



## Novartis CEO Calms Concerns Over Zolgensma launch

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Novartis AG is keeping quiet when it comes to specific sales of its gene therapy Zolgensma but CEO Vas Narasimhan has said that contrary to some analyst claims, the launch is going well.

There is huge interest in Zolgensma (onasemnogene abeparvovec), which was approved in the US for all three types of spinal muscular atrophy (SMA) at the end of May, not least because of the fact that it is the world's most expensive drug. The gene therapy comes with a price tag of over \$2.1m, although Novartis has also proposed an annuity-like model under which Zolgensma would cost \$425,000 annually for five years. (Also see "It's Official: Novartis SMA Gene Therapy Zolgensma Is World's Most Expensive Drug" - Scrip, 24 May, 2019.)

There have been noises that the launch has not gone so smoothly, especially following a 2 July investor note from analysts at Bernstein who said they had collected early coverage decisions on Zolgensma from 11 payers in the US and found them to be "surprisingly restricted." This reflected what the broker called "unexpected and material payer resistance to the Zolgensma price point."

However, speaking on a conference call for the Swiss major's second quarter results, Narasimhan rejected the Bernstein claims, saying that the Zolgensma roll out is on track and in line with expectations. He stressed the speed of the launch, with US approval coming on 24 May and the first patient treated on 7

June, but did not give specific sales or numbers of patients treated.

Narasimhan did point out that over 20 commercial plans covered by medical policies have been agreed, and "not all of these have been posted on external websites," he said, adding that Novartis is seeing very high approval rates for on-label patients via medical policy or through medical exception, a common process for new launches. He noted that a wide range of patients had been approved for Zolgensma treatment in terms of age (one month to 23 months) and weight (4 to 12kg), covering patients who are treatment-naïve or have been treated with Biogen Inc's SMA blockbuster Spinraza (nusinersen).

In terms of the contracting options that Novartis is offering, letters of intent for 17 commercial plans have been signed, although the terms have not been disclosed, the CEO said. The company is initiating discussions with the US Food and Drug Administration on a regulatory path for Zolgensma intrathecal dosing for older populations, while approvals in infants in Europe and Japan are expected in the fourth quarter.

Another important launch in Q2 was Piqray (alpelisib), the first drug to be approved for treatment of HR+, HER2-negative breast cancer with PIK3CA mutations and the first given the thumbs-up, along with its associated companion diagnostic test from Qiagen NV, under the FDA's Real-Time Oncology Review pilot program. Again Narasimhan said it was too early to give any sales figures but said, "We're pleased with the progress we're already making with payers, covering over 80% of the target population in the US [and] we're also seeing good uptake of the PIC3 mutation testing which is really

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New arrivals test US market receptivity (p7)



## from the editor

eleanor.malone@informa.com

The launch in the US of biosimilar versions of Roche’s anticancer monoclonal antibodies Avastin and Herceptin marks the beginning of a new era.

Roche has already seen the early impact of biosimilars for Herceptin: annual sales of the product declined by 16% in both Japan and Europe in 2018, following the entry of competing versions of trastuzumab in mid-2018 in both regions. By the first quarter of 2019, the decline was 44% in Europe, enough to push global revenues of the product into decline despite continued growth in China and the US. But the US is the largest market for the products, as well as for its Rituxan (rituximab), which could see biosimilar competition also in the US this year. Between them the trio of MAb’s generate 47% of Roche’s revenues, so these launches will be a real test for the company.

There has been much debate over how successful oncology biosimilars will be in the US, after the limited number launched for inflammatory and other indications have struggled to gain traction. We consider the outlook, taking into account contracting, discounting and rebating dynamics and the different commercial challenges for chronic versus limited-term therapy, on p7-8. For more on this topic, see our online-only infographics on the rise and coming fall of Herceptin and Avastin at [www.scrip.pharmaintelligence.informa.com](http://www.scrip.pharmaintelligence.informa.com). Meanwhile, in the inflammatory space, biosimilars are slowly eroding Johnson & Johnson’s US sales Remicade (infliximab) despite the success of J&J’s early defences. Read more about J&J’s latest financial update on p5-6.

# Scrip

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## Loss And Gain: Trade War Halves China Biotech VC Funding To US, But Asian Countries May Benefit

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The latest investment data have biotech executives in the world's two largest economies worrying.

Venture capital funding in the US biotech sector from China in the first six months of 2019 fell by nearly 60% compared to the same period of last year, due mainly to tightened investment security measures imposed by Washington, according to Pitchbook Data cited in the *Financial Times*. Actual VC funding from China in US biotech was tallied at \$725m, down from \$1.65bn in the first half of 2018.

The US has so far been the single largest destination for such investment from China, where strong demand for novel therapies has sharply driven up licensing and collaboration deals in recent years. Biotech is one of 10 pillar industries identified by China in the ambitious national "Made in China 2025" strategic economic plan.

Since the beginning of 2018 however, China and the US have engaged in a prolonged trade and tit-for-tat tariff dispute, and Washington instigated security reviews of investment in key sectors including biotech, citing national security concerns. US president Donald Trump last August signed into law an expanded Committee on Foreign Investment to the United States (CFIUS), extending the review time from 75 days to a potential 105 days for such investment.

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To read the rest of this story go to: <https://bit.ly/2XWD1wO>

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our focus this year.” (Also see *“Keeping Track: Novartis Scores Big Ahead Of US Memorial Day With Approvals For Gene Therapy Zolgensma, Oncologic Piqray” - Pink Sheet, 26 May, 2019.*)

Novartis, which has entered into an agreement with Foundation Medicine to develop a plasma and tissue test, is also exploring Piqray in other tumor types. Narasimhan revealed that the second half of 2019 will see trials start in HER2+ advanced breast cancer as well as triple-negative breast cancer, with Phase III studies for head and neck and ovarian cancers starting in the first half of next year.

As for the Q2 financials, core operating income rose 20% in constant currencies to \$3.65bn while sales were up 8% to \$11.76bn, ahead of analyst consensus estimates. Cosentyx (secukinumab) for psoriasis, psoriatic arthritis and ankylosing spondylitis soared again, contributing \$858m to the firm’s coffers, a 25% rise.

Novartis noted that sales of its second biggest earner, the multiple sclerosis therapy Gilenya (fingolimod), dipped 2% to \$825m. No sales figures were given for Mayzent (siponimod), the oral active secondary progressive MS drug approved by the FDA earlier this year. Narasimhan said the company’s focus was initially on educating physicians and identifying eligible patients using digital tools, with 90% of neurologists telling the firm in surveys that they are willing to prescribe Mayzent. (Also see *“FDA Backs Novartis MS Pill Mayzent With Broad Label” - Scrip, 27 Mar, 2019.*)

Other positives for Novartis included the performance of the heart failure treatment Entresto (sacubitril/valsartan), which leapt 81% to \$421m, though the spotlight is now very much on the eagerly anticipated readout of the PARAGON-HF trial of Entresto for preserved ejection fraction heart failure. Narasimhan said the study, which has a primary endpoint of

cardiovascular death and total heart failure hospitalizations, “will give us the best possible chance at succeeding in a patient population that’s never had an approved medicine.” The results will be presented at the European Society of Cardiology meeting in Paris in September.

Interestingly there was no mention on the conference call about another lacklustre performance for Novartis’ CAR-T treatment Kymriah (tisagenlecleucel). Q2 sales came in at just \$58m only slightly up on \$45m in the first quarter, although Novartis insisted that “strong demand continued.” Narasimhan also confirmed that Novartis has set aside \$700m to settle a doctor bribery lawsuit in the US. The case, originally brought seven years ago, involves payments made for speaker programs and other promotional events between 2002 and 2011, he said, noting that the company is keen to resolve legacy compliance-related allegations. ✨

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## US Generics Market Isn’t Stabilizing Yet, Sandoz Says

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Sandoz International GMBH set a pessimistic tone for the US generics market when its parent, Novartis AG, reported second quarter financial results on 18 July. The company said it does not expect a stabilization in US generic price erosion, contrary to what some other generic drug makers have indicated recently.

Sandoz is the first of the big generic drug players to report second quarter results, and with the business segment under pressure for several years now investors in drug companies like Teva Pharmaceutical Industries Ltd. and Mylan NV are anxious to see the US market deterioration stabilize. Higher annual price erosion in the US – in the double-digits – has been a persistent challenge for the generic drug industry since 2015. (Also see *“Generic Manufacturers Try To Up Their Game As US Pressure Persists” - Scrip, 16 Jun, 2017.*)

Generic drug makers have tried to pivot to complex products and biosimilars, branded products or geographic expansion to offset the US declines, but those efforts have had minimal success, particularly as the near-term commercial prospects for biosimilars in the US have dampened.

Mylan’s board of directors kicked off a strategic review a year ago and has yet to report back to investors with the results. (Also see *“Mylan To Explore Strategic Options, Claiming Investors Have Failed To Appreciate The Value” - Scrip, 8 Aug, 2018.*) Meanwhile, Teva is in the midst of a two-year restructuring program to reduce spending by \$3bn by the end of 2019 while paying down on a mountain of debt. (Also see *“A Trough Year For Teva, With A Turning Point Targeted For 2020” - Scrip, 13 Feb, 2019.*)

Investors in Mylan and Teva will be keen to hear positive mid-year updates from both. Mylan is preparing to outline its long-term strategic plan to investors during a meeting in New York on 31 July.

**Sandoz – buffered by the shelter of Novartis and a steady ex-US business – has held up better than some in the generics sector.**

Sandoz – buffered by the shelter of Novartis and a steady ex-US business – has held up better than some in the generics sector. But Novartis is still trying to revamp the business, with an emphasis on complex products. The company reached a deal with Aurobindo Pharma Ltd. to sell its US solid-dose generics and dermatology franchise for up to \$1bn. The deal remains on track to close in 2019, pending regulatory approvals, Novartis said.

Richard Francis, the CEO of Sandoz for five years, stepped down earlier this year amid the ongoing changes. SC124908 The company recruited GlaxoSmithKline PLC’s established products senior VP Richard Saynor to succeed Francis, and he joined the quarterly call for the first time.

Sandoz reported second quarter sales of \$2.4bn, a decline of 1% over the prior-year quarter, with volume growth of 10% offset by 7% price erosion mainly in the US. Excluding the US, net sales grew 7%. Biosimilars helped drive that growth, with 16% growth in biopharmaceuticals stemming from sales of Sandoz's biosimilar versions of Rituxan, Humira and Enbrel in Europe: Rixathon (rituximab); Hyrimoz (adalimumab); and Erelzi (etanercept), respectively.

The launch of several biosimilar versions of AbbVie's Humira last year in Europe are being closely watched. (Also see "Biosimilar Infliximab Success Paves The Way For Adalimumab In Europe" - Scrip, 16 Aug, 2018.) Hyrimoz has about a 22% share of the adalimumab market in Europe and is the number three biosimilar in the category, Sandoz reported.

**US PRICE EROSION CONTINUES**

Sandoz management said it was pleased with the second quarter results, driven by strong ex-US sales, and raised 2019 sales guidance to low single-digit growth. Nonetheless, Saynor said the company expects the US environment to remain challenging and the decision to raise guidance was based on momentum outside the US.

"We're very proud of how Sandoz is performing ex-US," Saynor said. "Within the US, our team continues to work hard in what is a challenging environment."

The US base business is continuing to decline in the mid-teens, consistent with historical declines, Saynor added. "We haven't seen yet a stabilization in the core generics business in the US."

