Phase III ECHO-201/KEYNOTE-252 study. Execs had been downplaying expectations, and Roche and Pfizer had already walked away from partnerships. Now NewLink is reviewing its development plans and Incyte's stock is half what it was after ASCO 2017 (see p7).

But sometimes the market can pass you by. The CETP inhibitor class seems to be one where it will be hard to win regardless of trial results. With the steady downward pull of failures for Pfizer's torcetrapib, Roche's dalcetrapib and Lilly's evacetrapib, by the time Merck delivered a stunning success with anacetrapib, the changing commercial landscape led Merck to walk away. For a smaller company, the pursuit might still be worthwhile. DalCor is developing dalcetrapib for a genetically defined subgroup and on April 5 announced it was expanding enrollment in its dal-GenE Phase III outcomes trial, strengthening the power of the trial.

So, persistence doesn't always pay off and moving quickly can backfire. Timing may be everything, but it's hard to get right.

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Phil Jarvis, Mike Ward

SUBSCRIPTIONS
Daniel Frere

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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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TO ADVERTISE, CONTACT
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Former Kite exec David Chang is keen to use smaller firm's focus to advance allogeneic therapy more rapidly. The start-up acquired Pfizer R&D team along with its allogeneic CAR-T programs and related IP.

IPO Update: Will Declining Returns Slow Fast Pace Of Biopharma Offerings?
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Offerings by Homology, Unum and Genprex at the end of March brought the first quarter's biopharma IPO total to 14 in the US, putting 2018 on track to beat the 2017 total of 42. But with the average return for this year's IPOs dropping, the pace of offerings could slow.

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Small German firm, Vasopharm, wants to be the first company to bring a therapeutic treatment to the European market for use in patients with traumatic brain injuries – but getting the drug through Phase III studies alone will be its biggest test yet.

Deal Watch: Allogene Gets Pfizer's Off-The-Shelf CAR-T Program, $300m Series A Backing
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Celgene reworks its collaboration with Abide, dropping its buyout option. Roivant gains Chinese rights to anti-infective lemafulin and adds a fifth candidate to Dermavant's pipeline, while pSivida acquires Icon and FDA-approved Dexycu for cataract surgery inflammation.

Finance Watch: Hua Medicine Raises $117.4m While Evaluating A Hong Kong IPO
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Hua, already considering an IPO in Hong Kong for up to $400m, closed concurrent VC rounds that will fund its late-stage diabetes program in China, but it may still need to go public to enter other markets. Also, Heron raised cash for its next commercial product, among other public company financings.

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Shire's Suitors: Takeda, Pfizer Seen As Likely To Bid; Amgen Could Enter Fray

JOSEPH HAAS joseph.haas@informa.com

While expectations are growing that **Takeda Pharmaceutical Co. Ltd.** will formally bid to acquire **Shire PLC**, market analysts are feverishly modeling all the options, and in addition to increasing odds for mega-merger specialist **Pfizer Inc.**, at least one analyst is making a solid case for **Amgen Inc.** to buy out the Irish specialty pharma.

Takeda revealed on March 28 that it was considering making an offer to acquire Shire, setting in motion a process under UK law that would require it to make a formal bid by April 25 or state that it was not making such an offer. But with Shire's position as a worldwide leader in rare disease therapies, speculation began that Takeda's announcement could prompt interest from other big pharma players such as Pfizer and **AbbVie Inc.**

As estimates of the buyout's cost have ranged up to $70bn – an amount that would require Takeda to take on significant debt and/or structure the deal with substantial equity going to Shire shareholders – the possibility was viewed as outside of the Tokyo firm's standard business development practices. Takeda CEO Christophe Weber applies strict criteria to potential acquisition deals, including that they must not negatively impact the pharma's credit rating or alter its dividend policy.

On April 5, however, Weber conducted a discussion limited to a handful of market analysts – and made off limits to news media – to update the situation. Deutsche Bank analyst Joseph Cairnes said that while no new details emerged, again, in keeping with UK M&A law, the briefing suggested that Takeda is growing more positive about the idea of bidding for Shire.

"In our view, the likelihood of a bid for the whole of Shire PLC emerging by the April 25 deadline has increased," Cairnes wrote in an April 5 note. It's likely he stressed "the whole of Shire" because the specialty firm has taken steps to begin assessing its performance as if the company were split into two units: rare diseases and neuroscience. CEO Flemming Ornskov said Shire would begin reporting on the business performance of the two potential units as of its first quarter earnings call and would reveal later this year whether it plans to seek a sell-off of the neuroscience business.

Cairnes said Takeda reaffirmed its commitment to its existing dividend and maintaining its investment rating, which could necessitate a creative structure to acquire Shire. This might include issuing new common shares of stock in Japan or making a cash-plus-shares offer for Shire, he said. Without question, though, Takeda would need to make additional moves after purchasing Shire to reduce its debt-to-earnings ratio, the analyst pointed out, such as divestiture of some of Shire's business.

"We see potential for divesting what Takeda deems non-core Shire assets after any acquisition," Cairnes said. "We would not expect these to include GI, oncology, CNS or rare disease assets."

TAKEDA WOULD GAIN MUCH

Morningstar analyst Karen Andersen said in a March 29 analysis that Takeda buying Shire would make sense due to a perceived low valuation for Shire and R&D synergy, with both companies building up presence in Cambridge, Mass. That view hasn't changed much, Andersen told *Scrip* on April 6.

"Takeda is indicating that they're pretty committed to the deal, and they have a lot to gain – the company has seen recent strong earnings growth but from a very low base, and it needs a solid, diversified portfolio of drugs in its focus areas," she said. "Shire (immunology, GI, hematology, neurology) fits the bill, and I think its neurology portfolio (*Vyvanse* and *Intuniv*) could have better success with Japan launches in the hands of Takeda." *Intuniv* (guanfacine) was introduced in Japan in 2017, with launch of Vyvanse (lisdexamfetamine) slated for this year.

Pfizer, openly on the lookout for a large, potentially transformative acquisition, continues to appear as a logical suitor for Shire, Andersen added.

In addition to its rare disease portfolio and pipeline, Shire also would give Pfizer a leg up in the hemophilia space. The US pharma's two-drug hemophilia franchise – *BeneFIX* (coagulation factor IX recombinant) for hemophilia A and *Refacto AF/Xyntha* (antihemophilic factor recombinant) for hemophilia B – brings in blockbuster annual revenue, albeit on the decline. BeneFIX totaled $604m in global sales in 2017, down 15% from 2016, while Refacto brought in $551m, down 1% year-over-year.

"I think Pfizer is another obvious suitor – there is consensus that Pfizer has both the ability and the need to do a big deal, and it has shown a commitment to its hemophilia portfolio (originally bought with **Wyeth**) through recent deals in gene therapy with **Spark Therapeutics Inc.** and **Sangamo Therapeutics Inc.**," the analyst said. "Acquiring Shire would make them an instant – and perhaps sustainable – leader in hemophilia. We also think Shire's rare disease and immunology portfolios would be a good fit, and are underappreciated by investors."

Pfizer signed a collaboration with Spark in 2014 to develop a gene therapy for hemophilia B, and then partnered with Sangamo on its gene therapy programs for hemophilia, including lead candidate SB525, last May. Hemophilia remains a highly competitive sector, especially as gene therapies advance, and **Sanofi** scooped up **Bioverativ Inc.** for $11.6bn this past January to bolster its pipeline and portfolio.

IF THINKING BIG, AMGEN

Big biotech Amgen has been deemed both a mega-merger acquisition target and a potential buyer, and could emerge as a "white knight" for Shire, Credit Suisse analyst Alethia Young asserted in an April 6 note. While Shire would not add to Amgen's current portfolio/pipeline areas of cardiovascular medicine, bone health and biosimilars, combining the two companies would bolster Amgen's oncology/hematology, neuroscience, nephrology, inflammation and genetic disease offerings, she said. Like Takeda, however, Amgen would need quite a bit of financial help to pull off the deal, Young noted, as it has about $35bn in cash and Shire's enterprise value is estimated at about $59bn presently. Outside the parameters of a typical Amgen deal, she

thinks the big biotech has the ability and incentive to make a buyout of Shire happen.

"We would also view a deal like this positively since it would bring a portfolio of assets under the Amgen umbrella," Young said. She noted that Amgen normally pursues acquisition targets with market capitalization in the $10bn-$15bn range and that offer a centerpiece asset such as *Blincyto* (blinatumomab) or *Kyprolis* (carfilzomib) or the additional of technical capacity, such as **deCode genetics EHF**.

Amgen enhanced its genetic therapies capabilities with the $415m purchase of Decode in 2012, while it picked up leukemia drug blinatumomab in a $1bn buyout of **Micromet Inc.** earlier that year. In 2013, Amgen paid $9.2bn for **Onyx Pharmaceuticals Inc.** and its myeloma drug Kyprolis.

From both bottom-line and top-line revenue perspectives, acquiring Shire would benefit Amgen very quickly and then over time, Young predicts. She projects that buying Shire would be about 30% accretive to Amgen's bottom line in 2019 and roughly 40% accretive in 2022. This assumes a deal in which Amgen would pay a 25% premium for Shire and derive only modest synergies from the transaction – about 10% savings in sales, general and administrative costs, and none in R&D or revenue. From 2019-2022, Amgen's compound annual growth rate with Shire's business factored in would be about 3%, Young projects, while the biotech's CAGR would be 2% over that period without the acquisition.

Morningstar's Andersen, however, does not view Amgen/Shire as an ideal match. "They [Amgen] are already stretched across multiple therapeutic areas (oncology, cardiology, bone health, neurology), and they need depth within these areas, not a portfolio that brings new focus areas," she said.

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Teva On Tenterhooks Over Fremanezumab As Celltrion Gets CRLs

KEVIN GROGAN kevin.grogan@informa.com

The nail-biting at **Teva Pharmaceutical Industries Ltd.** over whether its investigational migraine drug fremanezumab will get US approval by the summer is going to continue for a while as the manufacturing problems at partner **Celltrion Inc.**'s facility where the active ingredient is made have come to a head.

The trouble started in January when the FDA issued a warning letter to Celltrion citing an extensive number of GMP violations with many of the problems stemming from relaxed contamination controls. Now Teva has confirmed that its partner has received complete response letters (CLRs) from the FDA regarding two Biologics License Applications for two biosimilars the companies are seeking approval for - CT-P6 (trastuzumab) and CT-P10 (rituximab), versions of **Roche**'s *Herceptin* and *Rituxan*, respectively.

A Teva spokesperson told *Scrip* that the company and its South Korea-headquartered partner are actively reviewing the contents of the CRLs, adding that the firm "will continue to work closely with Celltrion with the goal of bringing the proposed trastuzumab and rituximab biosimilars to market in the US."

Analysts at Credit Suisse issued a note on April 3 saying that the CRLs were expected following the warning letter but it is still "somewhat disappointing given the emphasis Teva has placed on biosimilars and more complex generics for their recovery going forward." However, perhaps of more concern is how the CRL will affect the possible approval of fremanezumab.

Celltrion is the sole source for active ingredient manufacturing for fremanezumab, and while the FDA warning letter specifically referred to the fill/finish part of the facility, some observers are worried that many of the observations cited in the letter, particularly around the way Celltrion gathered data, could possibly be applied to the whole plant, including the manufacturing part.

The Credit Suisse team seem to think so, saying despite the priority review voucher (PRV) that Teva used as part of the filing for fremanezumab, "we assume the manufacturing issues Celltrion is dealing with will also lead to a delay in the product's approval." Using the PRV bought for $150m from an unnamed company in August 2017 means that the anti-calcitonin gene-related peptide (CGRP) monoclonal antibody has a Prescription Drug User Fee Act (PDUFA) date of June 16.

PharmaVitae analyst Oliver Spray is not so sure Teva will be badly hit, telling *Scrip* that he does not believe that the CRL will significantly delay the approval of fremanezumab. He stressed that the warning letter relates to the section of Celltrion's facility that concerns finished pharmaceutical manufacturing and not fremanezumab's API and "even if the approval were delayed, resolution of warning letters such as these typically takes between six-18 months from the point of issue, ie January. These means the issues may be resolved by the PDUFA approval date."

Spray acknowledged that if the FDA does conclude that the whole Celltrion site be considered under the CRL, it would have "significant ramifications for Teva," as a delayed approval could mean fremanezumab loses ground to **Amgen Inc.** and **Novartis AG** rival CGRP drug *Aimovig* (erenumab). The latter has an FDA action date of May 17, while the agency will decide on a third CGRP inhibitor – **Eli Lilly & Co.**'s galcanezumab - by October 24.

Having Celltrion as the sole supplier for fremanezumab is clearly a problem and while Teva CEO Kåre Schultz said on a fourth-quarter earnings call in February that the company was exploring the option of a second source to supply the active ingredient, finding another manufacturer is going to take quite a while.

The Credit Suisse analysts now assume that fremanezumab will get US approval in the first half of 2019, bringing in sales of $1.1bn by 2026. The drug, which was filed for approval in Europe last month, is key to Teva's efforts to prosper at a time when its generics business is facing serious challenges due to pricing pressure in the US and the launch by **Mylan NV** across the Atlantic of the first generic version of a 40mg dose of the Israeli group's multiple sclerosis blockbuster *Copaxone* (glatiramer).

