



Novartis's Zolgensma is World's Most Expensive Drug

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Novartis AG is setting new records as it prepares to launch Zolgensma, the spinal muscular atrophy (SMA) gene therapy developed by Novartis subsidiary AveXis Inc. The 24 May approval makes it the second gene therapy to clear the US FDA, and the largely expected price of about \$2m makes it the most expensive drug in the world.

Novartis anticipates that some payers will agree to an annuity-like model under which Zolgensma (onasemnogene abeparvovec-xioi) will cost \$425,000 annually for five years, but such agreements may be difficult to implement. The company also will negotiate value-based agreements, but executives from

Novartis and AveXis said during a media call that they couldn't provide any details about those confidential discussions.

Novartis CEO Vas Narasimhan and AveXis president David Lennon commented on such pricing and reimbursement models at Novartis' 22 May investor event, noting they expected limited uptake of the payment plan model.

Zolgensma is indicated for SMA patients under 2 years old with bi-allelic mutations in the survival motor neuron 1 (SMN1) gene, including pre-symptomatic infants and patients with SMA types 1-3. The FDA approved the gene therapy under priority review and a week ahead of the user fee deadline.

About 450-500 infants are born with SMA in the US each year. Type 1 SMA is the most serious form of the disease, preventing infants from being able to walk or talk or sit up on their own. Patients with this severe form of the disease eventually will require permanent ventilation and are not likely to live past 2 years old.

Zolgensma delivers a functional copy of the human SMN gene to provide for sustained SMN protein expression and interrupt disease progression from loss of neurons. The treatment is a one-time, weight-based intravenous infusion, but an intrathecal injection is in development to allow for the treatment of older patients, including those with the less severe SMA types 2 and 3.

The IV version of the gene therapy was approved based on the Phase I START and Phase III STRIVE studies of infants with SMA type 1. Zolgensma allowed patients to achieve milestones – such as rolling over, sitting on their own or even walking – and to live longer than SMA natural history would suggest.

ACCOUNTING FOR COST, EFFICACY OF NOVEL TREATMENT

When announcing the approval, Narasimhan noted it will launch Zolgensma immediately with product shipping within the next two weeks. AveXis will market the gene therapy and operate the OneGene Program that will help patients' parents with health insurance coverage questions and provide financial assistance to families that are uninsured or need help paying out-of-pocket costs for the gene therapy.

The Novartis CEO said Zolgensma is priced at 50% less than multiple value-based pricing benchmarks and pointed out that the \$2.125m price tag is within

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from the editor

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Novartis's stock gained more than \$7bn last Friday when the US FDA approved Zolgensma, its gene therapy for spinal muscular atrophy. This isn't far short of the \$8.7bn it paid last year to acquire the product's originator, AveXis.

Much has been made of the fact that Zolgensma is the world's most expensive drug. Nevertheless, as a treatment for the under-twos, which has maximal effect when given as early as possible, Zolgensma's capacity to bring cash into the company's coffers is limited. Given the rarity of the condition, it is unlikely to be able to book as much as \$1bn a year in the US, even at peak sales. In comparison, Biogen and Ionis Pharmaceuticals' antisense SMA treatment Spinraza,

which is approved for all ages, generated net US sales of \$854m last year, its second full year on the market.

Gene therapies are so new that long-term data on their duration of efficacy and eventual side-effects are not available, so it is not yet possible to truly compare the costs of treating SMA using Zolgensma with the cost of Spinraza or indeed with the cost of using neither (which is a death sentence for patients with the commonest form, type 1).

However, if gene therapies like Zolgensma meet their promise and prove to be effective one-time cures, then their price tag is actually a price cap, something that cannot be said for therapies that must be taken over the long term.

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AZ, Takeda, Novartis Praised For Medicines Access Work But More Is Needed

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AstraZeneca PLC, Takeda Pharmaceutical Co. Ltd. and Novartis AG are among the major pharmaceutical companies to have been singled out as models of good practice in terms of “equitable” drug pricing in a report from the Access To Medicine Foundation, an independent non-profit organization.

The report, which analyzes the practices and strategies of the 20 companies in the foundation’s Access to Medicine Index, says that firms are making progress in the way that they approach access to medicines, and some are working in “new inclusive ways that aim to reach people on very low incomes.” 17 of the 20 companies have now set relevant access goals, compared with just eight in 2010.

In addition, several companies have reoriented their R&D pipelines towards diseases that need new treatments, and are increasingly managing access to medicine as a strategic issue, while licensing and “equitable” pricing arrangements are on the rise.

But progress on other fronts is less encouraging, for example with regard to the consistency of company support for trade-related flexibilities like compulsory licensing, and the attention paid by companies to less profitable diseases. In some areas, just a handful of companies are carrying most of the burden of efforts to improve access to medicines in lower income countries.

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the cost-effective price range determined by the Institute for Clinical and Economic Review (ICER).

Upon approval of Zolgensma for all three types of SMA in infants, ICER amended its estimate of pricing that would be within a US cost effectiveness threshold of \$100,000-\$150,000 per quality-adjusted life year (QALY), saying that a price of \$1.1m to \$1.9m would be appropriate. However, the nonprofit drug price assessor also said on 24 May that a value-based threshold of \$100,000-\$150,000 per life year gained (LYG) would suggest an appropriate price range of \$1.2m to \$2.1m.