That outlook is more pessimistic than guidance provided by Teva and Mylan earlier this year. Teva CEO Kare Schultz indicated at the J.P. Morgan Healthcare Conference and again when reporting fourth quarter financial results that US price erosion appears to be abating. He said at the J.P. Morgan meeting that there has been a "dramatic change" in the pricing "death spiral."

SVB Leerink analyst Ami Fadia also said in a same-day note that Sandoz's outlook did not match with recent National Average Drug Acquisition Cost (NADAC) data, where price erosion has fallen to around 4% in recent quarters. NADAC estimates the national average drug invoice price paid by independent and retail chain pharmacies.

"As such, we remain cautious that the NADAC trends we've seen recently will translate to base business improvement across our generics coverage," Fadia said.

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# J&J US Pharma Sales Under Pressure From Pricing And Generics

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Johnson & Johnson's pharmaceutical business faced headwinds in the US in the second quarter with pricing pressure and the loss of patent exclusivity for the prostate cancer drug Zytiga (abiraterone). Management warned investors during a conference call on 16 July that an even greater negative impact from Zytiga will be felt in the third quarter.

US Pharmaceutical sales declined 2% in the quarter, driven by a 59.4% decline in US Zytiga revenues to \$198m. Worldwide sales of the drug declined 23.3% to \$698m in the quarter. Sales of Remicade (infliximab) in the US – under pricing pressure from the launch of biosimilars – also declined 12.7% to \$801m. Despite the lower sales, J&J's results beat analyst consensus

estimates, which had expected US pharma sales to decline 3%.

On top of the generic and biosimilar headwinds, J&J reported that net prices declined by around 6% in the US. The blood-thinner Xarelto (rivaroxaban) in particular faced pricing pressure, despite volume growth, because of higher rebates required due to changes to Medicare Part D reimbursement related to the donut hole. A pattern of continued price erosion offset by volume growth should continue, but remains in line with recent experience, vice chairman Joaquin Duato guided investors.

"We don't see that changing," Duato said. "What we think is in that context, we are positioned most favorably...because of the diversification of our portfolio."

Worldwide pharmaceutical revenues increased 1.7% in the second quarter to \$10.53bn, with headwinds offset by double-digit growth from nine key brands, including Stelara (ustekinumab), Tremfya (guselkumab), Darzalex (daratumumab) and Imbruvica (ibrutinib).



The IL-23 inhibitor Tremfya for plaque psoriasis continued its strong growth trajectory, with revenues up 86.5% in the quarter to \$235m. Psoriasis is a blockbuster therapeutic area with big competitive dynamics that investors are watching closely.

J&J committed, during a pharma investor event in May, to achieving above-market compound annual growth in the business between 2019 and 2023 and highlighted plans for 10 new drug filings by 2023.

SVB Leerink analyst Geoff Porges, in a 16 July note, pointed out that despite J&J's specific generic and biosimilar challenges and a negative foreign exchange impact, the company's results bode positively for large-cap pharma's second quarter reporting season.

"These isolated issues should not affect the reported Q2 results of large cap

biotech, but the general portfolio trends provide positive sector read-throughs," Porges said.

Double-digit growth coming from nine products suggest positive trends across multiple therapeutic areas, he said. Plus, the fact that J&J does not anticipate an increase in US pricing challenges and reiterated its expectations for a 6% overall pricing headwind in 2019 is reassuring, he added.

In oncology, Darzalex for multiple myeloma continues to be a big growth-driver for J&J, with worldwide sales up 51.6% to \$774m in the quarter. The company expects a new subcutaneous formulation of the product will help Darzalex maintain its dominant position in the market even as a new competitor, Sanofi's isatuximab, approaches. The company confirmed it filed the subcutane-

ous formulation of Darzalex with the US Food and Drug Administration on 12 July. The subcutaneous formulation dramatically reduces administration time to three to five minutes versus several hours for the existing intravenous formulation.

J&J is also in the midst of launching a new growth-driver, the antidepressant Spravato (esketamine), which was approved by the US FDA in March for treatment-resistant depression. The approval came with a risk evaluation and mitigation strategy (REMS), requiring controlled distribution due to risks of sedation and hallucination.

Distribution is limited to certified hospitals, pharmacies and outpatient care centers, and J&J reported that 1,600 centers have been certified, up from the 800 reported during the first quarter call. ✨

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## AM-Pharma Raises €116m To Finance Solo Phase III Trial

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AM-Pharma BV has persuaded a syndicate of established European venture capitalists, co-led by new investors LSP and Andera Partners, to back a multinational pivotal Phase III trial of its recombinant alkaline phosphatase (recAP) to treat acute kidney injury (AKI). The Bunnick, the Netherlands-based biotech has raised €116m (\$133m) and is now going it alone after it was told, at the end of the second quarter of 2018, that Pfizer Inc. would not be exercising an acquisition option secured as part of a 2015 deal.

In April 2015, Pfizer acquired a minority equity stake in AM-Pharma for \$87.5m and secured an exclusive option to acquire the remaining equity for a total \$600m. That option was exercisable on completion of the 301 patient Phase II STOP-AKI trial of recAP for the treatment of AKI related to sepsis. Pfizer declined to exercise that option after AM-Pharma reported mixed data from the trial of the once-daily IV recAP for three days in March 2018.

"We missed the primary endpoint which was to significantly improve kidney function, over the first seven days versus placebo. However, we did see a significant improvement in the long term kidney function after 28 days versus placebo

and we also saw a significant reduction in mortality of more than 40% and that has been unheard of and that makes us optimistic for the Phase III," Erik van den Berg, AM-Pharma's CEO, told *Scrip*. The results have been published in the *Journal of the American Medical Association*.

"We have taken back full control of the asset. The relationship with Pfizer is over although they continue to be a shareholder of the company and a strong supporter of the program. The collaboration has been valuable and had contributed to the Phase III readiness of the program," he added.

In the six months following Pfizer's decision, AM-Pharma had discussions with regulators at the FDA and EMA about what the company would need to show to secure approval to treat sepsis-associated AKI. "Discussions with the FDA and EMA indicate that we won't have to do two studies but just one pivotal study that will involve 1400 patients. We intend to conduct, at the start of 2020, a Phase III study in at least 100 hospitals in 12 different countries, so expanding the Phase II study, with a focus on hard clinical endpoints including mortality," van den Berg noted.

Following the company's discussions with the regulators, van den Berg spent

the past six months on the road drumming up support for the current venture round. "Given the current financing climate, we realised we had an opportunity to finance the Phase III program ourselves and with that become an independent pharma company taking this product to market. When we did the deal with Pfizer in 2015 I don't think that would have been possible," he explained.

The financing round was co-led by new investors LSP and Andera Partners, and includes founding investor Forbion together with other investors, Ysios Capital, Kurma Partners, ID Invest Partnersm BB Pureos Bioventures and Gilde Healthcare. Existing strategic investors – Abbvie, Shire and Pfizer have not participated.

While van den Berg declined to say precisely how much of a stake the current syndicate will have in the company he conceded that it was substantial. "This is the largest fundraising to date, it is more than double the amount we have raised in debt and equity, and preferred shares have been issued to the shareholders. With this financing we now have sufficient funds in-house to finish the large Phase III trial we have in mind," he added. ✨

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# US Market For Therapeutic Cancer Biosimilars Will Be Tested By Mvasi, Kanjinti Launches

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Amgen Inc. and Allergan PLC will be the first to test the US market's appetite for biosimilar versions of therapeutic oncologic agents with the partners' 18 July launch of Mvasi and Kanjinti, which reference Roche/Genentech Inc.'s Avastin (bevacizumab) and Herceptin (trastuzumab), respectively.

The US has been slow to embrace the few biosimilars that have reached market to date, largely due to commercial dynamics involving contracting practices, rebates and reimbursement. However, some analysts seem to think those hurdles are smaller or nonexistent when it comes to competing against Genentech's blockbuster cancer franchise.

It remains to be seen, however, whether oncologists in the US will be comfortable with the idea of prescribing biosimilars, rather than their well-known reference products, to treat new or existing patients with cancer.

Mvasi (bevacizumab-awwb), which was approved in September 2017, and Kanjinti (trastuzumab-anns), which was approved 13 June, are the first anti-cancer biosimilars to become available in the US.

The biosimilar launches mean the end of Genentech's stranglehold on sales of trastuzumab, a HER2/neu receptor antagonist that came to market in 1998, and bevacizumab, a vascular endothelial growth factor inhibitor first approved in 2004. (Also see "Sunset Begins For Roche's Herceptin As Amgen/Allergan Biosimilar Launches" - *Scrip*, 19 Jul, 2019.)

The biosimilars launched at risk because Amgen is embroiled in patent litigation with Roche.

## 15% DISCOUNT TO REFERENCE PRODUCTS' LIST PRICE

Mvasi and Kanjinti launched at a wholesale acquisition cost (WAC), or list price, 15% lower than that of their reference products, Amgen and Allergan said.

Kanjinti's WAC of \$3,697.26 per 420 mg multi-dose vial is 13% below the average sales price (ASP) of Herceptin. The WAC for Mvasi is \$677.40 per 100 mg and \$2,709.60 per 400 mg single-dose vial, which is 12% below the Avastin ASP.

"These figures do not include rebates or other discounts that would further reduce the net price (we do not believe that Amgen would disclose the discount)," Credit Suisse analyst Evan Seigerman said in a 19 July note to Amgen investors.

"We currently assume a net price discount of 35% to the innovator molecule – factoring in both the stated discount to the WAC and the additional rebates," Seigerman said. "We note that Amgen appears to be offering patient assistance programs for these assets, essentially selling them more like a branded product versus a traditional generic."

"We think that contracting/access in addition to policy around J-codes" for Medicare billing "and interchangeability will also impact uptake curves," Seigerman added. Neither Mvasi nor Kanjinti

is approved by the US Food and Drug Administration as interchangeable with their reference products.

Kanjinti is labeled for the same indications as Herceptin: treatment of HER2 overexpressing breast cancer, and HER2 overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma.

Mvasi's labeling does not include the Avastin indication for treatment of epithelial ovarian, fallopian tube, or primary peritoneal cancer as these uses are protected by orphan drug exclusivity. (Also see "Celltrion's Biosimilar Rituximab Brings Indication Carve Outs To US FDA Panel Review" - *Pink Sheet*, 12 Sep, 2018.) "We do not know if this will be a significant barrier to usage, but highlight the risk," Seigerman said of Mvasi's labeling carve-out.

## BERNSTEIN BULLISH ON UPTAKE

Bernstein analyst Ronny Gal took a look at the upcoming launches of biosimilars for Roche's top-selling cancer drugs Herceptin, Avastin and Rituxan (rituximab) – together representing about \$10bn in product sales for the Swiss big pharma – and predicted in a 4 June report that oncology biosimilars would see greater uptake than biosimilars for inflammatory diseases and cancer supportive care, such as Johnson & Johnson's Remicade (infliximab) for rheumatoid arthritis and other autoimmune diseases, and Amgen's long-acting neutropenia therapy Neulasta (pegfilgrastim).

The main factor for Gal's assessment was existing pricing dynamics for the innovator products, since Roche does not offer big discounts to hospitals, clinics and payers. He indicated that hospitals and clinics, in particular, may be inclined to use the biosimilars instead of the brand-name therapies because they resent Roche's pricing and distribution practices and may realize greater profits from discounted biosimilars.

In contrast, J&J and Amgen have been aggressive in defending Remicade and Neulasta, respectively, from biosimilar competitors, offering some combination of rebates, discounts and bundling with other products to incentivize payers to keep their branded medicines as preferred products.