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Biogen's SMA Ambitions Run Up Against A New Deep-Pocketed Rival

JESSICA MERRILL jessica.merrill@informa.com

After **Novartis AG** announced plans to buy the gene therapy developer **AveXis Inc.** on April 9 for $8.7bn, some Biogen investors were left wondering if Biogen shouldn't have been the acquirer instead. Now, Biogen will likely face a deep-pocked big pharma rival in the rare disease market it has dominated since the launch of *Spinraza* (nusinersen) in late 2016.

Spinraza has morphed into a more pivotal product to Biogen than many investors predicted, particularly as the big biotech's multiple sclerosis franchise matures. Spinraza generated $884m in 2017, a notably successful launch for a drug that targets an ultra-rare neurodegenerative disease. Analysts are forecasting blockbuster level sales for Spinraza in 2018 and beyond.

AveXis is developing a gene therapy for SMA that Novartis believes could be a single, one-time treatment for some patients with the inherited disease, which is caused by a single defective gene, the survival motor neuron (SMN1). Novartis highlighted AVXS-101 in a same-day conference call with management calling the treatment a potential cure based on the results of a small study in 15 infants.

The launch of a promising gene therapy that addresses the root cause of SMA could curb sales of Spinraza, which works as a chronic therapy. Spinraza is an antisense oligonucleotide, developed with **Ionis Pharmaceuticals Inc.**, that splices the SMN2 RNA to make full-length, functional SMN protein, essentially delivering the missing protein. Spinraza has a broad label for the treatment of children and adults, and it has demonstrated efficacy in patients with late-onset SMA as well as in infants and children.

SMA spans four types, varying in disease severity. Type 1 SMA is the deadly form that affects babies, while Type 2 is still severe, fatal for many patients before the age of 25. Type 3 and 4 are considered less deadly but progressively debilitating.

AVXS-101 is being studied in patients with Type 1 and Type 2 SMA. Novartis has a near-term timetable for launching AVXS-101 in the US; a BLA filing with the FDA is expected in the second half of 2018 with approval and launch expected in 2019, CEO Vas Narasimhan said during an April 9 conference call.

Biogen is working on its own gene therapy for SMA, revealing at the J.P. Morgan Healthcare Conference in January that it plans to move the product into the clinic in mid-2018, though it hasn't revealed much in the way of details about the product. The company announced another collaboration with Ionis in December to identify new antisense oligonucleotide drug candidates for the treatment of SMA.

Barclays analyst Geoff Meacham questioned why Biogen wasn't the acquirer of AveXis in a same-day research note. "We see this as a negative for Biogen, as acquiring a gene therapy approach for SMA could help protect and expand its growing franchise, anchored by Spinraza," he said. "We think Biogen missed an opportunity to capture a significant portion of the market by not acquiring AveXis."

Biogen has the financial capacity to make an acquisition of this size acquisition, he added. Biogen's Chief Financial Officer Jeffrey Capello has talked about the company's capacity to leverage up to $37bn in cash if needed, including some $7bn in cash on the balance sheet at the end of 2017.

Novartis paid a handsome premium for AveXis, however. Bernstein analyst Ronny Gal hypothesized that Biogen is unlikely to counter offer, not because of the cost, but because of antitrust issues.

"This increases pressure on Biogen's Spinraza. The acquisition puts the competing SMA program in the hands of a well-funded, payer-competent, global-reaching company," he said. Nonetheless, he acknowledged Novartis still faces some hurdles with the program, including addressing the duration of vector activity.

Credit Suisse analyst Alethia Young was more positive on the outlook for Spinraza and Biogen. "We think that Biogen still has a solid commercial strategy in SMA even with a large company like Novartis acquiring AveXis," she said.

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CONTINUED FROM COVER

As to whether Novartis has paid too much, Meunier acknowledged that "the valuation appears rich but allows Novartis to strengthen its pharma business with an innovative gene therapy platform." Indeed, there is more to AveXis than AVXS-1 and SMA.

It also has several ongoing gene therapy projects, based on AAV9 technology, which Novartis notes has been shown to efficiently cross the blood-brain barrier, making it "an attractive vehicle for CNS diseases". The most advanced drug candidates based on AAV9 are for Rett Syndrome – AVXS-201 – and AVXS-301 for a genetic form of amyotrophic lateral sclerosis (ALS) caused by mutations in the superoxide dismutase 1 gene; both projects are expected to be in the clinic by the end of this year or early 2019.

Novartis also has early gene therapy projects ongoing such as CGF166, in Phase Ib trials for hearing loss, and CPK850, also in Phase Ib for retinitis pigmentosa. Narasimhan made much on the conference call about how the company's pipeline will benefit from AveXis gene therapy manufacturing facility in Libertyville, Illinois, which Novartis noted is "capable of meeting patient demand post-approval," and additional facilities are planned.

PharmaVitae analyst Oliver Spray told *Scrip* that the substantial premium paid by Novartis "follows a recent trend in big pharma whereby companies are deploying vast sums of capital to gain rights to new technologies that have dramatically improved treatment outcomes." He added that AveXis' "highly-touted AVXS-101 is set to enter a market that lacks effective therapies and as such is anticipated to be accompanied with an expensive price tag," which will drive "multi-billion dollar annual sales allowing Novartis to eventually cover the costs of the deal."

Noting that Novartis was in a strong financial position to make this deal following the GSK deal last month, Spray added that its expertise in gene therapies would help the company add value to AveXis' portfolio. As well as the Luxturna pact with Spark, the Swiss major "has also gained valuable experience after collaborating with health professionals and patients while promoting the first gene therapy for blood cancers", its chimeric antigen receptor (CAR) T-cell therapy *Kymriah* (tisagenlecleucel), which gained US approval in August 2017 for pediatric acute lymphoblastic leukemia.

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Incyte/Merck's IDO Failure Casts More Shadow

EMILY HAYES emily.hayes@informa.com

The Phase III failure of the combination of **Incyte Corp.**'s IDO inhibitor epacadostat and **Merck & Co. Inc.**'s *Keytruda* in melanoma represents another knock on the new immuno-oncology class, raising uncertainty about prospects for other IDO candidates in development.

Epacadostat is the most advanced inhibitor of indoleamine 2,3-dioxygenase 1 (IDO1), an enzyme on the tumor microenvironment that plays an important role in immune response. **Bristol-Myers Squibb Co.** and Merck moved fast into Phase III studies with combinations of epacadostat with their PD-1 inhibitors – *Opdivo* (nivolumab) and Keytruda (pembrolizumab), respectively – in multiple tumor types, while developing their own earlier-stage IDO inhibitors.

However, Incyte and Merck announced April 6 that the combination of Keytruda and epacadostat failed to improve the primary endpoint of progression-free survival (PFS) and was unlikely to meet the coprimary endpoint of overall survival (OS) against Keytruda monotherapy in the Phase III ECHO-201/KEYNOTE-252 study of 700 patients with metastatic melanoma, according to an external data monitoring committee.

The announcement casts doubt on the space generally, including other epacadostat/PD-1 combination studies and in-house assets. It is the latest in a string of setbacks for the IDO class, which analysts have started to write off. **Roche** walked out on a development deal for the IDO inhibitor navoximod (GDC-0919) with **NewLink Genetics Corp.** in June 2017. This January, **Pfizer Inc.** handed back worldwide rights to EOS200271, an IDO1 inhibitor licensed from **iTeos Therapeutics SA**, after the candidate failed as a monotherapy in glioblastoma.

Other big tests are coming up. Bristol started a Phase III study of their IDO inhibitor BMS-986205, an asset gained through its buyout of **Flexus Biosciences Inc.** in 2015, with Opdivo in previously untreated metastatic melanoma in late November 2017. And NewLink started a Phase III study of its IDO pathway inhibitor indoximod with Keytruda or Opdivo at the end of December.

NewLink said in an April 6 statement that it is reviewing development plans for its IDO pathway inhibitor indoximod and NLG802, which is in Phase I. "This morning's announcement by Incyte and Merck on the ECHO-301 trial for patients with advanced melanoma is a disappointing result for the IDO field. Indoximod, NewLink Genetics' IDO pathway inhibitor, has a differentiated mechanism of action (MOA) which may demonstrate clinical benefit for patients where direct enzymatic inhibitors have not. In light of Incyte's announcement, however, NewLink is undertaking a review of its clinical programs and will provide an update when it is completed," the company said.

SEEKING ANSWERS

In the ECHO-301 study, the hazard ratio for the PFS result was 1.00 with a confidence interval of 0.83 to 1. In the survival analysis, which was less mature, the hazard ratio was 1.13 with a confidence interval of 0.86 to 1.49. Safety was consistent with previously reported data for the combination. Based on these findings, and at the recommendation of the external data monitoring committee, the study will be stopped, the partners said.

The study included an extensive biomarker panel and an analyses of biomarkers will be released between now and the end of the year, including the impact of tumor mutation burden and PD-L1-expression status.

"For epacadostat in melanoma, the next step is to analyze the data in detail to understand if there are any differences in the benefits observed within subgroups," Incyte CEO Hervé Hoppenot said during an April 6 investor call. The results will be presented at an upcoming medical meeting.

Hoppenot said that that the ECHO-301 results are obviously disappointing and have negative implications for the probability of success of other studies combining epacadostat with PD-1 inhibitors. Aside from the melanoma study just reported, eight other industry sponsored Phase III studies are ongoing with Merck's Keytruda or Bristol's Opdivo with epacadostat in metastatic lung cancer, renal cancer, bladder and head and neck cancer.

The biomarker analyses from the melanoma study will inform Merck and Incyte as to whether changes need to be made to ongoing studies, Hoppenot said. "Whether the results from ECHO-301 have any readthrough to other IDO1-based combinations beyond PD-1 remains an open question. We do intend to continue to investigate the potential of epacadostat in these settings, where preclinical or translational data are compelling," Hoppenot said.

Most of the combination studies have enrolled between 30 and 50 patients so there is "more than adequate time to do any modifications as may be needed," Incyte Chief Medical Officer Steven Stein said.

However, "even with reduced or no expectation for epacadostat, we are on a great trajectory toward becoming a fast-growing, innovative and profitable biopharmaceutical company," Hoppenot maintained. The CEO said that the strength of Incyte in 2018 will come from revenue growth of existing commercial products *Jakafi* (ruxolitinib) and *Iclusig* (ponatinib), plus royalties from Jakafi and *Olumiant* (baricitinib), a portfolio of near-term launches, and optionality in its early-stage portfolio.

RISE AND FALL OF IDO

Excitement around IDO as a mechanism to enhance performance of PD-1/L1 inhibitors safety reached a peak around the time of the American Society of Clinical Oncology annual meeting in June 2017 – when Incyte's stock was trading in the $130 range.

On Feb. 21, Incyte stock was trading at about $86 and on April 6 it closed down 22.93% to $64.02.

BMO Capital Markets analyst Alex Arfaei commented in an April 6 note that many investors were becoming skeptical about the melanoma study of epacadostat. "Our conversation with [Pfizer] management also indicated that it was not particularly bullish about the incremental benefit of IDO. Even the recent tone from [Merck]'s management was not particularly bullish about IDO," Arfaei said.

Keytruda monotherapy is likely to remain an attractive option in melanoma, which is expected to account for 15% of the $7bn forecast for Keytruda in 2018, Arfaei said.

Bernstein analyst Tim Anderson said in an April 6 note that "the writing seemed to be on the wall that this combination would not work, and that IDO in general remains a questionable target."

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Ferring Leapfrogs Into Late-Stage Microbiome Race With Rebiotix Buy

JESSICA MERRILL jessica.merrill@informa.com

Ferring Pharmaceuticals AS is taking a big leap into the forefront of the microbiome drug development space with the proposed acquisition of **Rebiotix Inc.**. The Swiss specialty pharma announced plans to buy Roseville, Minn.-based Rebiotix April 5 for an undisclosed sum, gaining a Phase III treatment for recurrent *Clostridium difficile* infection (CDI) that is a contender to be the first approved human microbiome product.

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Rebiotix's RBX2660 is in Phase III testing for the prevention of recurrent CDI, and the company also has a pipeline of early drugs in development coming out of its Microbiota Restoration Therapy (MRT) platform.

"We have a long-term view on the microbiome as the next frontier in life sciences where we want to play a part," Ferring Chief Scientific Officer Per Falk said in an interview. "Rebiotix is one of the leading – if not the leading – microbiome company today with the furthest progressed product offering that could be the first approved microbiome product in history."

Ferring has been investing in microbiome-based research for the past three years through a series of early collaborations including with the Karolinska Institute, Science for Life Laboratory, the Centre for Translational Microbiome Research, Intralytix and others. Falk has talked to *Scrip* before about Ferring's interest in the emerging field of microbiome research, and his view the field will develop slowly because of the complexity of the human microbiome.

Even now that Ferring is poised to acquire a late-stage microbiome-based drug, Falk told *Scrip* the Rebiotix acquisition is about more than the single near-term commercial opportunity.