ICER previously said \$900,000 was a cost-effective price for infantile-onset SMA type 1 based on the \$100,000-\$150,000 per QALY threshold.

Narasimhan pointed out that Zolgensma is priced at about 50% of the cost of chronic treatment with Biogen's Spinraza (nusinersen), which can cost \$4.1m over a 10-year period. Spinraza is an antisense oligonucleotide developed in partnership with Ionis Pharmaceuticals Inc.; it's approved to treat all types of SMA regardless of age.

Novartis/AveXis also maintained the gene therapy costs half or less of the estimated \$4.4m-\$5.7m cost of treating ultra-rare pediatric genetic diseases for 10 years.

Negotiations are under way with payers to reimburse the cost of Zolgensma over a period of up to five years or to receive a rebate if the gene therapy doesn't work. AveXis is working with the specialty pharmacy Accredo to offer pay-over-time options of up to five years with a big focus on state Medicaid programs, small payers and self-insured employers, but large payers also are showing interest in spreading out the gene therapy's cost over time.

Steve Miller, chief clinical officer for the pharmacy benefit manager (PBM) business within the health insurer Cigna Corp., said in an announcement about AveXis' pricing and reimbursement strategy that the payer is engaged in discussions with the Novartis subsidiary about "unique solutions" for reimbursing Zolgensma's cost, including installment payments and outcomes-based agreements.

Outcomes-based or value-based agreements would entitle payers to a discount

or rebate if outcomes are not as promised for patients treated with the gene therapy, i.e. if children require permanent ventilation or die within a given timeframe after Zolgensma infusion, Lennon said during the post-approval media briefing.

AveXis reported that advanced negotiations are under way with more than 15 payers and some have agreed to specific contract terms.

"We are thrilled to be able to offer our members access to this groundbreaking gene therapy, particularly in light of AveXis agreeing to place a portion of the cost at risk, contingent upon demonstrating continued performance over a five-year period," Harvard Pilgrim Health Care chief medical officer Michael Sherman said in the gene therapy maker's announcement, noting that Harvard Pilgrim covers treatment for a small number of newly diagnosed SMA type 1 patients each year.

AveXis also has launched an education program for payers called "Time is Neurons" to emphasize the importance of early diagnosis and treatment in SMA,

since lost neurons cannot be regained.

Outside the US, Zolgensma is under review in the EU and Japan under priority registration programs. While those approvals are pending, AveXis is providing access to the gene therapy under its paid Managed Access Program through the third-party provider Durbin.

LIMITATIONS ON ALTERNATIVE REIMBURSEMENT OPTIONS

Narasimhan and Lennon noted in the briefings with reporters both before and after Zolgensma approval that negotiations for alternative reimbursement models with payers – particularly Medicaid – are limited by regulations that restrict outcomes-based agreements and installment payment plans. Rebates and discounts in particular are limited by Medicaid best price calculations.

"Payers understand the value proposition," Narasimhan said on 22 May. "They are already paying these prices to care for these patients. The value proposition we come with, whether it is an upfront payment of an annualized payment is very compelling to them. And, honestly, for large payers, the overall budget impact is not that large. We are talking about tens of patients that may exist in a plan."

Installment plans are of interest to – and may be most helpful for – small private payers and Medicaid, because of their budget constraints, the Novartis CEO added.

Medicaid covers about half of the SMA population in the US, so Zolgensma will test its flexible reimbursement capabilities. US Centers for Medicaid and Medicare Services (CMS) administrator Seema Verma said in a 22 May briefing on the cusp of the SMA treatment's approval that the agency is exploring various options for covering gene therapy costs. (Also see "New Payment Models For Curative Treatments Have CMS' Attention, Verma Says" - Pink Sheet, 23 May, 2019.)

COMPETITIVE IMPACT MAY BE LIMITED INITIALLY

Spinraza has become a blockbuster product for Biogen, which reported \$518m in first quarter 2019 sales of the drug, since its approval at the end of 2016. (Also see "Biogen/Ionis's Spinraza Approved; Second Antisense Drug For Neurodegeneration In



Zolgensma is priced at 50% less than multiple value-based pricing benchmarks and the \$2.125m price tag is within the cost-effective price range determined by the ICER.”
– Vas Narasimhan.

2016" - *Scrip*, 28 Dec, 2016.) It launched in early 2017 with a list price of \$750,000 in the first year and \$375,000 in subsequent years. (Also see "Biogen Forecasts Gradual Launch For Life-Transforming Drug Spinraza" - *Scrip*, 26 Jan, 2017.) The antisense drug is administered with four loading doses over the first two and a half months of treatment then quarterly for as long as patients live after that.

Analysts said in notes on 24 May that while Zolgensma is a threat to Biogen's Spinraza revenue and Ionis's royalties from the drug, initially with its infant-only indication the gene therapy will not cut too far into Spinraza's pediatric and adult SMA market.

"Although Zolgensma is indicated for all SMA types, we expect the initial impact on Spinraza likely to be small (about -5% impact) due to small number of newly diagnosed SMA patients each year," Jef-

feries analyst Eun Yang wrote in a note for Ionis investors. She estimated that only about 400 infants are newly diagnosed with SMA each year versus a prevalence of about 7,000 US patients with SMA across all types and ages, all of whom are eligible for treatment with Spinraza.