Pfizer Inc., whose Remicade biosimilar Inflectra has struggled due to J&J's tactics to protect its product, is more optimistic about its oncology biosimilars. The company's Trazimera, a Herceptin biosimilar, gained FDA approval in March, while Zirabev, which references Avastin, got the nod in June, although neither has launched. Pfizer's rituximab biosimilar is under FDA review with a user fee goal date this month.

Pfizer Biopharmaceuticals Group President Angela Hwang noted in January that oncology drugs are administered for shorter periods of time than biologics for inflammatory conditions and patient turnover is greater, so doctors have more opportunities to start new patients on biosimilars to treat cancer. (Also see "Pfizer: Time To Face The Lyrica Pain" - *Scrip*, 29 Jan, 2019.)

Anticipation of better uptake for biosimilars in oncology may be why Amgen and Allergan chose to price Kanjinti and Mvasi at just 15% discounts to the WAC prices for Herceptin and Avastin, although the depth of additional discounting is unknown.

The disclosed 15% price cuts contrast with the 33% price discount that Coherus BioSciences Inc. offered for its Neulasta biosimilar Udenyca, which was on par with Mylan NV's Fulphila.

Such discounting may be necessary to compete with Amgen's branded product, since executives said during the company's first quarter earnings call in April that Neulasta retained a 90% share of the pegfilgrastim market, despite the launch of two biosimilars in the US, though Neulasta sales likely will see greater erosion as the year goes on. (Also see "Lower-Cost Competitors Hit Amgen's Blockbusters" - Scrip, 30 Apr, 2019.)

#### THE COMFORT FACTOR

Mvasi and Kanjinti will directly test oncologists' comfort level with the concept of biosimilars for cancer treatment.

Although Mvasi and Kanjinti are the eighth and ninth biosimilars to launch in the US, all of the other products that have reached market to date are used either for treatment of inflammatory conditions (such as biosimilars of Remicade) or for supportive care in cancer patients (such as copies of Amgen's Neupogen, Neulasta and the erythropoietin Epogen).

Some experts have predicted biosimilar adoption could depend upon the disease state, with physicians potentially more inclined to use them for inflammatory conditions than for a life-or-death diseases like cancer.



**"The adoption by doctors of biosimilars for curative clinical settings (cancer) is likely to be a slower ramp than chronic conditions (psoriasis)."**  
— Scott Gottlieb

"The adoption by doctors of biosimilars for curative clinical settings (cancer) is likely to be a slower ramp than chronic conditions (psoriasis)," former FDA commissioner Scott Gottlieb tweeted on 19 July in response to the news about the biosimilar launches. "This may not be rational, since biosimilars are just as safe and effective as brand counterparts. But we should expect this behavior."

#### FRUITS OF AMGEN/ALLERGAN PARTNERSHIP

Mvasi and Kanjinti are part of a commercialization deal between Amgen and Allergan that includes three other biosimilars in development, according to Informa's Biomedtracker database. Those products

are: rituximab (Phase III); infliximab (under FDA review); and Erbitux (cetuximab).

"Several years ago, Amgen made the strategic decision to invest in building a global biosimilars business, leveraging our nearly four decades of experience in developing and manufacturing best-in-class biologics," said Murdo Gordon, Amgen's executive VP of global commercial operations. "Following several recent launches in Europe, we are excited to be launching our first two biosimilars in the US, which will provide for immediate savings for Medicare patients and commercial payers."

"As the first products from our collaboration with Amgen to be launched in the US, Mvasi and Kanjinti reinforce our ongoing dedication to providing patients with additional treatment options," said David Nicholson, Allergan's chief research and development officer.

"We are excited about the progress we've made through this partnership and look forward to continued milestones together with our remaining biosimilar products."

AbbVie Inc., which has fought long and hard to keep biosimilar competition to Humira (adalimumab) at bay, is in a position to inherit Allergan's biosimilar partnership with Amgen if its \$63bn purchase of Allergan goes through. (Also see "AbbVie Pounces On Chance To Buy Revenues In \$63bn Mega-Deal For Allergan" - Scrip, 25 Jun, 2019.)

Amgen's Amjevita, a Humira biosimilar, is not part of its commercialization agreement with Allergan. Amjevita was approved in September 2016 but will not launch in the US until January 2023 under a patent settlement with AbbVie. ✨

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## Astellas Adds To Regenerative Medicine Portfolio In Hearing Loss Deal With Frequency

MANDY JACKSON [mandy.jackson@informausa.com](mailto:mandy.jackson@informausa.com)

Astellas Pharma Inc. continues to build up a regenerative medicine portfolio, most recently paying \$80m up front to develop and commercialize Frequency Therapeutics Inc.'s one-and-only clinical drug candidate – FX-322 for hearing loss – in ex-US markets. The deal announced on 17 July also gives Woburn, MA-based Frequency up to \$545m in development and

commercial milestone fees plus royalties on ex-US sales of FX-322. However, the upfront payment alone almost doubles the \$87m that the small company has raised to date, including \$74m in two venture capital financings.

Frequency is developing proprietary combinations of small molecule drugs that work together to stimulate progenitor cells

About 90% of adults with hearing loss have sensorineural hearing loss.



to multiply and create new cells in various diseases, starting with FX-322 for the very large sensorineural (noise-induced) hearing loss market. The World Health Organization estimates that 800 million adults have hearing loss globally and Frequency said 90% of all hearing loss is sensorineural.

FX-322 is designed to restore hearing function by inducing ear progenitor cells to grow hair cells. Damage to and/or loss of sensory hair cells in the inner ear causes sensorineural hearing loss.

"Mother Nature never intended us to go to rock concerts or put earbuds in our ears or sit on airplanes, all of which damage our hearing. This epidemic of hearing loss is related to so much of the world we live in – noise pollution," Frequency Therapeutics CEO David Lucchino told *Scrip*.

"We really think that we're going to have the potential to impact an extremely large market, such as hearing loss, with our hearing regeneration program," Lucchino said.

Frequency retains full US rights and development responsibilities for FX-322, but the company and Astellas will be jointly responsible for global clinical studies and will coordinate commercial launch activities.

A single intratympanic injection of FX-322 was well-tolerated with no serious adverse events and with hearing function improvements observed in multiple patients in a recently completed Phase I/II clinical trial in the US. A Phase IIa study is expected to begin in the fourth quarter of 2019 "and there will be additional studies beyond that we're also discussing with Astellas," Lucchino said.

### AN IDEAL REGENERATIVE MEDICINE PARTNER

Lucchino said Astellas was an ideal partner for the development of FX-322, because it is recognized as a leader in regenerative medicine, which matches the commitment of the pharma company's home country of Japan to this field. He noted that Astellas also has "a deep commitment" to diseases of the ear.

"Our interactions with Astellas go back a number of years and we've gotten to know them amongst a number of other larger pharmaceutical companies," Lucchino said.

"We continue to have a good strategic fit mutually and I think as we've developed the technology they've been very impressed

with our work and the overall strategic imperative we've taken," he added. "Over the last several months it's led to a serious conversation about a partnership, which has been recently culminated in the terms of this transaction."

The CEO of the four-year-old firm noted that Frequency's therapeutic candidates have the benefit of being regenerative medicines without requiring the removal and modification of cells from the body.

"Frequency's platform is designed to identify combinations of small molecules that selectively activate progenitor cells and [it's] doing all of this within the body," Lucchino said. "We're doing all of this within the body, creating sort of a localized healing response."

### 'FOCUS AREA' APPROACH

Astellas chief strategy officer and executive vice president Naoki Okamura said in a statement from the two partners that "FX-322 is a program that focuses on the mechanism of regeneration. Astellas is committed to exploring all types of partnership opportunities to turn cutting-edge science and technological advances into value for patients."

While the Japanese company does not identify hearing disorders as a strategic focus in its current mid-term plan, unveiled in May 2018, the acquisition of innovative technology and new solutions for high unmet needs do form an important part of its "focus area" approach, which has biology, modality/technology and disease as its three pillars.

Cell and regenerative therapy is considered a modality/technology of core interest, against the background of what is a highly supportive policy and regulatory environment in Japan for such approaches. (*Also see "New Japan PMDA Head Brings Strong Clinical, Patient Focus To Role" - Pink Sheet, 21 Jun, 2019.*)

Explaining its interest in the new deal, Astellas in Tokyo told *Scrip*: "FX-322 is a regenerative therapy and regeneration is one of Astellas' Focus Areas. There is a significant unmet medical need in the area of hearing loss, and current treatment options have significant limitations. We see FX-322 as a key strategic program for our Focus Area approach."

The company is taking a similar tack in ophthalmology, where it is pursuing Phase II trials with the retinal pigment epithelium cell therapy ASP7317 for dry age-related macular degeneration, following its \$379m acquisition of the US ocular regenerative medicine venture Ocata Therapeutics Inc. in 2016. This now operates as the Astellas Institute for Regenerative Medicine, based in Marlborough, MA.

The Tokyo-based pharma said the financial impact of the Frequency collaboration is reflected in its financial forecasts for its current fiscal year, which ends 31 March 2020.

### AN ACADEMIA-DERIVED PLATFORM

Frequency got its start in 2015 based on research from the labs of Robert Langer at the Massachusetts Institute of Technology and Jeffrey Karp at Harvard Medical School. The company raised its series A round in 2017 to advance its lead program in hearing loss and fund progenitor cell-stimulating programs in skin disorders, muscle regeneration and gastrointestinal diseases. (*Also see "Venture Funding Deals: Cell Medica Raises \$73.2m, Tango Dances In With \$55m" - Scrip, 16 May, 2017.*) It closed a series B round in

January to take FX-322 into Phase II studies this year.

While Frequency has identified other disease areas for its platform, the company and its proceeds from the Astellas deal remain primarily focused on the development of FX-322 for hearing loss.

However, in addition to a \$2m US Department of Defense Hearing and Balance Research Award grant it received in

May 2018, Frequency also won a grant for type 1 diabetes research from the Juvenile Diabetes Research Foundation in February 2018. It entered into a Cooperative Research and Development Agreement with Harvard University and the US Army Institute of Surgical Research, also in February 2018, related to small-molecule therapeutics for diseases and conditions involving muscle. Frequency's 40 employ-

ees work mostly at its headquarters in Woburn, north of Boston, but the company also has a "biological site of excellence" in Farmington, CT, where it has a strategic partnership with the University of Connecticut Medical School. 🌟

*Published online 17 July 2019*

*(With contributions from Ian Haydock in Tokyo.)*

## Boehringer Further Buys IPF Portfolio With Bridge's Autotaxin Inhibitor

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Bridge Biotherapeutics Inc. has reached a global licensing out and collaboration agreement with Boehringer Ingelheim GmbH for the South Korean biotech's early clinical stage molecule BBT-877 for the treatment of fibrosing interstitial lung diseases including idiopathic pulmonary fibrosis (IPF), in a deal worth as much as €1.145bn (\$1.29bn).

BBT-877, a potent small molecule inhibitor of autotaxin (ATX), is undergoing a Phase I trial in the US and is set to move into a Phase II global study in the next 12 months. The drug deregulates ATX, an enzyme involved in inflammation and fibrosis through the generation of a the lipid signaling molecule.

BBT-877 was originally discovered by South Korea's LegoChem Biosciences Inc. but has been under development as Bridge's lead asset since the company acquired exclusive worldwide rights for further development in 2017. The US FDA granted an orphan drug designation for use in IPF earlier this year.