"We are very intrigued by RBX2660 as it could be the first microbiome product on the market, addressing a huge medical need, but as an acquisition we really see it as a long-term R&D platform acquisition, where we use the front-runner product as a first step into the market," he said. "We can then build experience, build a presence, learn and improve that therapy and eventually bring other therapies as well."

Rebiotix CEO Lee Jones said the company had been seeking a partner as it approached the commercialization of RBX2660 and was impressed by Ferring's interest in the microbiome.

"There is a lot of industry talk about the microbiome and I see a lot of pharmaceutical companies interested but far and away Ferring was the most invested and the most knowledgeable," she said. Indeed, several drug makers are exploring the microbiome as a new frontier for drug development including some big pharmas like **Johnson & Johnson**, but there remains a lot of uncertainty about how and when microbiome based drugs will become a reality.

A RACE TO BE FIRST TO MARKET

RBX2660 is a product that builds on the success of basic fecal transplants to prevent recurrent CDI, only the product is a refined standardized collection of human organisms delivered via an enema. Other drug developers are also competing in this space, including Cambridge, Mass.-based **Seres Therapeutics Inc.**, which is also vying to be first to market with a microbiome-based drug. The company started a Phase III trial for SER-109, a consortium of bacterial spores from human donors, in the middle of 2017.

Ferring and Rebiotix believe RBX2660 may have an advantage over the competition because it is made from a broad consortium of microbiota, including both spore and non-spore forming organisms.

"I think that really differentiates us from the competition," Jones said. "Most of the other groups in clinical studies have tried to narrow the number of microbes and the types of microbes. We believe our product has demonstrated efficacy because of its diversity."

The product demonstrated efficacy in repeated Phase II studies. Rebiotix reported data from an open-label Phase II trial in 2017, showing that RBX2660 exhibited a treatment success rate of 78.8% in preventing CDI recurrence versus a historical control rate of 51.8%. The company is also working to develop a non-frozen lyophilized oral formulation of the product.

RBX2660 has received FDA fast track, breakthrough therapy and orphan drug designations, so it could be eligible for an expedited review.

Falk said Ferring is interested in exploring the Rebiotix platform in the areas in which it currently is focused, including gastroenterology and women's health. Rebiotix has early physician-sponsored clinical trials ongoing in pediatric ulcerative colitis and multi-resistant urinary tract infection.

"I see great opportunities for the microbiome in the fertility and obstetrics space," Falk said, pointing to areas like infertility, endometriosis and preeclampsia. "All of those are really key to Ferring going forward."

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AstraZeneca's License Of Ionis NASH Candidate Illustrates Still Hot Competition

JOSEPH HAAS joseph.haas@informa.com

Heading into the International Liver Congress, deal-making began to heat up again in the frenzied non-alcoholic steatohepatitis space, as **AstraZeneca PLC** in-licensed a candidate from **Ionis Pharmaceuticals Inc.** on April 9 under the two companies' R&D collaboration. A few days prior, **Eli Lilly & Co.** out-licensed its three NASH candidates to **Terns Pharmaceuticals Inc.**, a start-up Lilly's Asian venture arm funded just a year earlier.

AstraZeneca's pick up of IONIS-AZ6-2.5-L RX, to be known going forward as AZD2693, makes it the eleventh big or specialty pharma company to enter the NASH clinical development race. As it off-loaded assets to Terns, Lilly indicated an intent to remain involved in the space through its clinical development work in diabetes, a co-morbidity of NASH and its predecessor, non-alcoholic fatty liver disease (NAFLD).

CROWDED AREA

With the European Association for the Study of the Liver's annual meeting set to convene in Paris April 11-15, Biomedtracker shows 60 drug candidates in clinical development for NASH, including investigator-initiated programs. Sessions at the conference will consider the benefits and risks of targeting nuclear receptor pathways in NASH, an approach that encompasses Phase III drugs from **Intercept Pharmaceuticals Inc.** and **Genfit SA** as well as numerous mid-stage candidates, and assess biomarker performance to help determine future clinical endpoints.

There are four candidates in Phase III – Intercept's farnesoid X receptor (FXR) agonist obeticholic acid (OCA), Genfit's dual inhibitor of peroxisome proliferator-activated receptors (PPAR) alpha and delta elafibranor, **Gilead Sciences Inc.**'s apoptosis signal-regulating kinase 1 (ASK1) inhibitor selonsertib and **Allergan PLC**'s chemokine receptor 2/5 (CCR2/5) antagonist cenicriviroc – but none is expected to report pivotal data before 2019.

Beyond the leaders, there are 29 candidates now in Phase II or Phase IIb, along with 14 more in Phase I or Phase I/II. Along with Gilead, Allergan and now AstraZeneca, other commercial players developing NASH candidates include **Takeda Pharmaceutical Co. Ltd.**, **Novartis AG**, **Bristol-Myers Squibb Co.**, **Boehringer Ingelheim GMBH**, **Novo Nordisk AS**, **Pfizer Inc.**, **Shire PLC** and **Merck & Co. Inc.**

Lilly apparently regards the crowd as reason to largely get out, especially since the most-advanced candidate being shuttled to Terns is a Phase I FXR agonist (TERN-101), employing the same mechanism as Intercept's Phase III OCA as well as Phase II candidates at Novartis, Gilead and **Enanta Pharmaceuticals Inc.**. Terns also gets a preclinical semicarbizide-sensitive amine oxidase (SSAO) inhibitor, said to be nearing investigational new drug (IND) application submission, and another preclinical candidate to inhibit an undisclosed target that Terns says is well-validated in NASH.

TERNS' INITIAL FOCUS ON CHINA

Backed with a $30m Series A financing by Lilly Asia Ventures in April 2017, San Mateo, Calif.-based Terns plans to focus its initial drug development in China, while considering development down the road in other markets. Along with the Lilly candidates, Terns has three discovery efforts ongoing in NASH, as well as discovery-stage oncology programs in hepatocellular carcinoma, gastrointestinal cancer and chronic myeloid leukemia.

CEO Weidong Zhong, a former Gilead scientist joined by two other Gilead vets on the Terns executive team, said the deal positions his firm to study potential NASH combination therapy regimens early in clinical development. FXR agonism is thought to help regulate cellular pathways that modulate the synthesis of bile acids and effect processes of lipid metabolism, inflammation and fibrosis, while SSAO inhibition can address the upregulation of white blood cells in the liver in inflamed tissues, the company explained. In addition, soluble SSAO levels are elevated in NASH patients.

THIRD LICENSING FOR UNDER IONIS PACT

AstraZeneca's acquisition of AZD2693, an antisense compound employing Ionis' Ligand-Conjugated Antisense (LICA) and Generation 2.5 chemistry technologies, is the third in-licensed by the pharma under a collaboration first signed in 2012 and then expanded in 2015 to include cardiovascular, metabolic and renal disease.

Ionis says the combination of those two technologies offers high-affinity chemistry and efficient cell-specific targeting. Candidates employing both technologies are very potent, the biotech said, enabling infrequent, low dosing and potentially even oral dosing. In a statement, Ionis Chief Operating Officer Brett Monia said AstraZeneca's preclinical and clinical expertise helped advance the candidate quickly from discovery into development.

Designed to inhibit an undisclosed target in NASH, all Ionis revealed was that AZD2693 has started development. Ionis also has IONIS-DGAT2Rx in Phase II for NASH; the compound targets diacylglycerol acyltransferase-2 and is intended to reduce fat in the liver.

Ionis received a $30m licensing fee from AstraZeneca, which takes over all development and commercialization responsibilities. The biotech also could earn development and regulatory milestone payments up to $300m as well as tiered sales royalties topping out in the low teens. Those terms are virtually identical to those agreed upon under an agreement in February in which AstraZeneca licensed IONIS-AZ5-2.5Rx (AZD2373) from Ionis for a genetically defined form of kidney disease.

In late March, **Regeneron Pharmaceuticals Inc.** and RNA-interference firm **Alnylam Pharmaceuticals Inc.** announced a partnership to investigate genetic factors underlying chronic liver disease, potentially leading to novel targets for NASH therapies.

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AbbVie's Upadacitinib Safety Appears Improved In Largest, Longest RA Study

MANDY JACKSON mandy.jackson@informausa.com

AbbVie Inc. claimed an important win on April 9 when it reported positive efficacy and safety in rheumatoid arthritis for its JAK1 inhibitor upadacitinib in the drug's largest and longest Phase III clinical trial to date, including a lack of cardiovascular events that raised red flags in other late-stage studies.

The company engineered upadacitinib to specifically target JAK1 in an effort to produce a safer JAK inhibitor, but previously revealed Phase III data have shown a potentially higher risk of death from pulmonary embolism (PE) and deep vein thrombosis (DVT). However, as AbbVie readies its oral drug to compete with two other JAK inhibitors, results from the Phase III SELECT-COMPARE study showed better efficacy and fewer PE and DVT events for upadacitinib versus placebo and the company's blockbuster biologic *Humira* (adalimumab).

Upadacitinib is a key pipeline program for AbbVie as it attempts to fill the huge revenue drop that is expected to occur when Humira biosimilars hit the company in about five years, based on patent settlements with **Amgen Inc.** and recently with **Samsung Bioepis Co. Ltd.**

The company has forecast more than $6.5bn in peak annual sales for upadacitinib across multiple indications, but analysts view that estimate as optimistic in light of competition from **Pfizer Inc.**'s established JAK1/2/3 inhibitor *Xeljanz* (tofacitinib) and the JAK1/2 inhibitor baricitinib from **Eli Lilly & Co.** and **Incyte Corp.** Baricitinib is under US FDA review with an advisory committee meeting scheduled for April 23, following an initial rejection by the agency with a request for more data about the drug's safety and its two proposed doses.

Any safety concern for upadacitinib could make it hard for AbbVie's drug to steal sales from the two predecessors, so answering the outstanding question of cardiovascular risk is crucial in the coming months. With results from the SELECT-MONOTHERAPY study from December in mind, which raised new cardiovascular safety concerns, analysts had dueling assessments of the SELECT-COMPARE results and whether the data improved the drug's positioning in a competitive field.

ANALYST REVIEWS REMAIN MIXED

BMO Capital Markets analyst Alex Arfaei said in an April 9 note that the new Phase III results are "incrementally positive" for upadacitinib. However, Arfaei pointed out that while AbbVie contends that DVT and PE rates in the drug's trials are consistent with rates seen in the rheumatoid arthritis (RA) patient population in general, upadacitinib and its rival baricitinib both have DVT and PE events in their studies while the same hasn't been seen in studies of Xeljanz for RA.

BMO analysts are less optimistic than others about upadacitinib's revenue potential, with a forecast of about $2bn in 2023 revenue versus analyst consensus of $2.8bn in peak annual revenue, which still is less than half of AbbVie's 2025 guidance.

Meanwhile, Credit Suisse analyst Vamil Divan described the SELECT-COMPARE data as "encouraging and supportive of approval" in an April 9 note. "We note that there was one additional incidence of pulmonary embolism, though this was similar to placebo and less than the Humira group," Divan wrote. "There were also no patient deaths or major adverse cardiovascular events in the upadacitinib arm compared to two and two, respectively, in the Humira group and two and three for placebo. There was an uptick in serious infections for the upadacitinib group, but this was similar to that seen for Humira."

Investors appeared to be encouraged by the data, sending AbbVie's stock up 0.8% to close at $90.48; the stock rose more than 2% earlier in the day. The SELECT-COMPARE data were a welcome bit of good news following a major disappointment last month when rovalpituzumab tesirine (Rova-T) failed in a mid-stage small cell lung cancer trial, bringing the company's stock price down 12.8% on March 22.

IMPROVED EFFICACY VERSUS COMPARATORS

SELECT-COMPARE had three treatment arms – 15 mg upadacitinib dosed once daily (651 patients), 40 mg Humira injected every other week (327 patients) and placebo (651 patients) – all on top of methotrexate in RA patients with an inadequate response to methotrexate. The primary endpoint was a 20% reduction in pain and swelling at 12 weeks, according to standards developed by the American College of Rheumatology (ACR20).

AbbVie reported that 71% of patients treated with upadacitinib achieved ACR20, while 63% treated with Humira and 36% who received a placebo had an ACR20 response at week 12. ACR50 and ACR70 responses – both of which were secondary endpoints – were 45% and 25%, respectively, in the upadacitinib arm; 29% and 13% for Humira; and 15% and 5% for placebo at week 12.

"Upadacitinib demonstrated a 35%/30%/20% placebo-adjusted ACR20/50/70 and 8%/16%/12% Humira-adjusted ACR20/50/70 at week 12, respectively," BMO's Arfaei noted. "For comparison, in the Lilly/Incyte Phase III RA-BEAM trial, 4 mg baricitinib monotherapy demonstrated a 30%/28%/14% placebo-adjusted ACR20/50/70 and 9%/10%/6% Humira-adjusted ACR20/50/70 at week 12, respectively. With all the caveats of cross trial comparison in mind, the efficacy results of [upadacitinib]'s SELECT-COMPARE appear modestly better than [baricitinib]'s RA-BEAM."