Yang and William Blair's Matt Phipps said the Roche/PTC Therapeutics Inc. SMA candidate risdiplam is a bigger threat to Spinraza given the similar patient populations for the medicines. Roche has indicated that it will file the drug for approval later this year with approval anticipated in 2020. (Also see "Roche Makes Case For Its Oral SMA Drug Risdiplam As Filings Beckon" - *Scrip*, 6 Feb, 2019.)

"In our current estimates for Biogen's Spinraza, we have assumed the number of newborn patients treated with Spinraza will decrease dramatically in the second half of this year given the approval

of Zolgensma, with no newborns initiating Spinraza beginning in 2020," Phipps wrote. "However, we still believe Spinraza has potential to increase penetration in the near term in older type 2 and type 3 patients in the United States and continued growth outside the United States. Longer term, we see greater risk to the Spinraza franchise from the potential approval of PTC Therapeutics' risdiplam, given the similar mechanism of action and oral route of administration."

The share price for Novartis, which also saw the same-day approval of its potential breast cancer blockbuster Piqray (alpelisib), closed 3.7% higher at \$87.52 per share on 24 May, while Biogen declined 0.9% to \$227.06 and Ionis shares fell 3.6% to \$64.72. Roche rose 0.7% to close at \$34. ▶

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Google's Verily Makes Clinical Trials Pitch With Big Pharma Pacts

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Verily Life Sciences LLC, the health and life sciences subsidiary of Google parent company Alphabet, has unveiled deals with four pharmaceutical companies which it claims could transform clinical trials by implementing a more patient-centric, technology-enabled approach to research.

Pfizer Inc., Novartis AG, Sanofi and Otsuka Pharmaceutical Co. Ltd. have signed up to Verily's Project Baseline, which launched in 2017 and has seen the latter develop user-friendly devices, dashboards and analytical tools "that create an engaging experience for patients" and provide support to clinical study coordinators and researchers. Verily said that the platform provided "access to timely, normalized data that can streamline enrollment and management of studies," as well as enabling the collection of data like electronic health records (EHR), biometric or self-reported information "which may provide significantly more context about the value of an intervention."

In the last couple of years, Project Baseline has built a connected ecosystem with the aim of linking patients and advocacy groups with clinicians and health systems, with the participation of the likes of Duke University, Stanford Medicine, Google itself and the American Heart Association. Now big pharma is getting onboard.

Jessica Mega, Verily's chief medical and scientific officer, said, "Evidence generation through research is the backbone of improving health outcomes. We need to be inclusive and encourage diversity in research to truly understand health and disease, and to provide meaningful insights about new medicines, medi-

Clinical trials data revolution may bring power to the patient



cal devices and digital health solutions." She added that "Novartis, Otsuka, Pfizer and Sanofi have been early adopters of advanced technology and digital tools to improve clinical research operations and together we're taking another step towards making research accessible and generating evidence to inform better treatments and care."

The pharma firms are enthused about the potential of their Verily collaborations and each of them plan to launch clinical studies using the platform across a range of therapeutic areas, including cardiovascular disease, oncology, mental health, dermatology and diabetes.

Badhri Srinivasan, head of global development operations at Novartis, said, "Our ability to bring new medicines to patients quickly is often hampered by inefficient or limited participation in clinical trials. By combining our complementary sets of expertise, we have the opportunity to develop a new trial recruitment model that gives patients and their physicians greater insight into the process of finding treatments for their disease, and how they can participate."

Srinivasan oversees Novartis' Nerve Live digital platform for managing clinical trials which is based at its Basel campus and was showcased by the firm in January. At the time, he told *Scrip* that the monitoring of clinical trials across the pharma sector "is still largely manual," with much of it being conducted via spreadsheets, email and telephone calls, but in the case of Nerve Live, its predictive algorithms allow Novartis to see potential logjams in its clinical trials 12, 18 or 24 months down the road. (Also see "How Novartis Is Making SENSE Of Clinical Data In Digital Age" - *Scrip*, 6 Feb, 2019.)

Debbie Profit, head of applied innovation and process improvement at Otsuka, added that "the clinical research process is antiquated in many ways" and the collaboration with Verily "aims to redefine and redesign this process to make clinical trials more accessible to patients, and clinical research more precise and targeted." She claimed that Otsuka's early adopter status in the project would allow it to leverage real world data, through sensors, EHR integrations and other tools "to corroborate evidence around the treatments and interventions we are studying and at the same time reduce the burden on clinical trial participants."

Rod MacKenzie, chief development officer at Pfizer, said, "In clinical research, for several years now we have been pursuing

game-changing possibilities to deploy digital technology and data science to re-engineer how we operate. The science behind our potential new medicines is cutting edge, yet many clinical trial processes have remained relatively unchanged over decades [so] Pfizer is committed to exploring new technologies and innovative ways to conduct clinical research."

His views were echoed by Lionel Bascles, global head of clinical sciences and operations at Sanofi, who said that "our scientific knowledge has exploded over the past generation, but efficiently bringing these new breakthroughs from lab bench to patient requires us to greatly improve the way we conduct these complex clinical trials. Project Baseline will allow us to better recruit appropriate patients and more efficiently integrate data for a greater understanding of diseases, reconnecting trials to our patients' healthcare journeys."