The molecule showed superior efficacy and safety versus competing drugs in fibrosing interstitial lung diseases in pre-clinical studies, suggesting the possibility of a combination therapy approach with current standard treatments, said Bridge.

### WORTH €45M OVER NEAR TERM

Under the new agreement, which also includes South Korea, Bridge will receive an upfront and near-term milestone payment of €45m plus up to €1.1bn in clinical development, approval and sales mile-

stones, and double-digit sales royalties.

The two companies plan to focus primarily on the development of the molecule to treat IPF, which is one of Boehringer's main therapeutic focus areas and still has high patient medical needs.

"It is quite meaningful to reach a partnership with Boehringer Ingelheim, a global leader in IPF. Boehringer's expertise will further increase the potential of BBT-877 to be developed as a novel therapeutic that resolves unmet needs in IPF," said Bridge's CEO James Jungkue Lee.

Michel Pairet, Boehringer's board member with responsibility for the Innovation Unit, said the latest collaboration would further complement the private German firm's expanding fibrosing interstitial lung disease portfolio, and demonstrated its will to provide a next-generation treatment option for these patients.

At present, Boehringer's Ofev (nintedanib) and Roche's Esbriet (pirfenidone) are the only two approved drugs for IPF, and both are administered via the oral route. Ofev is now approved in more than 70 countries, including the US, Europe and Japan, and brought in total sales of €1.10bn (+29%) for the company in 2018.

### BOEHRINGER LEADS IPF TRIALS, DEALS RISING

IPF is a chronic disorder in which scarring and thickening of the lung tissue occurs due to unknown causes, impairing pulmonary function. In a recently published report, Informa's Datamonitor Healthcare estimates that in 2018, there were

305,450 incident and 940,840 prevalent cases in adults aged 20 and older worldwide, and forecasts those numbers to increase to 342,000 and 1.1 million respectively by 2027.

Boehringer leads industry sponsors with the highest overall number of clinical trials in IPF, followed by Roche. According to Datamonitor, industry-sponsored drugs in active clinical development for IPF are spread evenly across Phase I and Phase II, with only one other drug, Galapagos NV's GLPG1690, another autotaxin inhibitor, in Phase III.

Therapies in mid- to late-stage development focus on a wide variety of targets, and the majority of these are administered orally. Collaborations and deals in IPF have been increasing in general, indicative of global pharma's keen interest in R&D in the area and driving a number of M&A deals.

In 2017, Boehringer exercised an option to advance its collaboration with French biopharmaceutical company Inventiva Pharma to develop new IPF under a multi-year R&D partnership, originally signed in May 2016.

Earlier in July, Gilead Sciences Inc. agreed a deal worth \$5.05bn with Galapagos, an existing partner, that provides Gilead with access to six clinical compounds, including GLPG1690 in Phase III for IPF, as well as Galapagos's drug discovery platform. Analysts at Jefferies forecast GLPG1690 will achieve worldwide peak annual sales of \$850m for the IPF indication following a launch in 2020.

Early this year, Fibrocor Therapeutics LP licensed to Galapagos worldwide rights to develop and commercialize a small molecule inhibitor aimed at IPF and other indications.

### BRIDGE'S POSITIVE EARLY RESULTS

In May, Bridge announced positive interim results from a Phase I trial with BBT-877 at the American Thoracic Society International Conference.

In the single-ascending dose portion of the study, plasma concentrations increased in a dose-proportional manner, and all doses demonstrated safety and tolerability with only mild adverse events. Furthermore, there were no clinically related findings in safety assessments of the study, such as electrocardiogram, vital sign, laboratory biochemical/hematological profile, and urinalysis results.

"BBT-877 has shown potential as a best-in-class ATX inhibitor for treatment of IPF with favorable results in the first-in-human clinical study. These findings reinforce our continued collaborations with world-class pulmonologists specializing in IPF," said Gwang-hee Lee, Bridge's head of Translational Research, at that time.

The Phase I study of BBT-877 is expected to be completed by August 2019 and the multinational Phase II study is planned to be conducted in the US, Canada, Australia and multiple countries in Europe and Asia.

BBT-877 is the second molecule from Bridge with US IND clearance. The company is also developing BBT-401, a first-in-class anti-Pellino-1 compound for ulcerative colitis, and expects the first dosing in a selected patient group in February under a Phase II study.

Established in 2015, Bridge operates as a virtual clinical stage biotech engaged in the development of novel therapeutics focusing on areas such as ulcerative colitis, fibrotic disease and cancer. It closed a \$27.2m series C venture financing round in April and is gearing up to launch an initial public offering in South Korea's Kosdaq market this year. 🌟

Published online 18 July 2019



Boehringer Ingelheim To Boost Cancer Immunology Portfolio with Novel Cancer Vaccines:  
<https://bit.ly/2Z4GLJ1>

# Genentech Signs Up Sosei Heptares GPCR Smarts For \$1bn+ Deal

MIKE WARD [mike.ward@informa.com](mailto:mike.ward@informa.com)

Genentech Inc. has turned to Sosei Heptares to help it to discover and develop medicines that are capable of modulating G protein-coupled receptors (GPCRs), a very large and diverse

Genentech has agreed to pay Sosei Heptares \$26m in upfront and near-term payments, in addition to future milestone payments that may exceed \$1bn for achieving pre-specified research, develop-



gene family with a lot of promising drug targets within it. Under the terms of the deal, the collaboration will combine Sosei Heptares' GPCR-focused structure-based drug design capabilities with Genentech's discovery, development and therapeutic are expertise directed towards multiple Genentech-nominated GPCR targets. Genentech will be responsible for developing and commercializing potential new medicines for each novel target and will have exclusive global rights to them.

"In the partnership, we expect to apply our StaR platform to targets they have selected and take the initial DNA, engineer the protein, generate a stable receptor, solve the structure and select the conformation that Genentech will be interested in and use that for lead discovery. Genentech will take it from there and optimize drug candidates to take into the clinic against various disease indications that they are interested in," Malcolm Weir, Sosei Heptares EVP and chief R&D officer, told *Scrip*.

ment and commercialization events. Sosei Heptares is also eligible to receive royalty payments on net sales of future medicines emerging from the collaboration.

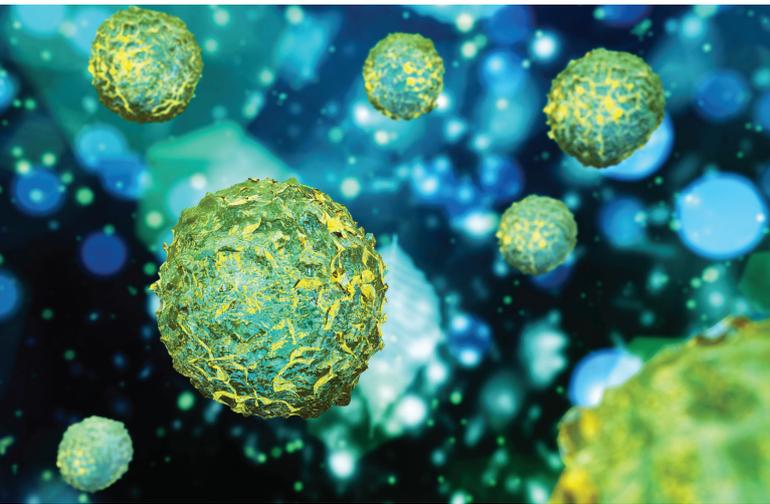
Like many other biotech companies with a technology platform capable of generating numerous candidate therapeutics, Sosei Heptares is pursuing a partnering and in-house drug development strategy. However, while the balance of activity at many western biotechs is shifting more to retaining more of their own assets and a scaling back of resources allocated to external programs, Sosei Heptares is still keen on the near-term revenues from partnerships. However, the company recently adopted a hybrid model of the two strategies when it partnered with the European venture capitalist Medicxi to spin out a program into two asset-centric vehicles. (Also see "Medicxi Links With Sosei Heptares For Orexin Agonist Vehicles" - *Scrip*, 5 Feb, 2019.) 🌟

Published online 16 July 2019

# Dainippon Closing In On Cell Therapy Specialist Cynata

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The Australian stem cell and regenerative medicine venture Cynata Therapeutics appears close to being acquired by Japan's Sumitomo Dainippon Pharma Co. Ltd. (SDP), as the companies confirm that negotiations are taking place but final terms remain to be agreed.



Agreement on any deal would provide SDP with access to novel technology for the large-scale commercial production of stem cells along with an early clinical stage candidate, as it looks to build its presence in regenerative medicine.

In a 19 July stock market disclosure - in turn prompted by a Price Query letter from the Australian Stock Exchange (ASX) three days earlier concerning recent fluctuations in its share price - Cynata confirmed that it "has received an indicative, non-binding and conditional proposal" from SDP.

This is "regarding a possible acquisition of all the shares in Cynata at a price of A\$2.00 [\$1.41] per share in cash," said the company, which has around 101.89 million shares outstanding.

Rumors around a possible acquisition have pushed up Cynata shares by 48% since the start of July, and they rose by 15.5% to AUD1.85 on 19 July alone after a trading halt was lifted following the ASX letter.

## CLOSE BUT NO CIGAR YET

Melbourne-based Cynata, formed in 2011, stressed that negotiations with SDP are still incomplete and remain subject to various conditions, including completion of due diligence and agreement of final terms.

The venture said that it had granted non-exclusive due diligence access by SDP following the acquisition proposal, but that "engagements with certain other parties" (presumably other potential acquirers) had continued.

"Cynata's discussions with such other parties have ceased," it added, presumably leaving SDP as the sole current potential bidder. The Japanese firm responded to Cynata's ASX disclosure by confirming it "has made the proposal for the acquisition of Cy-

nata and is negotiating," but again noted that "no formal decision has been made at this moment."

Cynata is headed by CEO and managing director Dr Ross Macdonald, who has extensive industry experience including at Stiefel (now part of GSK) and Sinclair Pharma PLC in the UK.

## SCALABLE PRODUCTION PLATFORM

Cynata's main proprietary technology is the Cymerus platform, which uses induced pluripotent stem cells (iPSCs) and precursor mesenchymoangioblasts to enable the economic, large-scale production of mesenchymal stem cells (MSCs).

The system uses as its starting material a master bank of iPSCs with "unlimited expansion potential" but which are derived from only a single blood donation. Usually, relatively few MSCs can be derived from each donation and the cells can lose potency as conventional culture expansion progresses, requiring new donors.

Mesenchymoangioblasts were originally identified by a team at the University of Wisconsin-Madison in the US, from which Cynata has been granted an exclusive global license to the relevant patents. The iPSCs are used to generate these cells, which are a common precursor for both MSCs and endothelial cells and can develop into multiple cell types.

Cynata, acquired in 2013 by Australian firm EcoQuest Ltd. and then renamed Cynata Therapeutics, has also licensed a broad portfolio of patents held by Fujifilm Holdings Corp. company Cellular Dynamics International Inc.

Agreement on any deal would provide SDP with access to novel technology for the large-scale commercial production of stem cells.

## PHASE II CANDIDATE

Cynata's in-house pipeline is led by the MSC therapy CYP-001, which met its clinical endpoints in a Phase I study for steroid-resistant acute graft-versus-host disease (GvHD). This showed a 93% overall response rate by day 100 with 14 of the 15 patients showing an improvement of at least one grade versus baseline.

The venture also plans to start this year a Phase II program in critical limb ischemia and a 448-patient trial in osteoarthritis, which would be one of the largest ever trials with MSCs.