The company said 29% of upadacitinib patients achieved clinical remission [Disease Activity 28 (DAS28) C-Reactive Protein (CRP)] at week 12 versus 18% in the Humira group and 6% of placebo patients. Low disease activity (LDA) based on DAS28(CRP) was observed at week 12 in 45% of upadacitinib patients, versus 29% for Humira and 14% for placebo.

AbbVie reported that upadacitinib also was superior to Humira in terms of pain reduction measured by the Patient's Assessment of Pain [Visual Analog Scale (VAS)] and physical function measured by Health Assessment Questionnaire-Disability Index (HAQ-DI) at week 12.

SELECT-COMPARE is ongoing, but at 26 weeks upadacitinib significantly inhibited radiographic progression as measured by the change in modified total Sharp score (mTSS) from baseline in 593 patients compared with 599 placebo-treated patients (0.24 versus 0.92, $p<0.001$).

AbbVie said there were no new safety signals detected in SELECT-COMPARE through week 26 and the serious adverse event (SAE) rate of 3.7% in the upadacitinib arm fell between the 4.3% SAE rate for Humira and 2.9% SAE rate for placebo. Serious infection rates were 1.8% for upadacitinib, 1.5% for Humira and 0.8% for placebo. There were no deaths in the upadacitinib group, two deaths in the Humira group (0.6%) and two in the placebo group (0.3%).

There were no adjudicated major adverse cardiovascular events (MACE) for upadacitinib, but there were two for Humira (0.6%) and three in the placebo group (0.5%). However, there were adjudicated venous thromboembolic events (VTE) for upadacitinib, including one patient with DVT (0.15%) and one with PE (0.15%). Three Humira-treated patients had a PE (0.92%) and one in the placebo group had a PE (0.15%).

"Today's results, which encompass the largest patient size and the longest randomized study duration to date for a upadacitinib trial, more than doubled the randomized patient experience on drug and showed comparable VTE rates for upadacitinib and placebo (0.3% vs 0.2%) through 26 weeks. Opposite, the rate of VTEs on Humira was higher at 0.9%, and there is no perceived increased risk of VTEs for RA patients on anti-TNFs," Leerink's Geoffrey Porges said in an April 9 note. "The total clinical experience of upadacitinib has now increased substantially without demonstrating a major risk for VTEs, which we believe reduces the risk of unexpected asset failure."

AbbVie noted that across its SELECT clinical trial program in RA, which includes six Phase III trials, "the rate of DVT and PE remains consistent with the background rate for the rheumatoid arthritis patient population."

Based on Phase III data reported to date, the company intends to make global regulatory submissions for approval of upadacitinib in the second half of 2018.

"SELECT-COMPARE is the fourth Phase III RA study to report out, but there is one more major trial expected later this quarter, the SELECT-EARLY trial. This trial will feature upadacitinib in patients that are either naïve to, or recently started on, methotrexate," Credit Suisse's Divan noted. "Upadacitinib has already shown effectiveness as a monotherapy, and has now demonstrated superiority to Humira. Success in early lines of therapy would be the final piece of the puzzle to build a case for a label for frontline treatment when AbbVie submits for FDA approval in [the second half of] 2018."

AbbVie also is developing upadacitinib for ulcerative colitis, ankylosing spondylitis, atopic dermatitis and giant cell arteritis.

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Allergan: Data Support Vraylar In Bipolar Depression

STEN STOVALL sten.stovall@informa.com

Allergan PLC and **Gedeon Richter PLC** believe they now have adequate evidence for their atypical antipsychotic drug *Vraylar* (cariprazine) in the treatment of bipolar I depression to file an sNDA with the FDA in the second half of this year. Vraylar is currently approved for the treatment of schizophrenia in adults and the acute treatment of manic or mixed episodes associated with bipolar I disorder.

The duo said it could now press ahead with the new cariprazine filing armed with positive top-line evidence from three pivotal placebo-controlled studies in bipolar I depression, RGH-MD-53, RGH-MD-54 and RGH-MD-56 after data from the former study met primary and key secondary efficacy endpoints. Vraylar has thus shown statistically significant improvements in bipolar depression symptoms in all three trials.

"RGH-MD-53 is the third of three pivotal trials of cariprazine in bipolar I depression and gives Allergan sufficient data to submit our sNDA in the second half of 2018 for that new and different indication," an Allergan spokesperson told *Scrip*.

If eventually approved, it would expand the existing label for cariprazine, an oral, once daily atypical antipsychotic. It is currently approved for the acute treatment of adult patients with manic or mixed episodes associated with bipolar I disorder at a recommended dose range of 3 to 6 mg/day, and for the treatment of schizophrenia in adults, with a recommended dose range of 1.5 to 6 mg/day. Allergan and Gedeon Richter hope to differentiate Vraylar in the crowded market of atypical antipsychotics using their medicine's different mechanism of action.

Cariprazine was discovered and co-developed by Hungary-based Gedeon Richter and is licensed by Dublin-based Allergan, in the US and Canada. For more than a decade both companies have conducted over 20 clinical trials enrolling thousands of patients worldwide to evaluate the efficacy and safety of cariprazine for patients suffering from a broad range of mental health illnesses.

Datamonitor Healthcare analyst Sultan Khan believes Vraylar has a strong chance of being approved to treat bipolar depression, despite Vraylar having in previous studies proved ineffective as adjunct therapy for treatment-resistant major depressive disorder, or MDD.

"Its previous failure in MDD may be due to its use as an adjunct whereas all of these RGH-MD trials seem to have used cariprazine as a monotherapy. The side-effect profile is really good versus other atypicals, with the major safety concerns such as weight gain and hyperglycemia at a minimum," Khan told *Scrip*.

He believes the main benefit is that if cariprazine is currently approved for bipolar mania and then if approved for bipolar depression "then you'll get complete coverage for a disease in one drug, as opposed to the need for combination therapy."

"Currently, **Eli Lilly & Co.**'s *Prozac* (fluoxetine) and *Zyprexa* (olanzapine) have the strongest evidence, so cariprazine would trump Zyprexa quite clearly on safety, which is known for its weight gain and hyperglycaemia, and also potentially remove the need for adjunctive antidepressant too," Khan said.

RGH-MD-53 was the second of two identical Phase III trials for Vraylar evaluating 1.5 mg and 3 mg of drug compared with placebo in adult patients with bipolar I disorder. Top-line results of the first Phase III study, RGHMD-54, were released in December 2017. RGH-MD-56 was a Phase II, randomized, double-blind, placebo-controlled, parallel-group clinical trial in adult patients with bipolar I depression.

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MEETING GROWTH CHALLENGES ROUNDTABLE PANEL PART 3:

Pursuing Growth Without Overreaching

BY MIKE WARD

Developing products that are clinically meaningful requires more than a novel approach to an unmet medical need. A panel of biotech executives and venture investors discuss how to meet the challenges of building a sustainable business from day one.

Three decades ago when biotech was in its infancy many of the pioneers had ambitions to create fully integrated pharmaceutical companies (FIPCOs). Picking low hanging fruit – recombinant versions of therapeutically relevant human proteins, such as insulin, human growth hormone, erythropoietin and tissue plasminogen activator – a number of the first movers prospered but many withered on the vine. The FIPCO model fell out of fashion and subsequent start-ups pursued strategies that took assets to proof of concept before licensing to established commercial organizations. The advent of personalized medicines and initiatives to incentivize development of therapeutics to treat orphan diseases has underpinned a renaissance of the FIPCO model. However, challenges still exist.

Scrip spoke with Gil Van Bokkelen, chairman and CEO of Athersys, Inc., Daniel R. Orlando, chief operating officer of Vericel Corporation, Robert McNeil, general partner and managing director of Sanderling Ventures and CEO of Dalcor Therapeutics, Ali Fattaey president and CEO of Curis, Inc., Mei Mei Hu, co-founder and CEO of United Neuroscience, Inc., Gregory Hanson, CFO of MabVax Therapeutics Holdings, Inc., and Dennis Podlesak, partner at Domain Associates LLC, in a roundtable interview about the challenges company executives face as they try to build their business. Sponsored by Freyeur & Trogue, Impactiv and rbb Communications, the roundtable took place during the J.P. Morgan Healthcare Conference in San Francisco.

Growth strategies are dependent on several factors. First, the founders and initial investors need to think about their ambitions for the assets they have: Are they looking to develop programs to proof of concept to then license or sell to other companies to commercialize asset by asset? Are they wanting to pursue a build-to-buy business model which usually involves early involvement with a potential purchaser? Or is the plan to create a standalone commercial scale company? Second, to achieve their ambitions they need access to clinically meaningful assets, capital and teams with relevant experience.

"Most companies end up partnering their main programs or lead portfolio assets with a big company, which sometimes leads to complete acquisition. Big pharma has been preying on biotechs for the past 10-15 years and increasingly we are now seeing big biotechs taking the same route," noted Athersys' Van Bokkelen.

Companies with platforms that can generate multiple therapeutic opportunities can buy the time they need to transform into commercial standalone entities. "We acquired our core regenerative medicine technology from the University of Minnesota and recognized that putting it into a platform that yields a number of clinical programs was the best route. It is our intention to take that all the way to the finish line but I understand that it is a long hard road. We have been at it for more than 20 years and not all organizations are going to be able to maintain consistent leadership, have consistency of vision or frankly have patient enough investors to be able to do that," he added.

Platforms As Springboards

During the 1990s, the biotech sector shifted from the FIPCO model where companies attempted to develop and commercialize therapeutics on their own – many crashed and burned following failures in their lead programs - to the less risky platform model that allowed biotechs to create a plethora of products that would be sold onto companies with established commercial infrastructures. The challenge of the platform model in the early days was that it was often a proxy for a fee-for-service approach that constrained the ability for companies to gain critical mass as they sold off the family silver. This gave rise to a hybrid model which saw companies generate license fees and milestones from the platform that were recycled into proprietary programs.

"What is important is to how to retain as much value as possible," added Curis' Fattaey.

In 2003, Curis signed a collaborative research, development and license agreement with Genentech that gave the Roche company an exclusive, global, royalty-bearing license to make, use, sell and

Ali Fattaey
President & CEO
Curis Inc.

Robert McNeil
Managing Director
Sanderling Ventures & CEO
Dalcor Therapeutics

Daniel R. Orlando
COO
Vericel Corporation

Dennis Podlesak
Partner, Domain
Associates LLC

Mei Mei Hu
Co-founder & CEO
United Neuroscience Inc.

Gil Van Bokkelen
Chairman & CEO
Athersys Inc.

Gregory Hanson
CFO, MabVax Therapeutics
Holdings Inc.

import small molecule and antibody Hedgehog pathway inhibitors for human therapeutic applications, including cancer therapy. Genentech subsequently granted a sublicense to Roche for non-U.S. rights to Erivedge (vismodegib), which was the first FDA approved medicine for the treatment of metastatic or locally advanced basal cell carcinoma.

"It was a different time and the company did give away commercial rights. At that time, I was at Onyx and it took a different route and retained all the commercial rights we could, and obviously it did very well," he noted.

Onyx Pharmaceuticals was the company behind Nexavar (sorafenib), co-developed and co-marketed with Bayer approved for renal cell carcinoma and currently the only targeted treatment available for first-line hepatocellular carcinoma patients, Stivarga (regorafenib), a tyrosine kinase inhibit approved for the treatment of metastatic colorectal cancer, and Kyprolis (carfilzomib), the proteasome inhibiting multiple myeloma treatment. Onyx was acquired by Amgen for $10.4bn in 2013.

While royalties from Eviredge – the company pulled in just over $9m in 2017 – have been important to Curis, the company is now looking to leverage as much as it can from the multiple partnering opportunities it platform offers, while retaining an ambition to become a profitably sustainable commercial organization.

In order to grow, Fattaey believes companies need to retain as much as they can and keep a close grip on development and marketing plans. "Mathematically, it is fairly simple. With one drug, you have four opportunities to access capital. One is equity and the other three are the commercial rights associated with the US, European and Asian markets. If you have two assets then you have seven options. The choices become a little easier – we don't have to choose one drug to give away in order to try and finance another one. By licensing commercial rights to markets we are never going to address -- we are not going to try and commercialize in Asia – we can hang onto assets and focus where we can target discrete disease populations. So we look at them and ask ourselves as a management team, board and company what do we strategically want to do about it? We are not interested in Asia so those commercial rights create a financial opportunity for us," he explained.

However, partners have to be able to offer more than just hard cash. "You have to ask yourself, are they willing to put in more commitment than just dollars? Are they willing to put their expertise into your drugs? That is what is important to us. In the case of Eviredge, Roche and Genentech continue to market it phenomenally across the globe," he added.

Having a broad platform creates the additional challenge for small biotechs of knowing what to focus on. Noting that her company is developing a technology that has potential in many areas, United Neuroscience's Hu asked: "We know we can go broad but do we want to do so all the way? Our constraint is whether we have the finances to take all the programs forward. It is a question of which ones we de-prioritize and maybe partner off?"