Susan Danheiser, director at Informa's Citeline, told *Scrip* that the collaboration was "indicative of the push pharma companies, big and small, are making to incorporate real world approaches to patient recruitment and data gathering into their clinical drug development programs." She noted that over 1,700 prospective, real world studies have been initiated or planned in 2018 and 2019 to date, according to Informa's Trialrove and "not surprisingly, two of Verily's partners, Pfizer and Novartis, are the top industry sponsors of these studies."

Danheiser went on to note that Verily is just one of several companies entering the market to support these efforts. "Leveraging Google to draw patients into their Baseline 'registry' could be a distinguisher, but this is yet to be seen." ▶

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Lilly Advances IL-23, Gastroenterology Ambitions With Mirikizumab In Crohn's Disease

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Eli Lilly & Co. is in the running to bring a fourth interleukin-23 (IL-23) inhibitor to market and reported Phase II results on 21 May for its candidate mirikizumab in Crohn's disease. It's the second inflammatory bowel disease (IBD) that Lilly's pursuing, in addition to ulcerative colitis – a pair of indications that could give it an edge in a crowded IL-23 field, though competitors also are moving ahead in the space.

Lotus Mallbris, vice president of immunology development, told *Scrip* that while gastroenterology is a relatively new therapeutic area for Lilly, the company worked with doctors and patients to design a clinical trial program that reflects current thinking in Crohn's treatment and attempts to address unmet needs. As a result, Mallbris said the Phase II results for mirikizumab in Crohn's disease showed endoscopy response and remission rates that are clinically meaningful and justify the initiation of a Phase III program later this year, including a head-to-head trial.

Mirikizumab's most advanced indication is its Phase III program in psoriasis, which Lilly anticipates reporting results from later

this year. It's an indication where three other IL-23 inhibitors and Johnson & Johnson's IL-12/IL-23 inhibitor Stelara (ustekinumab) already are approved in the US.

The FDA granted approval for AbbVie Inc.'s Skyrizi (risankizumab) in April, making it the third IL-23 inhibitor on the market for psoriasis in the US behind J&J's first-to-market Tremfya (guselkumab) and Sun Pharmaceutical Industries Ltd.'s Ilumya (tildrakizumab). (Also see "AbbVie's Humira Succession Plan Begins Taking Shape With Skyrizi US Approval" - *Scrip*, 24 Apr, 2019.)

IL-23 inhibition already is used in Crohn's disease following Stelara's approval for that IBD indication in 2016; Stelara also is pending at the FDA for the IL-12/23 inhibitor's use in ulcerative colitis (UC).

In addition to Lilly's ongoing Phase III UC program, in terms of other products targeting IL-23 only, AbbVie's drug has a slight edge over mirikizumab, since Skyrizi is in Phase III for both UC and Crohn's. Following close on their heels, Allergan PLC's brazikumab is in Phase II/III for Crohn's and Phase II for UC, while J&J's Tremfya is in Phase II/III for Crohn's.

ENDOSCOPIC DATA APPEAR PROMISING IN CROHN'S

Lilly's Phase II results for mirikizumab in Crohn's disease were presented at Digestive Disease Week (DDW) in San Diego, a meeting organized by the American Gastroenterological Association, American Association for the Study of Liver Diseases, American Society for Gastrointestinal Endoscopy and the Society for Surgery of the Alimentary Tract.

Mirikizumab could be a valuable addition to Crohn's treatment options based on the endoscopic and symptomatic responses seen in the Phase II trial.

The Phase II SERENITY clinical trial tested mirikizumab administered intravenously every four weeks at doses of 200mg, 600mg and 1,000mg versus placebo at a ratio of 2:1:1:2, respectively, in 191 patients with moderately to severely active Crohn's disease. The data reported at DDW covered the 12-week induction period; the maintenance phase of the study is ongoing.

The primary endpoint was endoscopic response defined as a 50% reduction from baseline in the severity of disease as measured by the Simple Endoscopic Score for Crohn's Disease (SES-CD). Endoscopic response rates were 10.9% for placebo versus 25.8% for the 200mg dose of mirikizumab ($p=0.079$), 37.5% for the 600mg dose ($p=0.003$) and 43.8% for the 1,000mg dose ($p<0.001$) – all statistically significant.

Secondary endpoints included a patient-reported outcome (PRO) measure of remission, defined as an average daily stool frequency of 2.5 or less and abdominal pain of 1 or less; endoscopic remission, defined as an ileal-colonic SES-CD score of less than 4, an isolated ileal SES-CD score on less than 2 and no subscore greater than 1; and safety.

PRO remission rates were statistically significant for only the two highest doses of mirikizumab: 6.3% in the placebo group, 12.9% for the 200mg mirikizumab dose ($p=0.346$), 28.1% for 600mg ($p=0.005$) and 21.9% for 1,000mg ($p=0.025$).

Similarly, endoscopic remission rates were statistically significant for the top two doses: 1.6% for placebo, 6.5% for the 200mg mirikizumab dose ($p=0.241$), 15.6% for 600mg ($p=0.032$) and 20.3% for 1,000mg ($p=0.009$).

"Endoscopy is the most objective imaging that you can have and something that physicians really want to see to give hope to their patients," Mallbris said, noting that Lilly was particularly pleased with the endoscopic response and remission outcomes based on feedback doctors have provided on the importance of these measures in effectively treating IBD patients.