Fujifilm currently has a license option for CYP-001 in GvHD, for which it would conduct a clinical program should this option be exercised. The extended deadline for this currently stands at 19 September, and it is not clear how the arrangement may be impacted by any acquisition of Cynata by SDP. The Cymerus MSC platform has also shown preclinical promise

across a broad range of other potential indications including asthma, diabetic wounds, heart attack and cytokine release syndrome related to CAR-T therapy.

The venture had a cash balance of around AUD7m at the end of June.

### GOOD STRATEGIC FIT?

Any acquisition would fit into SDP's strategic interest in cell and regenerative therapies, as the company looks to deal with the looming loss of US exclusivity in early 2023 for its global top seller, the atypical antipsychotic Latuda (lurasidone).

The company is already developing an allogeneic iPSC-derived dopamine neural progenitor therapy in Japan for Parkinson's disease (Phase I/II), along with an iPSC-derived retinal pigment epithelium therapy for age-related macular degeneration (pre-Phase I).

The policy and regulatory environment in Japan for cell and regenerative therapies is highly supportive, and the first MSC product was reimbursed and commercialized in the country in 2015, JCR's Temcell (licensed from another Australian firm, Mesoblast Ltd.) for acute GvHD after allogeneic bone marrow transplants.

SDP's cell therapy development activities suffered a major blow earlier this year after partner SanBio Co. Ltd.'s missed its Phase IIIb endpoint in ischemic stroke. (Also see "Surprising SanBio/Sumitomo Stroke Stumble Slams Stocks" - *Scrip*, 31 Jan, 2019.)

More recently, the Japanese firm's novel oral cancer stemness inhibitor napabucasin failed at Phase III for pancreatic cancer, although it remains in development for the larger potential indication of colorectal cancer. ✨

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## Interview: Mallinckrodt Deal Golden For Silence Therapeutics

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After signing a deal with Mallinckrodt PLC on the first anniversary of becoming CEO of Silence Therapeutics PLC David Horn Solomon has been reflecting on how transformational the pact will be and the progress the UK-based RNA interference (RNAi) specialist has made in the last year.

The collaboration gives Mallinckrodt an exclusive worldwide license for one preclinical asset, SLN500, that targets a specific protein in the C3 complement pathway and an option for up to two additional assets with different complement protein targets. Silence will be responsible for taking SLN500 through preclinical studies and a Phase I trial, after which Mallinckrodt will take over clinical development and responsibility for global commercialization.

It is a very early stage alliance – and the firms only confirmed that it focuses on the complement cascade, without specifying which diseases they are targeting – but Silence is in line for some healthy initial payments and follow-ons that mean the collaboration is worth potentially over \$2bn. In an interview with *Scrip*, Solomon noted that Silence is getting \$20m upfront, plus \$5m from an equity investment from Mallinckrodt which has bought 5.1 million shares for a 6.5% stake. The latter will also pay up to \$10m in research milestones for



David Horn Solomon

SLN500 and for each optioned asset, in addition to funding for Phase I clinical development including GMP manufacturing.

After that, "the numbers keep going up," Solomon said. The collaboration provides for potential added clinical and regulatory payments of up to \$100m for SLN500, as well as commercial milestones of up to \$563m. Should Mallinckrodt opt to license one or two additional assets, Silence could receive up to \$703m in similar payments per asset, plus tiered, low double-digit to high-teen royalties.

He added that the deal is "really transformational, validating our underlying technology and shows where we're going as a company." It involved a competitive process "as we are always talking to phar-

ma and Mallinckrodt came with an offer that was compelling."

The latter's chief scientific officer Steve Romano, former head of development of Pfizer Inc. is joining the Silence board and Solomon said, "I think he'll be a great sparring partner in the boardroom around our development programs, not only for the ones with them but our other ones in cardiovascular medicine and hematology as well."

The other projects he mentioned include Silence's lead candidate SLN124, a monthly subcutaneous injection which is going into a Phase Ib study in Europe in the second half of 2019 for the treatment of beta-thalassemia. Solomon is particularly excited about SLN360, which silences a component of lipoprotein a – Lp(a) – elevated levels of which have been associated with increased risk of cardiovascular disease.

SLN360 could be "the jewel in the crown," Solomon said, noting that a clinical trial authorization is anticipated to be filed in the second half of 2020. "Whether you're thin or fat, whether you diet and exercise or not, LP(a) levels are genetically determined and they are the predictive factor," he claimed, noting that other companies are also looking at the LP(a) area, citing Amgen Inc. and Arrowhead Pharmaceuticals Inc.'s gene-silencing partner-

ship and Novartis AG and Ionis Pharmaceuticals Inc.'s cardiovascular antisense pact, "and it's bringing a lot of excitement to the field." (Also see "Deal Watch: Novartis Opts In On Lipoprotein A Candidate From Akcea" - *Scrip*, 25 Feb, 2019.)

He went on, "We think like the statins where the number six statin, AstraZeneca PLC's Crestor (rosuvastatin), was the big winner, that there is plenty of space for multiple LP(a) lowering medicines and everyone agrees that gene silencing is the way to do it because you can lower the protein in the serum by 90%, we've already shown that in monkey data.

"If you can do that in humans, we believe that will lower risk and cardiovascular deaths still account for 40% of deaths globally. Statins are great, but they alone are not the solution so we need more tools in the toolbox."

Following the first approval last year for an RNAi therapeutic, Onpattro (patisiran) from Alnylam Pharmaceuticals Inc. (with whom Silence settled a patent dispute at the end of last year), Solomon told *Scrip* that "gene silencing is the hot topic" and other companies, notably Arrowhead and another RNAi specialist Dicerna Pharmaceuticals Inc. "are soaring." He pointed out that in November 2017, Silence, Arrow-

head and Dicerna all had the same market capitalization but "they got a quicker start in the clinic." (Also see "Alnylam Offering Value-Based Deals In EU For Breakthrough RNAi Drug Onpattro" - *Scrip*, 14 Nov, 2018.)

With the Mallinckrodt pact, SLN124 going into the clinic and the promise of SLN360, "we feel like we're in the midst of it now and I think investors acknowledge that." Shares soared 60% on the back of the news to 133.6 pence when the deal was announced (18 July) and continued to rise the day after.

Solomon signed off the Mallinckrodt deal a year to the day of his appointment as CEO and much has changed in that time, notably with the hiring in April of Giles Campion as head of R&D and chief medical officer - he occupied the same roles at Prosensa Holding BV, which was acquired by BioMarin Pharmaceutical Inc. in 2015 for \$680m.

April also saw the return of industry veteran Iain Ross as chairman, having held the post from 2005 to 2010, while Solomon is hardly short of experience either, having been CEO of Denmark's Zealand Pharma AS from 2008 to 2015. He said that "the name of the game is stability and now we want to get beyond the idea that Silence has been silent. We have the foun-

ation to build a very fine house. As you know, you get accretion in this business in two ways, through deals and results. We'll press on with deals first, and then we'll press on with results in the clinic."

### MALLINCKRODT'S ACTHAR FAILS FOR ALS

As for Mallinckrodt, the Silence collaboration was welcome news following the announcement earlier this week that it is permanently discontinuing a Phase IIb study of Acthar (corticotropin) gel for amyotrophic lateral sclerosis (ALS).

The company made the decision after a recommendation by the study's independent data and safety monitoring board following higher rates of pneumonia observed in ALS patients receiving Acthar Gel compared with those on placebo "and other adverse events specific to this patient population."

CSO Romano said, "It is critical to stress, however, that these findings do not impact the current positive benefit/risk profile of Acthar for use in current on-label indications," of which there are 19 approved by the FDA. These include infantile spasms and the treatment of acute exacerbations of multiple sclerosis in adults. 🌟

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## Takeda Brings Rare Disease Drugs To India But Access Questions Linger

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Takeda Pharmaceutical Co. Ltd. has introduced a line of products for lysosomal storage disorders in India, signalling early efforts by the Japanese company to dip into the ex-Shire PLC portfolio and step up momentum for the post-merger operation in the country.

Takeda, which completed its \$62bn acquisition of Shire in January this year, said that it had introduced idursulfase (available as Elaprased glocally) for Hunter syndrome, velaglucerase alpha (VPRIV) for Gaucher disease and agalsidase alfa (Replagal) for Fabry disease on the Indian market.

The launches, the firm said, build on its "heritage and commitment" to India

“

"The treatments are costly and no one can even afford installments." – Prasanna Shirol

and legacy of providing better health and a brighter future to patients with rare diseases, although it provided no details on how it expects to ensure access to the therapies in the largely self-pay Indian market.

### 'LOSING PATIENTS REGULARLY'

The international prices of the products are way beyond the reach of most patients in India, and patient groups are pressing for affordable access given that they view mere availability as of little consequence. For example, Elaprased intravenous solution (2mg/mL) is said to cost around \$3,282 for a supply of 3mL in the

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# Book a Table

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CONTINUED FROM PAGE 14

US going by data online, while VPRIV intravenous powder for injection 400 units comes in at around \$1,446; *Scrip* could not immediately verify if there have been any revisions to these prices. Prasanna Shirol, co-founder of the Organization for Rare Diseases India (ORDI), a national organization representing patients with rare diseases in the country, told *Scrip* that currently there is “no option” for most patients to access these new Takeda/Shire therapies in India.

“We are losing lot of patients regularly,” said Shirol, who is seeking an expansion of Shire’s Charitable Access Program for the products to more Indian patients in the country.

On whether innovative financing plans such as equal monthly installment (EMI) schemes could help improve access, Shirol declared: “The treatments are costly and no one can even afford installments.” EMI-based schemes typically allow patients to stagger the cost of therapy over a specified period. The annual cost of Elaprase was estimated at around INR4,400,000 (\$64,056) for a 10kg patient, going by data in a previous government policy document on rare diseases, which is currently on hold.

ORDI, however, indicated that it was open to suggestions on “creative” financial schemes to be worked out in-parallel by key stakeholders, including insurance companies and bankers.

“At ORDI, we are initiating no-interest or low-interest loans to support families affected by rare diseases,” Dr Harsha Rajasimha, co-founder of ORDI and co-director, Rare Diseases Systems Biology Initiative, George Mason University in Fairfax,

US, told *Scrip*. Currently this initiative is understood to be targeted towards emergency medical needs.

Patient numbers for Gaucher/Fabry disease and Hunter syndrome in India could not immediately be verified. Globally Gaucher’s, a rare inherited metabolic condition, is known to affect approximately 1 in 100,000 people in the general population, while nearly 8,000 to 10,000 people worldwide are affected by Fabry. Hunter syndrome is a serious genetic disorder that interferes with the body’s ability to break down specific mucopolysaccharides, also known as glycosaminoglycans or GAGs.

### POLICY FLIP-FLOP

The Indian access situation for the Takeda/Shire rare disease drugs is further complicated by the overall policy flip-flop for such therapies in the country. In December last year, India said it was keeping in abeyance the National Policy for Treatment of Rare Diseases announced in 2017, dashing hopes for access to a corpus fund with an initial outlay of INR1bn towards financing treatment of rare genetic diseases proposed in the policy.

ORDI told *Scrip* that it is aware that India’s ministry of health and family welfare is preparing the rare diseases policy based on the deadline they have from the court. The government had earlier this year sought nine months to come up with a new policy in a hearing before the Delhi High court; orders in certain previous writ petitions had directed the government to develop a national policy for tackling rare diseases.