Adopting Orphans

Homing in on discrete disease populations in specific markets offers biotechs an opportunity to cut their commercial teeth without over-reaching. Orphan diseases provide such a sweet spot. Although United Neuroscience's lead program is an Alzheimer's vaccine, Hu has no expectation that her company will try and take that all the way. "We are a small translational company and that is where our core is right now. We don't see ourselves commercializing an Alzheimer's vaccine as that would be a big leap for is. Our priority is to find a partner to do that," she noted.

Hu, like many biotechs, prefers orphan indications because she thinks she can handle them. "Many companies are being built to focus on rare diseases. They have a single focus, know the regulatory path and can commercialize them. For smaller companies like us that is a much more feasible option," she added.

Admitting that she started off with a pursuing a philosophy of being vertically integrated and doing everything, United Neuroscience's Hu has shifted her focus on what her company is good at and finding partners to supplement those areas where it is less accomplished. "That means you don't have to acquire them," she argued. If anything, she is awash with technology and rather than looking for technologies to acquire she is looking for partners that would use the platform in other areas.

"We have figured out a way to get the body to respond to endogenous proteins - no other vaccine can do that safely – and there are many that involved in chronic diseases. So if another company came to us and said they would like our technology to help them out we would look to figure out how it would also work for us. Even if you are outlicensing you are still committing to that relationship and dedicating resources. This is a constant calculus – for us right now we are approached by number of companies for different programs. Our primary focus, however, is to build our own pipeline," added Hu.

Funding Growth

Access to capital is a rate-determining step in the growth of early stage companies, for companies generating revenues, the task is less challenging. Describing his company as a different animal from others represented in the roundtable, Vericel's Orlando noted that its rapid growth in the past four years has been underpinned by the assets bought from Genzyme following its acquisition by Sanofi.

"We just launched our replacement product last year and have expanded the number of sales representatives from 21 to 28 and expect to increase that this year. We are in a rapid organic growth phase," he noted.

Indeed, Vericel reported its third straight quarter of 30% or higher revenue growth compared to the same quarter of the prior year for the fourth quarter of 2017 driven by both the accelerating uptake of MACI as well as substantial growth for Epicel. Total net revenues for the year ended December 31, 2017 were $63.9m, including $43.9m of Carticel and MACI net revenues, $18.9m of Epicel net revenue and $1.2m in license revenue. Total net revenues for the year ended December 31, 2017 increased 18% over 2016.

In guidance released at its full year results meeting, the company expects total net product revenues for the full year 2018, excluding additional license revenue, to be in the range of $73m to $78m. "We will continue on this path. With a strong balance sheet and an expanded sales force in 2018, have positioned the company for continued strong revenue growth that will take us to profitability," he added.

Access to sustainable revenues provides businesses with more flexibility. "Once you are a revenue generating company, your access to capital changes – you find you can be more creative accessing a debt and equity mix. Armed with such financial firepower, the company can now look at other options to fuel its growth. "For us, the interesting thing would be to make an acquisition of a product or company. That would require significant investment but it is the kind of thing we are discussing," explained Orlando.

If Vericel were to embark on the acquisition path, Orlando added,

it is currently most likely to buy something that fits well with its existing business. "We are in essence an orphan company and so have to be cautious. We don't do a lot of basic R&D and so would be looking at something like a cell therapy that is in the latter stages of development," he explained.

As it starts to replace Carticel with MACI, Vericel has freed up a lot of its manufacturing capacity. "We are a fairly rare entity in that we are a commercial manufacturer of cell therapies and there are many small companies that are inching their way to the market. Manufacturing quality product can be very difficult for some companies so there may be some opportunities there for us," he noted.

Indeed, with its strong revenue growth and improving balance sheet, Vericel is not short of opportunities. "We have people coming to us with companies that we might buy and sometimes they have financing support as well. We are, however, busy preparing ourselves for the growth we are experiencing right now – it is important not to get distracted. We have been a very disciplined company to date," he added.

Keeping A Lid On Costs

As capital preservation is essential for keeping biotechs on course, companies need to keep a tight rein on costs, not get over-leveraged, nor run out of cash. That means the executives with financial responsibilities will view growth strategies through a different lens.

As a CFO, MabVax's Hanson, who has had experience of building businesses both organically and through acquisition, agrees that he sees things differently. "At Avanir Pharmaceuticals, we took the organic growth route and intended to take our lead compound, the cold sore product Abreva, all the way. We ended up having to license the product to GSK because it went over the counter immediately and we didn't have a salesforce for that kind of product. If we could have detailed it, we would have kept it," he noted.

Avanir had previously licensed North American and other ex-European rights for Abreva (docosanol 10%) to Bristol Myers Squibb in 1996, a deal which was terminated a year later. The company then filed an NDA in 1998, licensed the US and Canadian rights to GSK in 2000. A few months later the product was approved by the FDA as an OTC treatment of oral herpes. Avanir subsequently sold a portion of its North American royalty stream to Drug Royalty, while licensing some European country rights to a number of regional pharma companies.

"In that way, we financed ourselves organically with license agreements with companies that would fund our R&D people – we had about 20 people who were funded at the time by various big pharma," he recalled.

The challenge for CFOs is when programs disappoint and decisions need to be taken to not continue as that can leave a company exposed to fixed costs. "As a CFO, I am a believer that when you have uncertainty you want to have variable costs because if you hire people you can have a pyramid of costs. You have to have more buildings, more chemistry labs, biology labs and, at that time, that worked out at about $50k per person in overheads. It is probably a higher number these days," he added. At the point when Avanir decided it needed to start a salesforce, the management team chose not to hire one but instead get a commercial capability through acquisition.

Having flirted with a monoclonal antibody platform, Avanir built a presence in the CNS space, ultimately succeeding with the approval of Nuedexta, a combination of the NMDA receptor antagonist dextromethorphan with quinidine sulfate, a cytochrome P450 enzyme inhibitor, in pseudobulbar affect.

Dextromethorphan with quinidine sulfate is also in Phase II studies in other indications including: agitation in Alzheimer's disease; amyotrophic lateral sclerosis; autism in adults; treatment resistant depression; central neuropathic pain in multiple sclerosis patients; diabetic peripheral neuropathic pain; and Parkinson's disease levodopa induced dyskinesia. Japan's Otsuka Pharmaceutical acquired Avanir at the end of 2014 for $3.5bn.

Although MabVax is a smaller company, Hanson is staying true to his philosophy of keeping costs variable. "It allows you to adjust if you have a delay. In my experience, clinical trials never get completed in the timeline you really want – things happen – it could be some regulatory issue or it takes longer than expected to bring on another clinical site," he explained.

"Organically, you can grow if you have massive amounts of funds, you have an investor that believes in you, will stay with you. If $150M came into our company that would be outstanding for us. We have backers who have invested time and time again but you have to be in line with your investors, your management, your board, know your markets and your assets to grow organically," he added.

Thinking about technologies that MabVax might bring in-house, a good fit, according to Hanson, would be antibody-drug conjugate (ADC) expertise. "We don't have ADC experience so finding a company that can provide that would be good. We are aware of companies like Seattle Genetics but they would be more likely to acquire us. We do look at technologies we don't have and look to acquire them and have had some discussions on that front to try and find the right fit. Figuring out the valuations of activities is usually the biggest challenge," he added.

This is the third installment of a multi-part coverage of the Meeting Growth Challenges Roundtable, sponsored by Freyeur & Trogue, Impactiv and rbb Communications, conducted during the J.P. Morgan Healthcare Conference in San Francisco.

Rigel Mulls Next Steps After Fostamatinib Fails In Kidney Disease

EMILY HAYES emily.hayes@informa.com

Rigel Pharmaceuticals Inc. sees positive signs in a failed Phase II study of its spleen tyrosine kinase (SYK) inhibitor *Tavalisse* (fostamatinib) and says it will consider next steps for development with potential partners.

The company reported topline data on April 3 from a Phase II study evaluating fostamatinib in immunoglobulin A nephropathy (IgAN), an autoimmune disease of the kidneys that progresses to end-stage renal failure in 25% of cases, which could mean dialysis and kidney transplantation.

Some 82,500 to 165,000 patients in the US have IgAN, also called Berger's disease, and there are no approved drugs, though angiotensin receptor blockers, angiotensin converting enzyme inhibitors and steroids are treatment options.

By decreasing spleen tyrosine kinase activation in the kidney, fostamatinib reverses inflammation and improves kidney function, according to the company. Fostamatinib also blocks the production of IgA molecules that polymerize and deposit in the kidneys, so it has a dual mechanism of action in IgAN.

Fostamatinib's lead indication is immune thrombocytopenic purpura (ITP) and an FDA filing has an April 17 user fee date. According to the company, the review is on track.

"We're not commenting on specific communication with the FDA … but let's say that we have regular communication with the FDA, and they continue to be normal collaborative interactions," Rigel Chief Medical Officer Anne-Marie Duliege said during an April 3 investor call.

The nephropathy study compared fostamatinib against placebo, using mean reduction in proteinuria after 24 weeks as the primary endpoint, in 76 patients with IgAN verified by biopsy and proteinurea of at least 500 mg/day. Higher proteinurea puts patients at greater risk for organ failure. Patients were randomized to placebo or one of two fostamatinib doses: 100 mg twice daily or 150 mg twice daily.

The mean reduction in proteineuria (sPCR) was 177 mg/g for placebo, which was greater than the 158 mg/g reported for the 150 mg fostamatinib group but lower than the 577 mg/g change for the 100 mg arm. These were not statistically significant differences.

The overall trial population was too varied and many did not have a substantial amount of disease, CEO Raul Rodriguez commented to *Scrip*.

There was a consistent dose-dependent reduction of proteinurea in a prespecified group of 45 patients with at least 1 gram/day of proteinurea at baseline, therefore more severe disease, but this was not a statistically significant finding. The median reduction in proteinurea at week 24 in these patients was 177 mg/g for placebo (n=14), 720 mg/g for the 100 mg group (n=16) and 803 mg/g for the 150 mg dose cohort (n=15).

Rigel said that the subgroup analysis was encouraging because there are no approved treatment options for this condition. "Patients with greater than 1 gram/day of proteinuria have an increased risk of disease progression and represent an unmet medical need. Current guidance for clinical trials in IgAN recommends studying patients with greater than 1 gram/day of proteinuria at entry. Further analysis, including histology, are expected later in the year," the company said.

"Consistently, in patients with a baseline proteinuria greater than 2 grams, fostamatinib treatment showed a similar trend toward a greater reduction in proteinuria as compared to placebo," the company added.

SOLID SAFETY DATA

Fostamatinib also demonstrated good safety, with mostly mild-to-moderate adverse events and no new signals, Rigel reported.

"The most frequent adverse events were diarrhea, nausea, headache, hypertension and vomiting. Two patients in the 100 mg BID dose group and four in the 150 mg BID dose group discontinued the study due to adverse events. There were six patients with serious adverse events (SAEs), two in each of the placebo, 100 mg and 150 mg dose groups. Of those six patients, one patient in each fostamatinib group had a drug related SAE. One patient had a fatal SAE, which was not drug related," Rigel said.

A small number of patients on fostamatinib had noninfectious diarrhea or hepatic disorder or hypertension and interestingly, there was also a high frequency of diarrhea in the control group, Duliege said.

SUPPORT KOL

Two key opinion leaders voiced support for the drug in this indication during Rigel's investor call.

Frederick Tam of the Imperial College in London said that he was encouraged by the degree of lowering of proteinurea in the study, noting that through a stepwise reduction of proteinurea, the "risk of renal failure can be reduced tremendously."

"If a drug comes along to specifically treat the pathogenesis of the underlying disorder, in this case the generation of IgA1 molecules, and can specifically, in sort of a silver-bullet-like manner, directly treat the core pathogenesis of the disease, that is a major advance. And that's what this data seems to indicate," said James Tumlin, University of Tennessee Health Science Center.

Furthermore, the safety profile means it can be given long term, which is important that patients may have chronic low-grade inflammation for many years before developing end-stage renal failure, Tumlin said.

NEXT STEPS UNKNOWN

The company is going to look at the data more carefully and think about next steps in consultation with key opinion leaders, regulatory agencies and potential partners.

During the call, Rodriquez said that Rigel believes it has identified the right patient population to test through this proof-of-concept study.

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The company has said it hopes to have a partner in Europe by early 2019, and while talks have focused on ITP and the second indication of autoimmune hemolytic anemia, a rare blood disorder, it believes a potential partner will also be interested in the nephropathy data.

Rodriguez explained in an interview that Rigel thinks development in IgAN should proceed, but it's unclear right now, with just topline data and prior to discussion and review, what kind of study will be needed as a follow up, in terms of phase and number of patients and other parameters. The company would definitely need a partner to cover the costs of further development.

"Today I cannot tell you we are definitely doing [another] study because I simply don't know what the cost or time would be," the exec told Scrip.

SELLOFF OVERDONE?

Rigel's stock closed down by 13.60% to $3.05 on April 3.

Jefferies analyst Eun Yang commented in an April 3 note that the selloff was overdone. The missed Phase II data was "somewhat disappointing" but does not change Jefferies' valuation or prospects for approval in ITP, Yang said.