Indeed, Bruce Sands, a medical professor and chief of the gastroenterology division at the Icahn School of Medicine at Mount Sinai and lead investigator of the SERENITY study, said mirikizumab could be a "valuable addition" to Crohn's treatment options based on the endoscopic and symptomatic responses seen in the Phase II trial.

In terms of safety, five patients across all of the mirikizumab doses (4%) reported one or more serious adverse event (SAE), while 81 patients (64%) reported one or more treatment-emer-

gent adverse event (TEAE) versus SAE and TEAE rates of 11% (seven patients) and 70% (45 patients) in the placebo group. Headache, weight gain and nasopharyngitis were the most common treatment-emergent side effects associated with mirikizumab.

The safety results were described as consistent with prior studies for the drug.

Phase II results in UC were presented during DDW in June 2018, showing clinical remission, clinical response and endoscopic healing rates that were statistically significant versus placebo for all doses of mirikizumab at 12 weeks. Adverse event rates were similar in the drug and placebo groups.

Biomedtracker said when the UC data were released last year that mirikizumab performed better on both efficacy and safety than Pfizer Inc's oral JAK inhibitor Xeljanz (tofacitinib), which was approved in May 2018 for UC. The analyst service gives the Lilly candidate a 64% likelihood of FDA approval for UC, which is 5% above average for drugs in the same stage of development for that indication.

PHASE III PLANNING ONGOING

Lilly is finalizing the design of its Phase III Crohn's disease program, but one pivotal study has been posted to clinicaltrials.gov to date. The 72-week trial will enroll 1,100 patients and run from June 2019 through May 2022, comparing intravenous and subcutaneous dosing of mirikizumab to IV and subcutaneous doses of Stelara and placebo.

"What is most important is that we address not only the regulatory requirements to get it approved and for the doctor to prescribe, but also to address what the doctor needs," Mallbris said. "The team are working day and night to put all of those items together for consideration, but at least the pivotal package is going to address the regulatory path that is both induction, maintenance and long-term extension."

The mirikizumab data may come two years too late to beat Skyrizi to market in Crohn's disease, however, since the primary completion dates for AbbVie's two pivotal Phase III trials in that indication are June 2020 and October 2020 with long-term extension study results expected in October 2025.

J&J also is running pivotal studies for Tremfya in Crohn's disease and ulcerative colitis monotherapy, and has initiated a Phase II study of Tremfya in combination with the TNF inhibitor Simponi (golimumab) in ulcerative colitis.

The Phase III program for mirikizumab in ulcerative colitis includes the LUCENT 1 induction study enrolling 1,160 patients with moderately to severely active UC and continuing through December 2021, the LUCENT 2 maintenance study enrolling 1,044 patients and lasting until March 2022 – both are placebo-controlled – and the LUCENT 3 long-term trial enrolling 840 patients treated with mirikizumab only and running through August 2023.

"This is our first entry in providing a mature research program" in gastrointestinal diseases, Mallbris noted. "We have several programs in gastroenterology that are in early research, both preclinical and also in humans." The programs benefit from both internal experts in the field and external partners, including doctors and patient advocates, she said. ▶

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Merck Buys Peloton On Eve Of IPO, Expands Kidney Cancer Portfolio

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Merck & Co. Inc. will bolster its oncology portfolio – particularly its kidney cancer franchise – with the purchase of Peloton Therapeutics Inc. for \$1.1bn up front in a transaction announced 21 May, during the week that the private firm was expected to launch its initial public offering.

looking to harness the ubiquitin proteasome system and target the extracellular enzyme CD73.

PT2977 – the only HIF-2 α inhibitor in the clinic, according to the Biomedtrack database – is an oral small molecule against a target that previously was believed to be intractable using small

of the PD-L1 inhibitor Bavencio (avelumab) with Inlyta.

Credit Suisse analyst Vamil Divan pointed out in a 21 May note that Merck is under increased pressure to pursue business development, including large transactions, as its reliance on Keytruda revenue grows, but Divan said more details on the “Keytruda and non-Keytruda parts” of the company’s business will be reviewed at an investor day scheduled for 20 June.

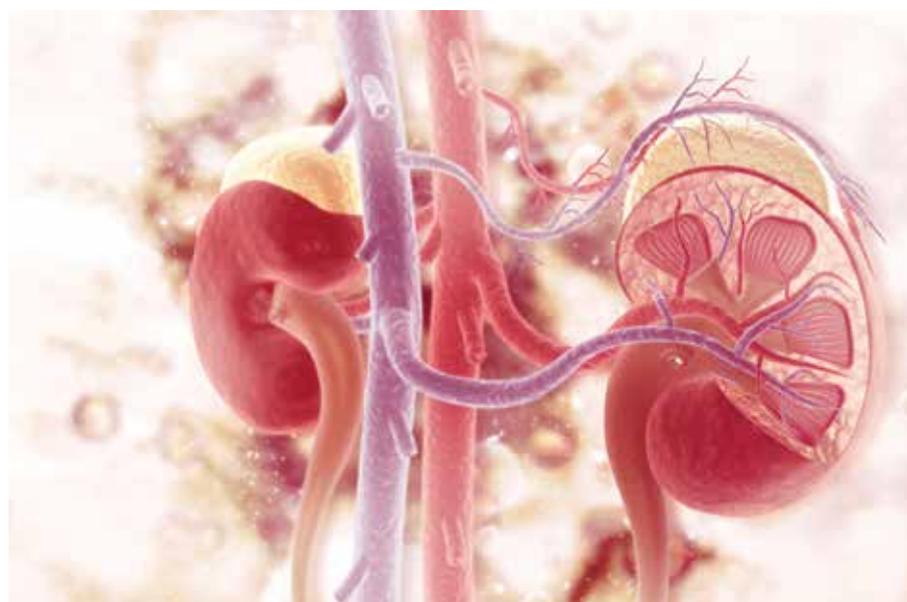
“As bullish as we have been on the Merck story for nearly 3 years now, the push-back from investors has been increasing on how leveraged the company is becoming to Keytruda’s success,” he wrote. “While management has not completed a larger deal since the Cubist Pharmaceuticals Inc. and Idenix Pharmaceuticals Inc. deals back in 2014, they have signed a number of smaller deals and clinical collaborations that we believe often get overlooked.”