“But so far patient advocacy groups have not been called for the consultation

meeting; we are hopeful that [they] call us for a discussion to take inputs from patient groups,” ORDI’s Shirol said.

Pricing and access issues notwithstanding, Takeda’s latest launch initiatives could be indicative of a shift in the Japanese firm’s overall approach to India following the sealing of the Shire deal.

Takeda’s general tone towards this market over the years has been markedly measured compared with some other global peers, and also against the backdrop of its own bullish outlook in 2010, when it first outlined medium- to long-term strategies for business expansion in India.

The Shire deal brought with it a range of on-market products in India, largely in the hematology segment including Advate (rDNA Factor VIII), Recombinate (rDNA antihemophilic factor) and FEIBA (anti-inhibitor coagulant complex) and probably now gives Takeda’s local portfolio the girth to move at a faster clip.

Takeda has also recently rejigged some key executive positions in the ICMEA (India, CIS, the Middle East (including Turkey) and Africa) region, where it hopes to sharpen its focus and emerge more agile following the integration of Shire.

Earlier this year, the Japanese firm appointed Andrey Potapov as area head, ICMEA, while another key executive, Taka Horii, who led the NEMEA (Near East, Middle East and Africa) area, was shifted to a new role as general manager for the Middle East. Takeda expects to evolve its operational focus from the NEMEA region to ICMEA as the acquisition and integration of Shire progresses. 🌟

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## Elios’ Phase IIb Melanoma Data Are Promising, But Present Tricky Issues For Phase III Vaccine Study

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**E**lios Therapeutics plans to advance its personalized vaccine for stage III and stage IV melanoma into Phase III – with a partner or on its own – following the release of Phase IIb top-line data that showed the vaccine can reduce the risk of disease recurrence by roughly 50% in patients who completed a full series of treatment.

Austin, TX-based Elios unveiled the data on 17 July, noting that in a per treatment (PT) population of 98 patients, a 29%

recurrence rate was seen in the treatment arm compared to 56% in the placebo arm. Overall, the study enrolled 144 patients and in this intent-to-treat (ITT) population, including patients who never received the vaccine or did not complete an 18-month course of therapy, the recurrence rate was 54% for the treatment arm versus 66% for placebo. The PT arm met statistical significance in the study’s primary endpoint of disease-

free survival (DFS), while the ITT data were clinically meaningful, but not statistically significant.

This creates a “math problem” for Elios in designing the planned pivotal Phase III study of the candidate, known as the tumor lysate, particle-loaded, dendritic cell (TLPLDC) vaccine, CEO Buddy Long told *Scrip*. An autologous cell therapy, the vaccine is produced from the patient’s own tumor and blood cells in a process that takes about two weeks from resection to injection, he said, much shorter than the three months or so typical of other autologous cell therapies.

In the study, patients whose melanoma recurred on standard-of-care (SOC) therapy were randomized to the vaccine or placebo. Treatment was initiated within three months of SOC completion, with patients scheduled to receive TLPLDC at months zero, one, two, six, 12 and 18. Evaluation of the primary endpoint of DFS at 24 months was performed in both the ITT and PT populations as co-primary analyses due to the high early recurrence rate often seen in advance melanoma patients, the company explained.

“I don’t think we’re going to get approval on PT; we’re going to get approval on ITT,” Long said. “When you evaluate a therapy, you have to look at the people who actually got it – but with the benefit that we’ve seen in the ITT, showing a statistical benefit on that is a math problem now. We don’t have a clinical or scientific problem, we need to power a study that appropriately is going to show the statistical value of that benefit that we’ve already seen in the ITT population.”

### SINGLE FOCUS OF TAKING TLPLDC TO A DEVELOPMENT PARTNER

Elios was founded in 2014 as a subsidiary of Orbis Health Solutions with a singular focus on TLPLDC in melanoma. The company began with a strategy of producing Phase IIb data that would entice a big pharma or other deep-pocketed partner to fund a Phase III program. (Also see “Cancer Immunotherapy Reaches A Tipping Point” - *Scrip*, 22 Oct, 2014.)

Long said now that his company – a direct subsidiary of Perseus Holdings USA, which is affiliated with Orbis – has the data in hand, it will plan to go ahead into Phase III with or without a partner. But he also conceded that the fastest path to bringing TLPLDC to patients is through a partnership.

“We’re not waiting on a partner,” Long said. “We are completely capable of taking this to the finish line on our own and so we are initiating a crossover phase from a fundraising standpoint, selecting banks in the next couple of weeks, and kicking that off in the next 60 days to run full steam ahead as a standalone product. Any company has to have that posture – we can’t count on the right partner being ready at the right time.”

To date, Elios has had what Long calls “coming attractions” talks with potential partners, but also has had to deal with a recent lack of enthusiasm for the cancer vaccine concept.

In melanoma, Biomedtracker lists seven vaccine candidates in clinical development for melanoma, including TLPLDC. The most advanced are Polynoma LLC’s seviprotimut in Phase III, KAELE-GemVax’s telomerase peptide vaccine GV1001 in Phase II, and Vaccinogen Inc.’s OncoVax in Phase I/II for melanoma and Phase III for colorectal cancer. GV1001 also was investigated in non-small cell

lung and pancreatic cancers as well as hepatocellular carcinoma, but those efforts are suspended. “The bottom line for everyone has been ‘we love the team, love the technology, love the concept, but we’ve got to see a positive clinical benefit in one indication,’” Long noted. “Whatever we do in the immunotherapy space, the bottom line is fundamentally there needs to be a post-immune response that can create an army of tumor-reactive T cells that can not only function as a monotherapy but also combine with other therapies out there that do anything with T cells.”

In addition to its monotherapy study, Elios has been running an open-label trial for patients’ whose melanoma recurs in which they can go on TLPLDC monotherapy or combination therapy with any SOC agent. It also is running a Phase I/II study testing the vaccine with the physician’s choice of checkpoint inhibitor therapy, but Long says the most important thing Elios can do is demonstrate TLPLDC’s efficacy as a monotherapy.

“One thing that is lacking in combination trials is there’s theoretical synergistic benefit, but a lot of times it hasn’t been proven in a rigorously scientific fashion that you have single-agent efficacy that would translate into theoretical, practical benefit in a combination,” he said.

### SAFETY PROFILE COULD BE IDEAL FOR COMBINATION THERAPY

However, monotherapy efficacy plus the vaccine’s safety profile might position TLPLDC for combination with a wide range of therapies.

In the Phase IIb monotherapy study, about one-third of patients reported an adverse event, mostly grade 1 or 2 events. By contrast, typical cancer studies often have AE rates of 80% to 90%, sometimes even 100%, with 70%-80% of AEs deemed treatment-related. In potential combination regimens, TLPLDC’s safety profile mean patients can add its benefits with little or no physical cost, Long asserted.

“We don’t create a systemic immune response, we create a cellular immune response,” he explained. The autologous process creates a therapy that delivers a patient’s complete repertoire of tumor antigens to the immune system, yielding a dual innate and adaptive immune response that triggers the immune system to recognize, seek and destroy antigen-containing cells, the company says.

Because the vaccine expresses pathogen related to the patient’s own molecular profile at the cellular level, this enable the immune system sees the antigen as a pathogen, Long said. “The actual presentation of the antigen does not carry any of the autoimmune or other immunological side effects,” he added.

Manufacturing of the personalized vaccine can occur in roughly 48 hours by taking advantage of the process in which monocytic cells turn into dendritic cells, the exec said. “There’s a certain point in time where [the transforming cells] become extremely phagocytic and the delivery mechanism we have takes tumor antigen and captures it in a particle that is phagocytized into the cytotoxic dendritic cell,” he continued.

Down the road, Elios believes its vaccine technology can be applied to a broad range of solid tumors, but the work in recurrent advanced melanoma comes first, Long said. 🌟

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# Positive Results Move Anemia Contender Enarodustat Towards First Filing

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Japanese firm Torii Pharmaceutical Co. Ltd. and parent Japan Tobacco Inc. (JT) are planning a marketing authorization filing in Japan for their oral inhibitor of hypoxia inducible factor-prolyl hydroxylase (HIF-PH), following positive results in comparative Phase III trials.

The new top-line results came from two pivotal studies conducted in Japan with enarodustat (JTZ-951) in either anemic patients with non-dialysis-dependent chronic kidney disease (CKD) or with hemodialysis-dependent CKD and receiving erythropoiesis stimulating agent (ESA) therapy. The open label trials compared the JT/Torii drug with the ESA darbepoetin alfa (marketed in Japan by Kyowa Hakko Kirin Co. Ltd. as Nesp) over a 24-week period.

While the companies stopped short of releasing detailed results, they said the top-line results “achieved the non-inferiority criterion” in terms of difference in mean hemoglobin at weeks 20, 22 and 24, and both studies met their primary endpoints. Enarodustat showed a “favorable” tolerability profile, and the results in combination with other studies pave the way for an approval filing in Japan, the companies said.

JT told *Scrip* that it could not comment further at this stage on the precise timing of the submission, given that the Phase III trials are still ongoing.

## COMPETITIVE CLASS

In common with other HIF-PH inhibitors, enarodustat acts to mimic hypoxia to promote iron mobilization, endogenous erythropoietin and red blood cell production. The main advantage of the new class of agents is improved safety and efficacy over the aging ESAs, along with more convenient once-daily oral (as opposed to intravenous) dosing.

Some trials have flagged up serious safety concerns in patients receiving ESAs, including increased risk of thrombotic events, hemoglobin cycling and hypertension, which has affected their use in recent years.

The new HIF-PH inhibitors also reduce or eliminate the need for concomitant use of IV iron products, although these may still be recommended in end-stage CKD and iron depletion is a often seen in dialysis patients.

Competition and development activity in the HIF-PH space is already intense however, and in Japan much may depend on the timings of filings and approvals. Around 13 million people in the country are estimated to suffer from more advanced CKD, but there is a lower incidence of diabetes in those with CKD-related anemia than in the west.

AstraZeneca PLC/FibroGen Inc.’s roxadustat was the first in the wave of new oral HIF-PH inhibitors to be approved, in China late last year. (Also see “First Approval For AZ’s Roxadustat With China Green Light” - *Scrip*, 18 Dec, 2018.) Multiple others are now coming up behind, including Akebia Therapeutics Inc.’s vadadustat (li-

censed to Mitsubishi Tanabe Pharma Corp./Otsuka Pharmaceutical Co. Ltd.), which is in Phase III. Others include GlaxoSmithKline PLC/Kyowa Kirin’s daprodustat (Phase III) and Bayer AG’s molidustat (both Phase III).

In Japan, the current indications are that approval filings for both vadadustat and daprodustat are planned for this year (in fiscal 2019 ending next 31 March in vadadustat’s case), while US NDAs are expected in 2019 and 2021 respectively.

The main advantage of the new class of agents is improved safety and efficacy over the aging ESAs.

In top-line data from two Phase III Japanese trials released this March, vadadustat (MT-6548) also met its primary non-inferiority endpoints in both non-dialysis-dependent and hemodialysis patients, again for mean hemoglobin levels versus darbepoetin alfa.

Enarodustat was originated by JT, which signed a deal with subsidiary Torii at the Phase II stage in October 2017, for co-development and commercialization in Japan. Torii, acquired in 1998, acts as JT’s manufacturing, sales and marketing operation in Japan, and paid an undisclosed upfront licensing fee to its parent as part of the deal.

The molecule has been out-licensed to JW Pharmaceutical Corp. for development and commercialization in South Korea.