Yang said that Jefferies' valuation is largely based on the first two indications of fostamatinib – ITP and autoimmune hemolytic anemia – and the failed study does not impact the company valuation.

"Upon FDA approval in ITP, we see >100% upside from current valuation likely," Yang said.

BMO Capital Markets Do Kim also viewed the market reaction as overdone. The Phase II data were uninspiring but expectations for this indication were limited and little value had been assigned to the indication, Kim said in an April 3 note.

"With today's stock weakness, we believe the upside for Tavalisse approval could exceed 100%, above our prior scenario of 50%-70%. Our probability of approval remains at 80%," Kim said.

Results in immune thrombocytopenic purpura, however, had been somewhat mixed. The NDA is supported by three Phase III studies of fostamatinib in ITP, two of which are small randomized placebo-controlled studies (Studies 047 and 048) and the third is an open-label extension study (Study 049). Results in one of the studies did not meet statistical significance, due to one additional responder in the placebo group, but overall results from the studies appeared similar (18% of Tavalisse treated patients achieved a sustained response [SR] in each study, compared to 0% and 4% of the placebo groups).

Biomedtracker analysts have concluded that in combination, the data are highly statistically significant and it is likely that the drug will be approved.

The company announced a downsizing of R&D staff in September 2016 in order to devote more resources to getting ready commercially for the launch of fostamatinib in immune thrombocytopenic purpura. As part of the downsizing, the company closed its antibody development program and said it would be focusing on small molecules for immunology and oncology indications.

Fostamatinib has had a rocky development road.

Previously, the drug demonstrated mixed results in Phase III studies of rheumatoid arthritis and partner **AstraZeneca PLC** returned worldwide licensing results. The drug failed to show noninferiority to **AbbVie Inc.** *Humira* (adalimumab) in a mid-stage study.

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Celgene's Terrie Curran On Building, Broadening The I&I Franchise

MANDY JACKSON mandy.jackson@informausa.com

Celgene Corp. has invested billions of dollars in its inflammation and immunology (I&I) franchise through internal development as well as partnered programs and acquisitions, so a few setbacks on the path to diversifying its revenue beyond hematology and oncology are merely hurdles, not roadblocks.

On April 2, Celgene announced the immediate departure of President and Chief Operating Officer Scott Smith, a move analysts view as related to the recent setbacks in I&I. Smith was global president of that business until taking over as president and COO in April 2017. The current head of the I&I franchise, Terrie Curran, will report directly to CEO Mark Alles. Celgene is also reorganizing its executive team, which, combined with Smith's departure, Jeffries analyst Michael Yee thinks could help in turning Celgene's execution around.

Scrip spoke with Celgene's Terrie Curran, president of the I&I business, about the path forward for the franchise's flagship product *Otezla* (apremilast) and the group's growth markets of gastrointestinal diseases and neurology. The company is still evaluating a pair of recent setbacks within the I&I franchise, including a refuse-to-file letter the US FDA issued at the end of February for ozanimod in the treatment of multiple sclerosis, but it's pushing ahead with additional Otezla indications and a pipeline of new therapies.

"We've really got three core strategies across the franchise and one is optimizing, or maximizing, Otezla," Curran said. "The second is launching ozanimod and creating a neurology business and presence. The third is to be a leader in [inflammatory bowel disease (IBD)]."

All three goals will help Celgene diversify outside of its large hematology and oncology business, anchored by the multiple myeloma blockbuster Revlimid (lenalidomide), which generated $8.2bn in 2017 sales or about two-thirds of the company's $13bn in total revenue. One of the biggest risks for Celgene is generic competition for *Revlimid*, which has key patents expiring as soon as 2023, but Evercore ISI analyst Umer Raffat said in a March 27 note that the company's recent legal moves suggest a settlement defining generic entry is coming soon.

Otezla is a phosphodiesterase-4 (PDE4) inhibitor approved to treat psoriasis and psoriatic arthritis – two indications where competition has heated up, resulting in aggressive discounting by companies launching new biologics for the autoimmune diseases. New products hit Otezla sales

especially hard in the third quarter of 2017, causing Celgene to lower its sales expectations for the year.

The drug's sales did increase throughout 2017, however, with Otezla bringing in $1.28bn for the year and expectations of $1.5bn in sales for 2018. Celgene is positioning the small molecule as the preferred brand before injectables, driving reimbursement by a majority of health plans in the US and capturing endorsements from certain ex-US payers.

"In the US, we're now in a position where we have 80% of lives covered without step-through biologic," Curran said. "That's been really important for us to secure, because the Otezla profile as an oral compound with a really compelling safety and tolerability profile really plays earlier in the treatment paradigm, so it was really critical for us to secure that position – post-topical, pre-biologic."

She noted that about 60% of psoriasis patients are untreated and said Otezla can be a compelling treatment option for those who are earlier in their disease and aren't ready for treatment with biologics.

"That's the segment that we're really focusing on in the US and ex-US," Curran said. "We're really just into the second year of reimbursement in some of the key markets outside the US. We really see some incremental revenue gains in some markets that are doing particularly well."

EX-US GAINS, NEW INDICATIONS

Otezla won reimbursement in Japan at the start of 2017 and patients treated in community-based rheumatologist offices have access to the drug, versus hospital settings where biologics are the primary treatments. The drug also gained "a very good reimbursement position" in the post-topical, pre-biologic setting in France – another key market – last year, Curran said, and incremental gains in other ex-US markets are ongoing.

"In terms of life cycle expansion for Otezla, we've really kind of doubled down and looked at other opportunities," she said. "We've got an ongoing scalp [psoriasis] study, we're looking at pediatric psoriasis – looking at studies in that mild-to-moderate population where there's a high unmet need – and Otezla's profile really appeals to that patient group."

Celgene also plans to begin a Phase III program for Otezla this year in ulcerative colitis (UC) after disclosing positive Phase II proof-of-concept data for the drug in that indication in February.

"Based on the exciting profile that we saw emerging in the Phase II as well as some other clinical and biomarker and histology results, we're really excited to move Otezla forward and initiate a Phase III program in UC this year. [That's] an opportunity to grow that revenue and then we'll continue to embark on numerous programs to really kind of maximize the compound."

OZANIMOD LEADS EXPANSION

However, the S1P receptor modulator ozanimod is the lead compound in Celgene's push into gastrointestinal (GI) diseases, in addition to being the company's first neurology asset. The small molecule is in Phase III for UC.

"We completed a strategy refresh last year as we acquired … additional programs in GI and in neurology. We did a kind of deep dive into the different kind of therapeutic areas in neurology that really fit with our capability," Curran said.

"I think that neuroinflammation is right in our wheelhouse and the work that we have in our early R&D space. We're … continuing to look at compounds or therapeutic areas that are adjacent to MS," she continued. "Having said that, I think we've cast our net wider than that from a [business development] perspective and looking at all the areas that meet our criteria – unmet need, a compound that's differentiated, markets that are high touch, like MS, where there's a reasonably small prescriber base."

In the GI market, Curran said, "despite the development of lots of biologics in the IBD space, there's still a tremendous unmet need. There's no branded oral options available. We're fortunate enough now to have ozanimod, which is in Phase III for UC, and mongersen in Phase III for Crohn's … and Otezla is moving into a Phase III program now. So we have three assets in this area, and potentially we see an opportunity where we're beginning to look at standalone therapy for each of these assets or utilizing in combination, so we'll be kind of exploring both of those."

Mongersen (GED-0301), an antisense oligonucleotide targeting Smad7 messenger RNA (mRNA) that was licensed from **Nogra Pharma Ltd.**, was the big disappointment in 2017 that set off a significant decline in Celgene's stock price. The company ended two Phase III clinical trials for GED-0301 in Crohn's disease in October based on the recommendation of the trials' data monitoring committee.

"We're still looking at the [Phase II] data for the UC indication and we're still looking at subsets of the population and continuing to analyze it, so I expect some time this year [we'll reveal more data]," Curran said.

EARLY-STAGE EXTENDS TO LUPUS, FIBROSIS

Two key earlier-stage programs for the I&I group take Celgene into a new indication and a new broad disease area – systemic lupus erythematosus (SLE) and fibrosis. The immunomodulatory drug (IMiD) CC-220 is in a Phase IIb trial for SLE that started in mid-2017, while the c-Jun N-terminal kinase 1 (JNK-1) inhibitor CC-9001 is being studied in a Phase II proof-of-concept trial for the treatment of idiopathic pulmonary fibrosis (IPF).

SLE "is an area where there have been many compounds studied and many have failed and there are very few treatment options for the patients," Curran said.

Celgene Corporate Vice President and Head of I&I Clinical R&D Ted Reiss said the company has multiple fibrosis programs in early development through late-stage clinical development, with CC-9001 for IPF as the lead asset for the segment.

Non-alcoholic steatohepatitis (NASH) is another area of interest within the fibrosis field, and that's where Celgene is working with its partner **Forma Therapeutics Holdings LLC** on a preclinical program under the companies' 2013 agreement, amended in 2014, to develop drugs that regulate protein homeostasis.

"NASH is a complex disease," Reiss said. "There's a number of organizations trying to attack this disease in a number of different ways. As we're considering it, we're thinking about the fibrotic part of the disease."

Celgene is continuing to look to its partners for help in diversifying the company's pipeline, including new disease areas, like GI, neurology and fibrosis. It signed an agreement with **Prothena Corp. PLC** in March to help extend Celgene's neurology interest beyond neuroinflammation to include neurodegeneration.

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Humira, Biologics Dominate Pharma Sales In 2017

JOHN HODGSON john.hodgson@informa.com

For the sixth year running, **AbbVie's** *Humira* (adilumumab) is the world's best selling drug, with nearly $19bn in global sales in 2017, over $10bn clear of its nearest rivals, **Amgen's** *Enbrel* (etanercept, $8.58bn) and **Celgene's** *Revlimid* (lenalidomide, $8.19bn). And for the first time since recombinant DNA became a significant drug production technique, there are more biologicals than non-biologics in the top 30.

Humira's sales were up 14.6% on 2016 levels, a remarkable achievement for a mature product. According to historical drug sales data compiled by Medtrack, AbbVie has had 15 consecutive years of sales growth since its launch in 2003, an uninterrupted record matched by **Roche's** *Xolair* (omalizumab, also launched in 2003) and beaten only by **Eli Lilly's** osteoporosis peptide analog, *Forteo* (teriparatide (rDNA origin) injection) with 16 years of continuous growth. The difference, of course, is that Forteo's annual sales have been much smaller than Humira's, just $1.75bn in 2017 making it just the 74th best selling drug.

The top cancer drug is Celgene's Revlimid, its 17.4% annual sales growth edging it ahead of an almost stagnant *Rituxan* (rituximab).

Eight biologics and two non-biologics make up the top ten best selling drugs for 2017. Overall, 16 of the top 30 drugs are biologics, the first time biologics have been in the majority, thanks to the emergence of **Merck & Co's** immuno-oncology compound *Keytruda* (pembrolizumab).

Keytruda, in at number 22 up from number 94 in 2016, was one of five drugs to make it new into the top 30 for 2017. The other four incoming and the five outgoing drugs were all non-biologics.

So out went two **AstraZeneca** drugs, respiratory stalwart *Symbicort* (budesonide and formoterol) and cholesterol-lowering cardiovascular drug, *Crestor* (rosuvastatin calcium); **Boehringer Ingelheim's** *Spiriva* (tiotropium bromide), **Gilead's** hepatitis C fix, *Sovaldi* (sofosbuvir), and the former poster-child of personalized medicine, *Gleevec/Glivec* (imatinib) from **Novartis AG**.

Sovaldi's year-on-year fall of 75.9% from sales of just over $4bn in 2016 to $964m in 2017 was the largest ever single-year percentage fall for any multiple blockbuster since sales of **Pfizer's** *Neurontin* (gabapentin) fell 77% after its loss of exclusivity in 2005. Other drugs have relinquished larger dollar values of sales in a year, including Sovaldi itself in 2016 ($5.3bn) and **Otsuka's** *Abilify* (aripiprazole; down $4.7bn) in 2015.

As Sovaldi departed the top 30 list, in came AbbVie's and **Johnson & Johnson's** Imbruvica (ibrutinib), and three fixed-dose combinations for infectious diseases - **GlaxoSmithKline's** *Triumeq* and Gilead's *Genvoya* (both for HIV infections) and Gilead's *Epclusa* for hepatitis C.

HUMIRA VERSUS LIPITOR

Humira continues to break drug sales records, and it is close to rivalling Pfizer's *Lipitor* (atorvastatin) for the title of the best-selling drug of all time.