“While maybe not the size of deal that some have been hoping Merck to pursue, Peloton’s initial focus on RCC is complementary to where Merck is already finding success with the recent approval of Keytruda + Pfizer’s Inlyta in 1st line RCC based on the positive KEYNOTE-426 trial,” Divan added.

Credit Suisse is acting as financial advisor to Merck on the Peloton deal.

PT2977 TO BE TESTED IN CHECKPOINT INHIBITOR-REFRACTORY RCC

Ongoing studies for PT2977 include a Phase II trial in von Hippel-Lindau (VHL) disease-associated RCC, a Phase II study in combination with Exelixis Inc’s VEGFR-targeting Cabometyx (cabozantinib) in metastatic RCC (mRCC) and a Phase I/II dose-escalation and dose-expansion study in mRCC, including an expansion arm in glioblastoma multiforme (GBM). Phase I/II monotherapy data for PT2977 to date have “demonstrated favorable safety and early signs of anti-tumor activity” in advanced or metastatic RCC, Merck and Peloton said.



Acquiring Peloton will expand Merck’s kidney cancer portfolio

The deal gives venture capital investors a return of at least 3.5 times the \$304m invested in Peloton to date, based on the VC funding total the Dallas, TX-based company disclosed in documents filed with the US Securities and Exchange Commission (SEC) in support of its planned IPO. The return will be 7.2 times Peloton’s VC total if the company’s investors receive all \$1.15bn in additional fees that Merck has committed to pay based on certain regulatory and sales milestones.

Merck’s potentially multibillion-dollar investment will add Peloton’s first-in-class hypoxia-inducible factor-2 α (HIF-2 α) inhibitor PT2977 to the big pharma’s oncology portfolio along with other preclinical candidates targeting HIF-2 α for the treatment of cancer and other diseases, including PT2567 for non-oncology indications. Peloton also has research-stage programs

molecules, Peloton noted. HIF-2 α is a transcription factor normally involved in red blood cell and blood vessel production, but when dysregulated it can drive aberrant blood vessel growth and cell proliferation in diseases such as renal cell carcinoma (RCC).

Kidney cancer is an important indication for Merck’s blockbuster PD-1 checkpoint inhibitor Keytruda (pembrolizumab), which leads the IO class with \$7.2bn in 2018 sales. (Also see “Merck’s Keytruda Lead Widens Over Competing Checkpoint Inhibitors” - *Scrip*, 1 Feb, 2019.)

Merck reported Phase III data for Keytruda in combination with Pfizer Inc’s tyrosine kinase inhibitor Inlyta (axitinib) in first-line advanced RCC in February. Analysts predicted that Keytruda plus Inlyta could be a preferred regimen compared with Pfizer and Merck KGaA’s combination

HIF-2 α is aberrantly activated as a result of inactivity of the VHL tumor suppressor, which is observed in more than 90% of clear cell RCC cases; clear cell RCC is the most common form of kidney cancer.

In terms of VHL-associated RCC, with a diagnosis rate of one in every 36,000 births, Peloton estimates that about 20,000 people in the US and EU have VHL disease, a condition in which RCC diagnoses and deaths are common. Since there are no approved drugs for VHL disease, the company has said it will seek orphan drug designation for PT2977 in VHL-associated RCC.

Peloton planned to use its IPO proceeds to initiate a Phase III clinical trial testing PT2977 versus Novartis AG's Afinitor (everolimus) in previously treated mRCC in the second half of 2019, according to its amended S-1 registration statement filed with the SEC on 13 May. The study is designed to enroll 688 patients who received up to three prior treatment regimens, including at least one prior immune checkpoint inhibitor and one VEGF/VEGFR-targeting therapy.

The company's 13 May SEC filing indicated that it would gross up to \$159.4m from the sale of 9.4m shares at \$15 to \$17 each, before shares sold to meet over-allocments, in an offering that IPO-tracking firm Renaissance Capital expected to price during the week of 20-24 May.

Peloton first filed for an IPO on 26 April, seeking up to \$115m. (Also see "IPO Update: Pace Of US Offerings Slows As 13 Biopharmas Go Public In 2019" - *Scrip*, 1 May, 2019.) Just before that initial SEC filing, the company closed a \$150m series E venture capital round in February. (Also see "Finance Watch: Scripps Research Models A New Way To Fund Translation" - *Scrip*, 26 Feb, 2019.) It launched in 2011 with \$18m in series A funding and a portfolio of drug candidates licensed from University of Texas Southwestern Medical Center. (Also see "Cancer drug start-up Peloton raises \$18M" - *Scrip*, 29 Jul, 2011.) ▶

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 @PharmaScrip

Lured By Its Discovery Platform And Pipeline, Amgen Bids For Nuevolution

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Clearly impressed with their ongoing drug discovery collaboration, Amgen Inc. has now offered to buy Nuevolution AS for \$166.8m in cash, representing at SEK32.5 (\$3.37) per share a premium of 169% to the biotech's closing price on 21 May, the day before the offer was announced, and which is being unanimously recommended by the Copenhagen-headquartered group board and main shareholders.