## ESA EROSION IN JAPAN

Datamonitor Healthcare’s *Anemia In Chronic Kidney Disease* report expects sales of the older ESAs to hard hit by both direct biosimilar competition and the new HIF-PH inhibitors. AZ’s roxadustat is expected to replace Amgen Inc.’s Epogen (epoetin alfa) as the global market leader in anemia in CKD, reaching sales of \$1.9bn in 2024.

In Japan, while it is still unclear which HIF-PH inhibitor will be first to market, the first biosimilar version of Nesp (darbepoetin alfa) - an authorized version produced by Kyowa itself - was approved nearly a year ago.

Elsewhere in their anemia franchise, JT and Torii also recently announced positive top-line, Japanese Phase III results for Riona (oral ferric citrate hydrate; JT-751) in adults with iron deficiency anemia. Comparing the product with Ferromia (oral sodium ferrous citrate) the study met its primary non-inferiority endpoint.

Riona (licensed from Akebia) is already approved in the country for hyperphosphatemia in adults with CKD both on dialysis or not, and a filing is now planned for the additional indication of improving iron deficiency anemia. ✨ Published online 16 July 2019

# GSK's Zejula Poised To Take On Lynparza In First-Line Ovarian Cancer

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**G**laxoSmithKline PLC's poly ADP-ribose polymerase (PARP) inhibitor Zejula (niraparib) could have an edge over rivals as a first-line maintenance therapy in ovarian cancer based on results from the positive Phase III PRIMA trial in the broad population.

The double-blind, placebo-controlled study met its primary endpoint of a statistically significant improvement in progression free survival for women regardless of their biomarker status, GSK reported on 15 July. AstraZeneca PLC and Merck & Co. Inc.'s market-leading PARP inhibitor Lynparza (olaparib) is approved for first-line maintenance treatment for ovarian cancer, but in women with BRCA mutations.

Lynparza has had the first-mover advantage, given that it was the first PARP inhibitor to reach the market in 2014. It was approved for a first-line maintenance therapy indication by the US Food and Drug Administration in December after a rapid weeks-long review. (Also see "First-Line Ovarian Cancer Approval Solidifies Lead For AstraZeneca's Lynparza" - *Scrip*, 19 Dec, 2018.) But only about 10% to 15% of ovarian cancer patients have BRCA mutations, so Zejula could have a competitive advantage targeting a larger patient population.

GSK estimates that 300,000 women are diagnosed with ovarian cancer worldwide every year, but only 15% of those patients are BRCA+ and thus eligible for first-line treatment with a PARP inhibitor. Around 22,000 women are diagnosed with ovarian cancer in the US each year, GSK said.

Lynparza has a bigger foothold on the market, however. It was approved in 2014 in second-line ovarian cancer, initially in women with BRCA mutations, but later labeling was expanded to all comers regardless of mutation status in the second-line and eventually to BRCA-mutated breast cancer.

Zejula was approved in March 2017 as the third PARP inhibitor to market for recurrent ovarian cancer, but it was the first to include labeling for women with and without BRCA mutations. (Also see "Broad Label Gives Tesaro's Niraparib A Head Start In Ovarian Cancer" - *Scrip*, 28 Mar, 2017.) Another PARP inhibitor, Clovis Oncology Inc.'s Rubraca (rucaparib), is also approved for recurrent ovarian cancer regardless of BRCA mutation status.

## PRIMA IS KEY TO TESARO VALUATION

Now, Zejula also is poised to benefit from GSK's commercial muscle. The big pharma purchased Zejula with the acquisition of Tesaro Inc. for \$5.1bn in January. (Also see "GSK Embraces PARP Promise With Tesaro Buy" - *Scrip*, 3 Dec, 2018.) The approval of Zejula as a first-line ovarian cancer treatment has been considered a key to justifying the value of the deal.

During an interview with *Scrip* at the J.P. Morgan Healthcare Conference in January, GSK Oncology Therapeutic Area Head Axel Hoos credited Tesaro for running a broad Phase III trial in all-comers and speculated that the success of PRIMA would carry the

acquisition. (Also see "J.P. Morgan Notebook Day 2: Biogen, GSK, Bluebird, Roche, Amgen, Biohaven, Lilly And FDA's Gottlieb" - *Scrip*, 9 Jan, 2019.)

Jefferies analyst Peter Welford said in a 15 July research note, "Zejula's potential to expand PARP use beyond BRCAm patients was a key justification for [GSK's] £4bn Tesaro acquisition and this required a positive outcome for Zejula in the PRIMA study." Nonetheless, he pointed out the commercial implications will only become clear when the magnitude of the benefit is revealed, particularly in important subgroups.

GSK did not provide detailed results from the trial and said it will present the data at an upcoming medical meeting. The study assessed the efficacy of Zejula as maintenance therapy as measured by progression-free survival versus placebo.

GSK has a ways to go if Zejula is going to catch up to Lynparza, which generated \$237m in the first quarter, putting it on a blockbuster trajectory for 2019. GSK reported first quarter sales of Zejula of £42m (\$54.5m), including sales only since the closing of the Tesaro deal on 22 Jan.. Clovis Oncology's Rubraca generated \$33.1m in the first quarter. Pfizer also has launched a fourth PARP inhibitor, Talzenna (talazoparib), approved for BRCA-mutated breast cancer last year.

Jefferies' Welford forecast that Zejula could generate peak revenues of \$550m from the front-line ovarian cancer indication.

## LOTS OF PHASE III TRIALS UNDERWAY

AstraZeneca and Merck have big expansion plans for Lynparza, including in prostate cancer and pancreatic cancer. At the American Society of Clinical Oncology (ASCO) meeting in June, the companies presented new data, showing Lynparza nearly doubled PFS in patients with germline BRCA-mutated metastatic pancreatic cancer in the Phase III POLO study. (Also see "AZ/Merck & Co's Lynparza POLO Study 'Practice Changing' For Pancreatic Cancer Subgroup" - *Scrip*, 3 Jun, 2019.)

The companies plan to file for FDA approval in pancreatic cancer later this year, a niche market opportunity, but one they would be poised to have to themselves for a notable period of time.

GSK also has ambitious development plans for Zejula, as the PARP inhibitor story is still just unfolding. A Phase III trial testing Zejula in combination with a novel PD-1 inhibitor in first-line ovarian cancer is underway, called FIRST. Another Phase III trial, BRAVO, is testing Zejula for the treatment of HER2-negative, BRCA-mutation positive breast cancer and a third Phase III trial is studying Zejula in combination with a PD-1 inhibitor in patients with triple-negative breast cancer.

GSK is also partnered with Johnson & Johnson on a development program for Zejula in prostate cancer in combination with Janssen's androgen receptor inhibitor Zytiga (abiraterone) in first-line castration-resistant prostate cancer. 🌟

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# Key Catalyst In August For Mologen As IMPALA Phase III Colorectal Cancer Reports

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Preparations for the read-out of the pivotal Phase III IMPALA trial, evaluating Mologen AG's immunotherapy lefitolimod as a maintenance therapy in metastatic colorectal cancer patients, are at an advanced stage, with top line results now expected in August, Stefan Manth, the German biotech's recently installed CEO said in an interview.

Mologen's lead product "is the best-in-class TLR9 agonist and the most advanced product candidate among the TLR9 agonists in the world," according to the company, which was founded in 1998.

Lefitolimod is a small molecule consisting of natural DNA in a unique structure and stimulates the TLR9 pathway, leading the re-activation of both the innate and the adaptive immune surveillance systems.

Various studies have shown that lefitolimod triggers a broad immune response, and that it has a good safety profile.

## IMPALA DATA COMING

The IMPALA data readout next month should reinforce that view, CEO Manth said. The pivotal Phase III study's primary endpoint is overall survival, while secondary study endpoints include progression-free survival, safety and tolerability, as well as quality of life.

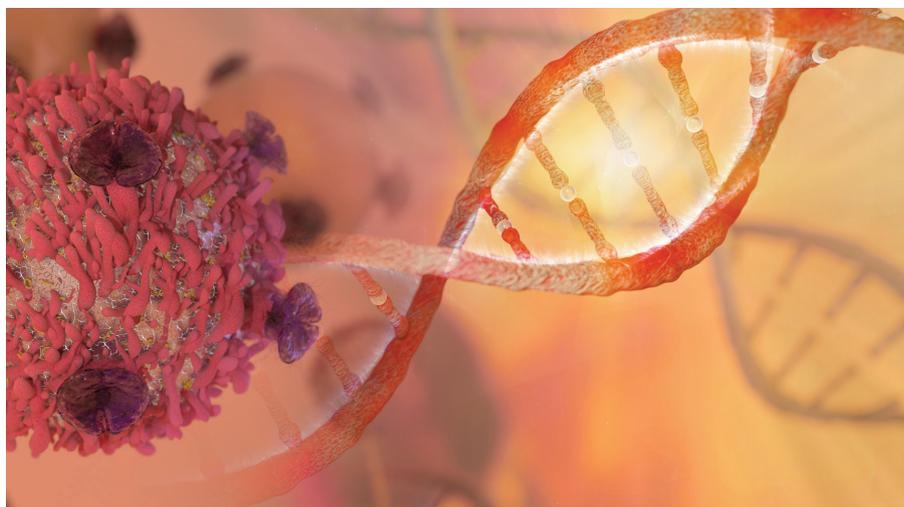
IMPALA is being conducted with more than 540 patients at 122 sites in eight EU countries. It is designed as maintenance therapy in patients with partial or complete response to first-line chemotherapy versus local standard of care.

## OTHER INDICATIONS

Mologen is also testing the compound in other therapeutic areas.

"With lefitolimod, we are pursuing further promising approaches beyond the IMPALA trial, for example in anti-cancer and anti-HIV combination studies," Manth told *Scrip*, adding that lefitolimod was also Phase III-ready in small-cell lung cancer.

Lefitolimod, whose immune-stimulatory potential has been studied in a Phase I



**"Lefitolimod is the best-in-class TLR9 agonist and the most advanced product candidate among the TLR9 agonists in the world." - Mologen**

trial in HIV, is about to enter a Phase IIa trial in combination with broadly neutralizing antibodies in HIV, with an initial trial evaluation expected in 2021.

Also underway is a Phase I combination study of lefitolimod in combination with Bristol-Myers Squibb Co.'s checkpoint inhibitor Yervoy (ipilimumab) in various cancer indications. The evaluation is being conducted at the University of Texas MD Anderson Cancer Center.

"At the time that this trial was conceived Yervoy was the only checkpoint inhibitor on the market. It's a typical Phase I oncology trial where we're looking at a diversity of tumors in patients that have basically exhausted all their therapeutic options," Manth said.

A Phase IIa trial studying the combination of lefitolimod and Yervoy in different indications is now planned, including malignant melanoma. Manth declined to elaborate further, explaining that "the Anderson Cancer Center is in the driving seat for this program."

Beyond lefitolimod, Mologen's follow-up, next-generation project EnanDIM is a family of TLR9 agonists comprising distinct immune response patterns that allows the tailor-making of individual EnanDIM molecules for different therapeutic approaches, such as combination immunotherapy in oncology, adjuvants for vaccines, and against infectious diseases.

Manth said preclinical studies in combination with different checkpoint inhibitors indicate the EnanDIM-family could be an ideal partner for combination immunotherapy.

The first EnanDIM candidate is expected to be Phase I-ready in the second half of 2019, and is available for partnering or co-development, the CEO said.