The Biggest Selling Drugs of 2017

	$m	Change from 2016	Rank 2017 (2016)	Sales companies	Disease group
Humira	18,908	14.6%	1 (1)	AbbVie; Eisai	Inflammation
Enbrel	8,584	-7.2%	2 (2)	Amgen; Pfizer; Takeda	Inflammation
Revlimid	8,187	17.4%	3 (6)	Celgene	Cancer
Remicade	7,734	-12.6%	4 (4)	J&J; Merck & Co; Mitsubishi	Inflammation
Rituxan	7,508	1.3%	5 (5)	Roche	Cancer
Herceptin	7,128	3.5%	6 (8)	Roche	Cancer
Avastin	6,796	-1.3%	7 (7)	Roche	Cancer
Xarelto	6,151	11.2%	8 (11)	Bayer; J&J	Cardiovascular
Opdivo	6,048	27.8%	9 (16)	BMS; Ono	Cancer
Eylea	5,929	14.1%	10 (12)	Bayer; Regeneron; Santen	Ophthalmic
Prevnar 13	5,601	-2.0%	11 (10)	Pfizer	Infectious
Lyrica	5,290	1.9%	12 (13)	Eisai; Pfizer	CNS
Lantus	5,116	-19.1%	13 (9)	Sanofi	Metabolic
Eliquis	4,872	45.7%	14 (24)	BMS; Pfizer	Cardiovascular
Neulasta	4,798	-1.8%	15 (14)	Amgen; Kyowa Hakko Kirin	Cancer
Imbruvica	4,466	57.8%	16 (33)	AbbVie; J&J	Cancer
Harvoni	4,370	-51.9%	17 (3)	Gilead	Infectious
Tecfidera	4,215	6.2%	18 (20)	Biogen	Inflammation
Advair Diskus	4,033	-14.9%	19 (15)	GSK	Respiratory
Stelara	4,011	24.1%	20 (28)	J&J	Inflammation
Januvia	3,995	-4.3%	21 (18)	Merck & Co; Ono	Metabolic
Keytruda	3,809	171.7%	22 (94)	Merck & Co	Cancer
Copaxone	3,801	-10.0%	23 (17)	Teva	Inflammation
Genvoya	3,732	148.6%	24 (86)	Gilead; Torii	Infectious
Epclusa	3,510	100.3%	25 (70)	Gilead	Infectious
Victoza	3,445	15.6%	26 (30)	Novo Nordisk	Metaboliic
Triumeq	3,338	41.8%	27 (46)	GSK; ViiV Healthcare	Infectious
Lucentis	3,325	1.9%	28 (27)	Novartis; Roche	Ophthalmic
Gilenya	3,185	1.0%	29 (29)	Novartis	Inflammation
Truvada	3,170	-13.9%	30 (22)	Gilead; Torii	Infectious

Data for Enbrel, Opdivo and Gilenya include estimates for unreported sales from Japan or Asia partners

Humira overtook Lipitor's peak sales back in 2014 and surpassed it's inflation-adjusted peak sales in 2016. But there are still two records to go. Humira will have to outsell all other compounds for another four years to beat Lipitor's record 10 years occupying the number 1 slot.

If it does so, it will also beat the one remaining record, that for cumulative sales total since launch.

Lipitor's record up to 2017 is $154bn, and that is increasing by around $2bn each year. Humira is currently $38 billion behind Lipitor but the question is not whether but when Humira will overtake Lipitor.

Humira patents are starting to expire but have been bolstered by extended-use and manufacturing claims to give significant protection until at least 2022. If AbbVie continues to push up sales, Humira will overtake Lipitor by 2019: even if loss of exclusivity bites, Humira will become the best selling drug of all time by 2020.

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Humira's Records

- Highest annual drugs sales ever; $18.908bn (2017);
- Highest annual drug sales (inflation-corrected); overtook Lipitor in 2014 and continues to pull away;
- Second-longest continuous period of sales growth; 14 years (2003-2017) behind Lilly's Forteo (15);
- Second-longest period as the highest selling drug; six years, behind Lipitor (10);
- Second-highest cumulative sales; $116bn by 2017, behind Lipitor ($154bn by 2017).

Humira Stacks Up 20 Years Of US Market Exclusivity

JESSICA MERRILL jessica.merrill@informa.com

AbbVie Inc. appears well positioned to maintain the US commercial exclusivity of its blockbuster autoimmune disease drug *Humira* (adalimumab) for 20 years from its launch, many of those years as the world's top-selling drug. The company announced the resolution of a second patent dispute April 5, this time with **Samsung Bioepis Co. Ltd.**, which will protect Humira's market exclusivity in the US until June 30, 2023.

In Europe, Samsung's biosimilar version of Humira can launch earlier, on Oct. 16, 2018. The biosimilar, *Imraldi*, was approved by the European Commission in August 2017.

Samsung Bioepsis, a joint venture between **Samsung BioLogics** and **Biogen Inc.**, has had three tumor necrosis factor inhibitors approved in Europe, where it already markets a biosimilar version of *Enbrel* (etanercept) called *Benepali*, and a biosimilar of *Remicade* (infliximab) called *Flixabi*.

Two Humira biosimilars have been approved in the US – **Amgen Inc.**'s *Amjevita* and **Boehringer Ingelheim GMBH**'s *Cyltezo* – though neither has launched due to ongoing patent disputes. A third biosimilar from **Sandoz International GMBH** is pending at the FDA, with action expected in the second half of 2018, according to the *Pink Sheet*'s FDA Performance Tracker. Samsung wouldn't comment on the status of its Humira biosimilar in the US and it has not publicly disclosed whether or not it has filed an application with the FDA.

The outstanding question now is if other manufacturers will settle with AbbVie on the same 2023 timeline. AbbVie has a strong IP estate for Humira, with some patents extending into the 2030s.

Samsung's patent deal with AbbVie gives Amgen a five-month head start in the US market, since AbbVie and Amgen reached a patent dispute agreement last year that allows Amgen to launch Amjevita beginning Jan. 31, 2023. The timeline for launch in Europe is the same, Oct. 16.

Under the latest agreement with Samsung Bioepis, all pending patent litigation will be dropped, and the South Korean biosimilar developer will owe AbbVie royalties on sales of its biosimilar under a licensing agreement.

The timeline for biosimilar entry leaves AbbVie in a strong position. If a similar timeline holds up for other potential biosimilar entrants, it means AbbVie will have maintained US market exclusivity for Humira for 20 years. The anti-TNF was originally approved by the FDA on Dec. 31, 2002 and launched in 2003. The blockbuster biologic – approved for a range of conditions from rheumatoid arthritis to ulcerative colitis and psoriasis – has generated some $112.71bn in cumulative sales since launch.

Humira has broken all sorts of industry records, having grown into the top-selling drug in the world for six years running and generating nearly $18.4bn in global sales in 2017.

The company forecasts that sales of Humira will pass $21bn by 2020, though ex-US sales are expected to slow in 2018 due to the emergence of biosimilar competition.

Humira is on track to have sold over $200bn in cumulative revenues since its launch in 2003 through 2023, making it the most successful drug commercially ever, according to Bernstein Research analyst Timothy Anderson.

But Humira isn't the only drug to have a 20-year plus US commercial exclusivity window. When it comes to biologics, it's not unusual. But for small molecule drugs, the market exclusivity window for some of the most commercially successful drugs was more like 14 or 15 years. **Pfizer Inc.**'s statin *Lipitor* (atorvastatin) had about 15 years on the market before the first generic competitor entered, as did **Bristol-Myers Squibb Co.**'s blood thinner *Plavix* (clopidogrel).

When it comes to the other marketed anti-TNFs, Amgen's *Enbrel* (etanercept) was approved by FDA in November 1998 and the company has so far fended off biosimilar competition. FDA approved Sandoz's etanercept biosimilar *Erelzi*, but it hasn't launched due to ongoing patent litigation. FDA removed two indications from the already-approved label earlier this year, in what could be a legal strategy on the part of Sandoz.

The third TNF inhibitor on the market, **Johnson & Johnson**'s *Remicade* (infliximab), was approved by FDA in August 1998, and faced the first biosimilar competitor from *Inflectra* (infliximab-dyyb) from Pfizer]/**Celltrion Inc.** in 2016, marking 18 years of US market exclusivity. The launch of Inflectra has only highlighted the challenges biosimilars face when interchangeability isn't on the table and brand drug makers can negotiate favorable rebates with payers for high-volume products.

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'We Jumped' At Opportunity To Take On Pfizer's CAR-T Program, Allogene's Chang Says

JOSEPH HAAS joseph.haas@informa.com

With the research team, facility and intellectual property coming over from **Pfizer Inc.** under the deal creating **Allogene Therapeutics**, the new allogeneic CAR-T therapy company is able to hit the ground running, CEO David Chang said in an interview.

The new firm's April 3 agreement with Pfizer conveys not only 17 allogeneic CAR-T assets and their intellectual property, but the entire R&D team that had been working on the program for several years. "So there is no loss of momentum or in terms of continuity of what they've been doing," Chang told *Scrip*.

The opportunity arose during a celebratory dinner over Gilead's purchase of Kite, and the deal was signed 150 days later.

Pfizer's outsourcing of its CAR-T programs is noteworthy enough, but equally attention-grabbing was that the top execs from **Kite Pharma Inc.** – Arie Belldegrun, who will serve as chairman, and Chang, serving as president and CEO – are leading the charge at Allogene. Belldegrun was CEO at Kite, while Chang was chief medical officer and R&D chief when the biotech sold to Gilead Sciences Inc. for nearly $12bn last year. Less than two months later, Gilead/Kite's autologous CAR-T therapy Yescarta (axicabtagene ciloleucel) obtained US FDA approval for certain B-cell lymphomas.

Chang noted that he and Belldegrun did not expect to be helming a new CAR-T biotech so quickly, but found the opportunity to take over the program Pfizer had put together too good to pass up. Pfizer licensed the lead program, the Phase I UCART19, from **Servier SA** in 2015, while the 16 preclinical candidates were developed by Pfizer and **Cellectis SA** under their collaboration signed in 2014.

NEW DOOR OPENED AS OLD ONE CLOSED

At a dinner to celebrate the closing of the Gilead/Kite transaction last November, one of the bankers who helped arrange the deal told Chang and Belldegrun that Pfizer was looking to move the allogeneic CAR-T program. "They were looking for an entity or group of people who would be interested in taking over and continuing to work on it," Chang said. "When that came to Arie's and my attention, it took probably less than a minute to recognize why this is something we would be very interested in."

From that dinner to signing, the deal only took 150 days to come together. "We jumped into it," Chang told *Scrip*.

The launch of the first CAR-T therapeutics has increased anticipation for the next advances in the space, particularly off-the-shelf options. Chang noted that the data they were able to review in due diligence on UCART19, including data not in the public domain, convinced them Pfizer had proof of concept.

Allogene hopes to begin Phase II studies of UCART19 in acute lymphoblastic leukemia in 2019; Chang said the company hopes to work out plans for the 16 preclinical assets within six months. At least half of them address targets that might be applicable for solid tumor therapy, he added. "Much to our surprise, because Pfizer as a large company largely has been silent about what they are doing in their collaboration with Cellectis, the [two companies] have done a lot, much to the credit of people in the cell therapy unit," Chang said. "That ranges from preclinical assets going after different targets as well as trying to improve the underlying science that is needed to make allogeneic cell therapy work. When we saw that, it was very clear from our perspective that this is an exceptionally unusual opportunity."

Pfizer is not letting go entirely – as a Series A investor, it took a 25% ownership interest in Allogene.

Chang is eager to stick with a small, dedicated company, which is why he didn't go over to Gilead. He said Allogene's narrower focus should help advance the Pfizer/Cellectis programs more quickly. "We could have stayed and continued to work as part of Gilead, but that would have taken much longer, in my view."

"It's not surprise how a large company operates compared to how a smaller company operates – there are some differences in speed of decision-making and how you set priorities," Chang explained. "For Allogene, allogeneic cell therapy will be the top priority. I don't want to speak for Pfizer, but I don't think that was necessarily the case [there]."

Chang and Belldegrun also provide the edge of expertise, from Kite's experience on regulatory requirements for CAR-T therapeutics and foundational knowledge about the necessary manufacturing processes. "We will enhance the manufacturing group to speed up the manufacturing and make the process more consistent and reproducible," Chang pledged.

Along with a quicker process than the ex vivo engineering of cells taken from the patients themselves in autologous therapy, an allogeneic product means a reduced manufacturing cost, "which can hopefully bring down the cost of treatment a little bit," Chang said. An autologous therapy takes three weeks or more to engineer before the cells can be infused back into the patients, he noted.

NEW HORIZONS FOR ALLOGENEIC THERAPY

There are still challenges in moving from autologous to allogeneic treatment, like patients' reaction to the engineered T-cells and graft-versus-host disease – but Chang thinks the clinical data show that gene editing to remove certain T-cell receptor genes along with a purification process can overcome that.

Dealing with the patient's host immune response after the allogeneic therapy is infused requires "a fine balance," he added, because the therapy needs to be active in the patient's body long enough to be effective but not too much longer than necessary for safety reasons. "Some of the work still going on is about what is the optimal time to maintain these engineered cells in the body," the exec said. Allogene hopes the work of Pfizer and Cellectis will provide a general foundation for all allogeneic CAR-T therapies, but conceded that other companies are working on these issues as well. "And we'll be paying very close attention to the field," he said.