Founded in 2001, Nuevolution is an innovator in small-molecule drug discovery. Its internally developed DNA-encoded drug discovery platform, Chemetics, has been designed to rapidly select drugs for an array of tough-to-drug disease targets.

PLATFORM PARTNERSHIPS

The platform's technology has been validated by multiple collaborations, notably deals entered in 2016 with Amgen and Almirall SA.

Nuevolution also has ongoing drug development deals with Johnson & Johnson, Merck & Co. Inc., Novartis AG, Boehringer Ingelheim GmbH, GlaxoSmithKline PLC and Lexicon Pharmaceuticals Inc.

It is uncertain how those collaborations might be impacted by a takeover of Nuevolution by Amgen.

In late 2016 Almirall licensed exclusive worldwide development and commercialization rights to Nuevolution's small-molecule retinoic acid-related orphan nuclear receptor gamma T (ROR γ T) inhibitor program for inflammatory skin diseases, including psoriatic arthritis.

That same year, Nuevolution licensed Amgen an exclusive option to develop and commercialize small-molecule cancer and neuroscience therapies using the Chemetics platform to discover targets of interest to Amgen that are difficult to make using traditional methods.

In 2018, Amgen opted-in on two programs and is now covering development costs. Under that deal, which spans multiple undisclosed targets, Nuevolution was to handle early-stage research, while Amgen was to collaborate on late-stage research and be solely responsible for preclinical studies, clinical trials, and commercialization.

Nuevolution's website said it had successfully addressed several challenging targets by the identification of drug-like small molecules using its Chemetics platform that enables DNA-encoded synthesis of billions of chemically diverse drug-like small molecules and can rapidly and efficiently screen and optimize those compounds.

Raymond Deshaies, senior vice president of global research at Amgen said in a statement that buying Nuevolution will enhance the acquirer's drug discovery capabilities.

"To achieve our vision, we will need to embrace compelling opportunities, like this one, which will significantly expand Amgen's ability to discover novel small molecules against difficult-to-drug targets and with greater speed and efficiency."

He added, "We highly value our collaboration of the past three years with Nuevolution and are excited to incorporate their expertise and DNA-encoded library discovery platform technology more holistically into Amgen's research moving forward."

PIPELINE DREAMS

Before the takeover offer from Amgen, announced on 22 May, Nuevolution's expressed strategy had been to create a stable revenue stream through partnerships that can support the long-term development of Nuevolution's wholly owned assets.

In addition to out-licensing deals, Nuevolution has more than ten ongoing programs, developing a portfolio of preclinical drugs which it had intended to move some into the clinic itself or with a partner. Its most advanced internal candidate, NUE20798, has come from Nuevolution's BET-BD1 program where data in animal

cancer models highlight that it may have synergistic effects in combination with immunotherapies.

AND INFLECTION POINTS

Nuevolution's pipeline is set to deliver multiple inflection points over the coming 12–18 months. That fact might have played a role in Amgen's decision and timing to make a takeover offer for the biotech.

The Copenhagen-based biotech said its three largest shareholders, representing in aggregate 59% of the shares and votes in Nuevolution, have entered into undertakings to accept the Amgen offer, conditional only upon the offer being declared unconditional not later than 1 September 2019 and upon Amgen not committing any material breach of applicable laws or regulations.

Stig Løkke Pedersen, board chairman at Nuevolution, said: "We have conducted a comprehensive analysis to ensure that we are acting in the best interest of the company and the shareholders. Considering the significant premium and the undertakings from the three largest shareholders to accept the offer, our conclusion is that the offer is fair and we are unanimous in the decision to recommend the offer of SEK 32.50 per share." ▶

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Boehringer Doubles Down On Deafness With Rinri Backing

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The UK's Rinri Therapeutics, a spin-out of Sheffield University, has bagged two major pharma players in Boehringer Ingelheim GmbH and UCB Group, to help fund development of its cell-based therapy to restore hearing.

Rinri has secured £1.4m in seed funding from the venture capital arms of BI and UCB and the health-centered business incubator BioCity. Based on the pioneering work of Marcelo Rivolta, a world leader in the field of sensory stem cell biology, Rinri's underlying technology seeks to reverse neuropathic sensorineural hearing loss (SNHL) through the repair of the damaged cytoarchitecture in the inner ear.

Detlev Mennerich, investment director at Boehringer Ingelheim Venture Fund (BIVF), who has joined the Rinri board, told *Scip* that he became aware of Rivolta's work through a paper published in *Nature* in 2012 about the restoration of auditory evoked responses by human embryonic stem cell-derived otic progenitors. BIVF hired him as a consultant for one of its other hearing loss companies and "since then,

we had regular exchanges with him about the novel developments in the emerging field. Rivolta had very interesting data and while working together asked us how we could translate the data and what the next steps would be to industrialize the data."