"We are confident to be able to advance a molecule from the next-generation technology EnanDIM into clinical development by end of 2019. We are convinced that this strategy will significantly drive the value of Mologen." ✨

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# AbiVax Equipped To Enter Anti-Inflammatory Market

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Boosted by a recent €12m cash injection from leading healthcare investor Sofinnova Partners, France's AbiVax can now focus on steering its flagship anti-inflammatory ABX464 through three key mid-stage trials.

Sofinnova has bought 1.5 million new shares at the market price of €8 each to take a stake of around 12.7% in AbiVax. The money will be used to fund three Phase II trials of ABX464 in ulcerative colitis, rheumatoid arthritis (RA) and Crohn's disease and some of the money will also be allocated to advance ABX196, which is in Phase I/II for liver cancer.

In an interview with *Scrip*, CEO Hartmut Ehrlich said that Sofinnova first approached AbiVax at the end of last year, and the funding process sped up when a partner at the investor, Kinam Hong, "picked up the torch." He said that getting a quality backer like Sofinnova on board alongside founding shareholder Truffle Capital, which now holds a 45.8% stake, is a validation of the firm's approach.

Ehrlich noted that following promising results of the Phase IIa study in ulcerative colitis, a dose-ranging Phase IIb trial has been launched in 232 patients evaluating three escalating doses of once-daily oral ABX464 (25 mg, 50 mg and 100 mg) against placebo.

The company is also launching a Phase IIa study of ABX464 in combination with methotrexate (MTX) in patients with moderate to severe active RA who had an inadequate response to MTX and/or anti-TNF biologicals. Another Phase II trial, in 30 patients with Crohn's, is scheduled to start enrolling around the end of this year.

While the indications that AbiVax is pursuing are highly competitive, Ehrlich stressed that they are still areas of high unmet medical need. In ulcerative colitis, whether patients have been treated with Pfizer Inc.'s oral JAK inhibitor Xeljanz (tofacitinib), Takeda Pharmaceutical Co. Ltd.'s intravenous Entyvio (vedolizumab) or an anti-TNF, while two-thirds of the patients respond to therapy, about half lose their initial response, he said.



Hartmut Ehrlich

"With the biologicals and JAK inhibitors, we've opened a new chapter in treatment for these patients but when it comes to long-term outcomes, there is still a lot left to be desired. This is why the field is screaming out for additional molecules preferentially with a new mechanism of action, which is why ABX464 is so interesting," Ehrlich said, adding that the therapy is being evaluated in a number of pre-clinical models for multiple sclerosis, Parkinson's disease, psoriasis, nonalcoholic steatohepatitis (NASH), psoriasis and pulmonary arterial hypertension.

ABX464 started life as an HIV drug, but AbiVax noted that "given the complexity of the US and European regulatory processes to develop an HIV cure," it saw greater opportunities in the inflammatory space (although an investigator-initiated study is scheduled to be initiated by the end of 2019). However chief medical officer Jean-Marc Steens told *Scrip* that more than 200 patients from the firm's HIV and ulcerative colitis programs have been treated with ABX464 and the safety and tolerability profile is excellent, with no evidence of the severe infections associated with anti-TNFs or Xeljanz.

The Sofinnova money extends AbiVax's cash runway to the end of the second quarter of 2020 and Ehrlich said this gives the Paris-based group, which has around

25 staff, most of whom are in R&D, "sufficient time and resources to leverage maximum value in ongoing partnering discussions." He hopes to be able to announce a deal by the end of the first quarter next year and AbiVax ideally wants to ink a pact with a global pharma player that wishes to license the drug for all disease areas, saying "it would be difficult to actually slice and dice different indications among different companies and not be totally in control."

AbiVax's share price has suffered a bit this year, trading now at around €9.20 and down from the 52-week high of €12.80. Chief financial officer Didier Blondel admitted to some frustration that the promise offered by the firm is not reflected in the share price and noted that listing on the Euronext Paris is perhaps not as easy these days as on the neighboring markets in Belgium and the Netherlands.

Those markets "have recently had nice flagship biotechs with nice stories," said Blondel, who was speaking to *Scrip* just a couple of days after Belgium's Galapagos NV unveiled its \$5.1bn R&D expansion with Gilead Sciences Inc.. He added that while Sofinnova and Truffle are long-term players when it comes to healthcare investment, "there are only a few specialized investors in France where biotech is a difficult sport to play. We need to educate and explain and make our story unique," he added.

In an investor note issued on July 16, Goetz Partners analyst Chris Redhead wrote that the investment by Sofinnova was a strong endorsement of AbiVax and "clinical data to date suggests that ABX464 could take a meaningful share of the \$70bn anti-inflammatory market." The unmet potential of the latter is well illustrated by the Gilead and Galapagos deal, he said, noting that "although anti-TNF drugs have transformed inflammatory therapy, 30%-40% of patients fail or cease to respond [and] there is a need for a safe effective orally available alternative."

The backing from Sofinnova "adds to our confidence for AbiVax securing a major licensing deal over the next 12 months," Redhead concluded. 🌟

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



Click here for the entire pipeline with added commentary:  
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## PIPELINE WATCH, 12-18 JULY 2019

Event Type	Lead Company/Partner	Drug Name	Indication	Comments	Change To LOA (%)	LOA (%)
Phase III Published Results	GlaxoSmithKline/J&J	Juluca (dolutegravir/rilpivirine)	HIV/AIDS	SWORD-2; The Lancet HIV, 12 July, 2019	0	100
Phase III Published Results	Biohaven Pharmaceutical	rimegepant, fast-dissolve tablet	Acute Migraine	BHV3000-303; The Lancet, 13 July, 2019	0	94
Phase IIIb Updated Results	Teva Pharmaceutical	Ajovy (fremenezumab)	Migraine Prevention	FOCUS; Reduced Migraine Days	0	100
Phase IIb/III Updated Results	Allergan/Merck & Co	atogepant	Episodic Migraine	Encouraging Results	0	57
Phase III Trial Suspension	Polyphor AG	murepavadin, Intravenous	Hospital-Acquired Pneumonia	PRISM-UDR, MDR; Due To ADRs	-38	17
Phase III Top-Line Results	Torii Pharma/Japan Tobacco	enarodustat (JTZ-951)	Anemia Due to CKD, Dialysis-Dependent	MBA4-5 (Japan); Met Primary Endpoint	0	23
Phase III Top-Line Results	Torii Pharmaceutical Co., Ltd.	enarodustat (JTZ-951)	Anemia Due to CKD, Dialysis-Independent	MBA4-4; Met Primary Endpoint	0	23
Phase III Top-Line Results	GlaxoSmithKline plc	Zejula (niraparib)	Ovarian Cancer, First-Line Maintenance	PRIMA; Positive PFS Results	0	100
Phase III Trial Initiation	Eli Lilly & Co/Incyte	Olumiant (baricitinib)	Alopecia Areata	BRAVE-AA2; In Adults	0	62
Phase III Trial Announcement	Johnson & Johnson	Ad26.Mos4.HIV vaccine	HIV-1 Prevention	MOSAICO; First P3 Efficacy Study	0	27
Phase III Trial Announcement	AM-Pharma B.V.	recAP (alkaline phosphatase)	Sepsis-Associated Acute Kidney Injury	SA-AKI; In 12 Countries	0	25
Phase III Trial Announcement	Seattle Genetics, Inc.	tucatinib	Breast Cancer, Metastatic	w/T-DM1; HER2-Positive	0	13
Phase III Trial Announcement	Novartis/Akcea/Ionis	TQJ230, antisense	Cardiovascular Disease	Lp(a)HORIZON; To Reduce CV Risk	0	14
Phase IIb/III Trial Announcement	Seelos Therapeutics, Inc.	SLS-005	Mucopolysaccharidosis III	Type A and B; Open-Label Study	0	0
Phase IIb/III Trial Announcement	Portola Pharmaceuticals, Inc.	cerdulatinib	Peripheral T-Cell Lymphoma	CELTIC-1; Relapsed Disease	0	12

Source: Biomedtracker | Informa, 2019

# Road Ahead Unclear For Polyphor's Intravenous Murepavadin

ALEX SHIMMINGS alex.shimmings@informa.com

Polyphor Ltd. has decided to close the two Phase III trials of murepavadin iv for hospital-acquired and ventilator-associated bacterial pneumonia (HABP/VABP) that were put on a voluntary temporary hold in May, spelling the likely end for the program.

The Phase III trials – PRISM-MDR and PRISM-UDR – were evaluating murepavadin in patients with nosocomial pneumonia but a higher than expected incidence in acute kidney injury in the drug arm of PRISM-MDR led to the original halt.

Now the company says the increased creatinine concentration in the serum of patients indicating a higher than expected frequency of acute kidney injury in the drug arm has been confirmed by an analysis of all patients in the study arm. There was no increase in the incidence of mortality in the murepavadin arm compared with control – the 28-day mortality rates were 30.0% and 37.5% respectively.

Murepavadin (POL7080) is the most advanced outer membrane protein

targeting antibiotic (OMPTA) that Polyphor is developing, and the company stressed that the halt affected the iv formulation only. Development of inhaled murepavadin and the wider OMPTA program continues. The inhaled formulation of murepavadin is being investigated for cystic fibrosis patients with chronic infections caused by *Pseudomonas aeruginosa* and non-cystic fibrosis bronchiectasis.

The company does hold out some hope for the iv murepavadin version, saying it has identified “a number of options and activities – some of which have already started – to potentially improve the benefit risk ratio of the intravenous formulation of murepavadin for the treatment of HABP/VABP.” It will evaluate these options in the coming months and give an update on the whole development program with the publication of the half year results on 4 September, it said.

Others, however, are less optimistic. Despite Polyphor's intentions for the iv formu-

lation, Deutsche Bank analysts said in a 17 July note that the “program's overall feasibility is now clearly in serious doubt.”

They expect the company will end up announcing efforts to preserve its finances and focus them on its other pipeline assets: balixafortide, OMPTA and inhaled murepavadin.

Balixafortide (POL6326) – Polyphor's next most-advanced product – is a CXCR4 antagonist just entering Phase III for use in combination immuno-oncology, and much now rests on that program, to the Deutsche Bank analysts' consternation. “Given our view over the high risks associated with balixafortide's Phase III trial we believe the company may be wise to seek partners to help co-fund ongoing development and enable investment in new potential indications,” they said.

The analysts believe Polyphor will need refinancing in 2021, and this will largely depend upon the results of the Phase III balixafortide study. 🌟

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## APPOINTMENTS

Executive	To Company	New Role	From Company	Previous Role	Effective Date
Jim Harold	Acino International AG	General Manager, Latin America	Novartis Pharma Services AG	President and Head, Middle East and North Africa	1-Jul-19
Diane C. Young	Celldex Therapeutics	Chief Medical Officer and Senior Vice President	GTx Inc	Chief Medical Officer	24-Jun-19
James Randall Owen	Navitor Pharmaceuticals	Chief Medical Officer	Acadia	Senior Vice President, Clinical Development and Chief Medical Officer	15-Jul-19
Christopher White	Ocular Therapeutix Inc	Head, Business and Corporate Development and Senior Vice President	Silver Creek Pharmaceuticals	Chief Operating Officer	11-Jul-19
Kim Stratton	Orphazyme AS	Chief Executive Officer	Shire Pharmaceuticals	Head, International Commercial, Specialty and Rare Disease	1-Oct-19
Mariam Charafeddine	Vaccitech Ltd	Chief Medical Officer	AbbVie	Medical Director	15-Jul-19

Click here for all appointments: <https://bit.ly/2oHWRYN>

Source: Medtrack | Informa, 2019

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