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New Novartis CDO Bodson Outlines Digital Health Ambitions

MIKE WARD mike.ward@informa.com

With a wealth of data management experience from his time at Sainsbury's Argos, EMI Music, Bragster.com and Amazon, Bertrand Bodson is relishing the opportunity of marrying digital technologies and data science to enhance the development and delivery of treatments to patients. He believes it will not only shake up the conventional pharma commercial model it will also catalyze a cultural shift within the industry.

Bertrand Bodson

"I think big gains will be made by fundamentally changing the way we work across the entire product lifecycle. From research and development to manufacturing to – how we engage and educate doctors and patients about our products and services. A successful digital transformation also requires a culture change – we need to unleash the power of our people as well as adopt more agile ways of working. Having joined **Novartis AG** from the retail sector, I can also see the benefits of us shifting from a mainly product-oriented company to one more focused on enhancing the customer experience – digital, data and technology will be the key to making that happen," he told *Scrip*.

Describing the digital health opportunity as a blank canvas, he is excited at the opportunities to reimagine medicine and the use of technology to solve some core healthcare challenges, including access to medicines. "Digital technologies and data science have the potential to help us unlock the next chapter in medical innovation, from transforming our commercial models to enhancing the customer experience and accelerating the pace at which we find and get drugs to market," he added.

In his new role, Bodson says success will involve bringing new, more targeted, more effective drugs to the market quicker and more efficiently. "It's combining data and patient insights to design improved clinical trials that reflect the diversity and needs of patients, ultimately generating better outcomes for patients," he added.

Bodson expects data science and digital technologies to have an impact across the whole value chain. Indeed, he envisages a future in which patients, supported by providers and their own personal medical data, will be empowered to play a more active role in managing their own disease prevention and treatments. Furthermore, he anticipates increasingly integrated payer-provider systems exerting greater oversight of doctor decision-making to control costs and improving outcomes.

"Physicians and other healthcare providers will play an important – but different – role in guiding patients through the healthcare system, focused on informing them about their conditions, and helping them make key decisions about their care," he forecasts.

To achieve its digital health ambitions, Novartis will need to look outside its traditional competitor space and work with external partners and experts in data, digital and design who bring with them a start-up mentality. "The best partners will be those who can help us make the most of our data and offer us deep expertise in addressing specific challenges using the latest digital technologies e.g. solving data privacy issues across the healthcare industry," he noted.

Moreover, he is keen for Novartis to embed across its whole business some of the agile working practices of start-ups into its own culture to encourage small cross-functional teams of seven to eight people who are empowered to make fast decisions focused on customer/business needs. It means supporting a culture that encourages curiosity and learns from failure. Bertrand believes such teams can have more impact than much larger teams. He wants the company to be considered the destination of choice for future talent, "not just for those focused on the science, but that tech and data experts too are excited by what we can all achieve together".

As part of its strategy to keep disruptive digital health developments on its radar, the company's German arm has launched a Digital Health Award to identify promising start-up ideas. This year's competition attracted more than 80 entries.

BOOSTING PATIENT ENROLMENT

Specifically, one area Novartis is focusing on is how it can apply next generation data science to clinical processes. With its Nerve system, a computing mechanism it began co-developing with Quantum Black in 2016, Novartis is using predictive analytics to design, monitor and generate insights across its global operations. The program combines data on clinical trial operations from multiple internal systems, applying machine learning and advanced analytics, to predict and monitor trial enrolment, trial cost and trial quality. This is enabling Novartis to increase automation, maximize efficiency and make data-driven decisions and has already delivered a 10-15% reduction in patient enrolment times in pilot trials.

"We will also have the capability for deeper analysis and more complex data-driven decision making, such as a dosage planning system that will help us better calculate the exact amount of drug we need to produce for our clinical trials to remain operational at the highest levels – ensuring we avoid both shortages and surpluses, which of course cost time and money," he explained.

Published online 6 April 2018

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

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

Selected clinical trial developments for the week 30 March–5 April 2018

LEAD COMPANY/PARTNER	COMPOUND	INDICATION	COMMENTS
PHASE III RESULTS PUBLISHED			
Bristol-Myers Squibb Co.	*Opdivo* (nivolumab) plus ipilimumab	advanced renal cell carcinoma	CheckMate 214; *NEJM*, Apr. 5, 2018.
ArQule Inc./Daiichi Sankyo Co. Ltd.	tivantinib	liver cancer, second line	METIV-HCC; *The Lancet Oncology*, Apr. 3, 2018.
PHASE III INTERIM/TOP-LINE RESULTS			
Eli Lilly & Co.	*Cyramza* (ramucirumab)	liver cancer, second line	REACH-2; met overall survival and PFS endpoints.
Gedeon Richter PLC/Allergan PLC	*Vraylar* (cariprazine)	bipolar I depression	RGH-MD-53; met primary endpoint.
GenSight Biologics SA	GS010, gene therapy	Leber's hereditary optic neuropathy	REVERSE; well tolerated, efficacy noted.
UPDATED PHASE III RESULTS			
Evolus Inc.	*Evosyal* (prabotulinum-toxinA)	wrinkles	EVB-003; met primary endpoint.
PHASE III INITIATED			
Denovo Biopharma LLC	enzastaurin plus chemotherapy	diffuse large B-cell lymphoma	ENGINE; with or without the DGM1 biomarker.
Retrophin Inc.	sparsentan	focal segmental glomerulosclerosis	DUPLEX; a global study.
Radius Health Inc.	*Tymlos* (abaloparatide)	osteoporosis	ATOM; in male patients.
Adamas Pharmaceuticals Inc.	ADS-5102 (high dose amantadine)	multiple sclerosis	With walking impairment.
PHASE II INTERIM/TOP-LINE RESULTS			
ThromboGenics NV	THR-317 (anti-PIGF)	diabetic macular edema	Well tolerated, initial efficacy signs.
Conatus Pharmaceuticals Inc./ Novartis AG	emricasan	liver failure	POLT-HCV-SVR; signs of efficacy.
Bio-Path Holdings	prexigebersen plus cytarabine	acute myeloid leukemia	Early antileukemic signs.
Dr. Reddy's Laboratories Ltd./ Aegis Therapeutics LLC	DFN-02 (intranasal sumatriptan)	migraine	Pain reduced, symptoms alleviated.
MediciNova Inc.	MN-001 (tipelukast)	non-alcoholic steatohepatitis (NASH)	Triglyceride levels reduced, well tolerated.
UPDATED PHASE II RESULTS			
Rigel Pharmaceuticals Inc.	fostamatinib	Berger's disease	Well tolerated, mixed results.
Sellas Life Sciences Group Inc.	*NeuVax* (nelipepimut-S) plus trastuzumab	breast cancer, triple negative, adjuvant	Positive interim data.
Symic Biomedical Inc.	SB-030	peripheral arterial disease	SHIELD; improved outcomes.

Source: Biomedtracker

Sofinnova Targets Later Stage Firms With €275M Healthcare Crossover Fund

MIKE WARD mike.ward@informa.com

European biotech and medtech companies have a new source of growth capital to tap. Sofinnova Partners, which has for the past four decades focused on seed and series A venture funding of life science start-ups, has launched the Sofinnova Crossover I fund with €275M ($340M) to finance cash thirsty later stage biotech and medtech companies.

"Raising money in seed and series A rounds has never been easier for European life science start-ups. The challenge they face is accessing capital to finance their growth as they mature. This new fund is our first to designed to help companies build sustainable businesses," Antoine Papiernik, Sofinnova Partners managing partner and chairman, told *Scrip*.

In the past four decades, through eight capital funds, Sofinnova Partners has focused exclusively on creating companies with seed and series A financing and it has an impressive track record – notable successes include **Actelion Pharmaceuticals Ltd.**, **Ablynx NV** and CoreValve. "With that focus, we were never able to participate in subsequent rounds as they grew," he added.

With the new fund, Papiernik is targeting private companies that might be looking to go public within an 18 month to two year timeframe or microcap public companies wanting to break away from local European exchanges and list in the US. "Companies will usually be 5-10 years old and will have demonstrated proof of concept with Phase II data and expect significant readouts in the next 24 months that will enable them to go public, generate liquidity or be bought," he explained.

Having attracted more money than its original target of €250M, Sofinnova Crossover I seeks to invest about 75% of its funds in biopharma and 25% in medtech opportunities. Geographically, the focus will primarily be on European (80%) opportunities with the remainder earmarked to participate in syndicates backing US businesses.

While some of the traditional backers of its early stage funds, such as the French sovereign fund Bpifrance and the French insurance company CNP Assurances, are backing the new fund, Sofinnova has also been be able to attract new investor groups. "We have two Chinese investors and got a lot of European and Asian family fund offices – which is new for us – supporting the fund. I have visited China four times in the past year and there is an appetite for these assets, while the risk profile of the fund is more attractive to family offices than our capital funds," he added.

Sofinnova has recruited a new team of four partners to manage the crossover fund. Heading the team will be industry veteran Jacques Theurillat, who has both operational and investing experience from his time at Serono, where he held many executive positions including deputy CEO, and co-founding and running the Ares Life Sciences fund. Joining him will be Tom Burt, who was with Jacques at Ares but has also worked at Peel Hunt, Piper Jaffray and the Novo Growth Equity fund, and Kinam Hong, who previously managed the Exane Equinox fund and spent 10 years as an investor and analyst covering the biotech sector, including at Citigroup investment research where he focused on small- and mid-cap companies. A fourth partner has yet to be announced as the recruit is currently on gardening leave.

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Nordic Nanovector ASA has announced that ***Luigi Costa*** will step down as chief executive officer by mutual agreement with the board following a further delay in the development of its key product Betalutin. A search for a new CEO will begin immediately. Nordic Nanovector said that to ensure a smooth transition, Mr Costa had agreed to be available to the board until the end of July 2018. Luigi Costa said: "Nordic Nanovector has recently taken a significant hit to its market valuation and credibility with the Norwegian investment community. As CEO, I have to take full responsibility for this."

Dr. Kenneth Newman has resigned from his position as chief medical officer at **Verona Pharma** to pursue other opportunities, effective April 30. The company has begun the search for a replacement.

Medigene AG has appointed ***Dr. Kai Pinkernell*** chief medical officer and chief development officer. Pinkernell has been with Medigene as Senior vice president and chief medical officer since February 2016. Before joining Medigene, he held various management positions at Miltenyi Biotech GmbH, Bergisch Gladbach, Germany.

DalCor Pharmaceuticals today announced the appointment of ***Dr. Fouzia Laghrissi-Thode*** as chief executive officer, effective April 3. Laghrissi-Thode is currently on the board of directors for DalCor. Laghrissi-Thode has more than 20 years of pharmaceutical industry leadership experience including leading the DalCor's dalcetrapib Dal-HEART program. Most recently, she was vice president at AstraZeneca of the US renal-cardiology therapeutic area.

PureTech Health has made ***Edward J. "Tad" Stewart*** president and chief executive officer of its affiliate, Commense. In this new role, Stewart will focus on advancing Commense's lead program towards the clinic, growing the company's microbiome-based development capabilities and expanding leading business development and finance activities. Stewart most recently served as senior vice president of business development and head of commercial business at Merrimack Pharmaceuticals.

Argenx, a clinical-stage biotechnology company developing antibody-based therapies for severe autoimmune diseases and cancer, today announced the appointment of ***R. Keith Woods*** as chief operating officer. Woods was most recently as senior vice president of North American operations for Alexion Pharmaceuticals Inc.

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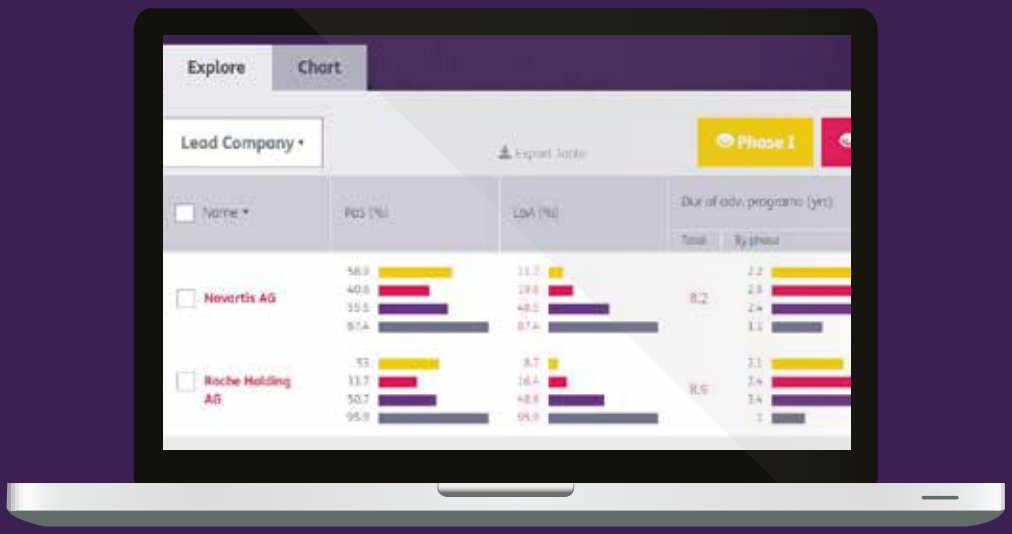

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