Over 90% of disabling hearing loss cases are sensorineural in origin, involving the degeneration of the specialized nerve or hair cells of the inner ear. Once these cells become damaged, they will remain that way, so SNHL is incurable.

Damage to these cells occurs naturally as part of aging, but other factors such as exposure to loud noise, illness, medication, genetics or trauma can also cause this type of hearing loss, Rinri noted. The World Health Organization estimates that over 5% of the world's population have disabling hearing loss; SNHL affects 64 million patients in the US and 34 million in Europe.

Data generated so far have shown that repairing the auditory nerve by using human embryonic stem cells helped restore hearing in gerbils. Mennerich

said that "if the impressive preclinical *in vivo* regeneration data translate into human, the technology has the potential to be a game-changer in the way SNHL is being treated."

Mennerich noted that the £1.4m will help Rinri complete preclinical protocols and sort out the transfer to a contract research organization which will prepare the product for trials. In a year or so, he expects the company to go to the markets for a Series A financing. "We should close that by the end of next year," he said, adding that Rinri would be in a position to cover the costs of a Phase I/IIa trial in about two dozen patients.

He believes that Rinri will be an attractive investment option. Referring to the gerbil data, Mennerich said the founders had seen impressive results for hearing improvements in less than two months, "so we expect to see a clinical result in a short time, these are not atherosclerosis or multiple sclerosis trials where you have to wait quarters or years to get your clinical signal."

BIVF, which has €250m under management, has a three-pronged focus for its investments – immuno-oncology, infectious diseases and regenerative medicine – hence the backing for Rinri. Mennerich told *Scrip* there was a different risk profile with each prong, “because with I-O, if it works in one indication, you can imagine it may work in a couple. With the regenerative medicine approach, you do not have a platform potential, most of these companies are *bona fide* single trick companies, there’s no portfolio behind. It’s one target, one disease and if it works, it’s super.” (Also see “Boehringer Ingelheim Is Getting Bets In Early In IO Space” - *Scrip*, 18 Sep, 2018.)

In parallel with the financing, Rinri has appointed as CEO Simon Chandler, who joins from IP Group, where he was re-



Detlev Mennerich

sponsible for early stage investments and company-building for UK university life science spin-outs. On the board, Menner-

ich will be joined by Erica Whittaker, head of UCB Ventures, and Claire Brown, investment director at BioCity.

The Rinri investment is the second foray by BIVF into hearing loss as it also participated in the €10m Series B financing of Germany’s Acousia Therapeutics in May 2018, having originally invested back in 2012. The company has identified an undisclosed target for drugs that could protect existing sensory hair cells in the inner ear from the anticancer drug cisplatin, which has been associated with hearing loss. The lead candidate, ACOU085, is in preclinical studies and could enter the clinic in 2020. (Also see “Protecting Against Hearing Loss: Acousia Pursues A New Approach” - *Scrip*, 14 May, 2018.) ▶

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Santhera Shores Up Finances With Chiesi Deal For Raxone

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Santhera Pharmaceuticals AG is making the bold move of outlicensing to Chiesi Farmaceutici SPA its only revenue generator – Raxone for Leber’s hereditary optic neuropathy (LHON) – to raise funds for the Swiss company’s pipeline.

The privately owned Italian group is paying CHF50m (\$50m) upfront and near- to mid-term sales milestone payments of up to CHF55m for the rights to Raxone (idebenone) in LHON and all other ophthalmological indications worldwide except the US and Canada. The deal also gives Chiesi an option to fully acquire Santhera’s

Raxone business as the latter puts its focus firmly advancing its pipeline, notably the Duchenne muscular dystrophy (DMD) candidates Puldysa (idebenone) and vamorolone, acquired from Actelion Pharmaceuticals Ltd. spin-off Idorsia Pharmaceuticals Ltd. last year. (Also see “Santhera To Snap Up Second DMD Drug As Idorsia Climbs Aboard” - *Scrip*, 21 Nov, 2018.)

Santhera chief executive Thomas Meier told *Scrip*, “People were a bit concerned that the value of the pipeline may not be really transparent, because we have limited funding and obviously

we are short of cash. What we have done is bring forward future profits that allow us to invest in a pipeline that people attach a lot of value to.”

He added that rather than seek out an ophthalmology-focused partner, the company wanted to link up with a rare disease specialist. In that space, “you need to talk with key opinion leaders and have a good relationship with patient organizations,” Meier said, and Chiesi fits the bill. “It is a very highly reputable company that has a reach into territories where we have no presence,” he noted and the firm is well-equipped to take Raxone forward.

Raxone has been a decent earner for Santhera, with 2018 sales of CHF31.7m, a 38% increase year-on-year, and Meier noted that guidance for this year was CHF35-37m. Given the product’s growth prospects, it begs the question as to why the deal is being done now with Chiesi.

He told *Scrip* that there were still six years left in terms of patent protection as Raxone was approved in 2015 and benefits from orphan drug designation in Europe which guarantees ten years’ exclusivity. “The longer we wait, the shorter the

Switzerland’s Santhera joins forces with Italy’s Chiesi for Raxone



TURN TO PAGE 14

Artificial Intelligence DEALS IN PHARMA

Over the past two years, pharmaceutical companies have signed an increasing number of alliance deals with specialists in artificial intelligence and machine learning. This is a snapshot of key deals and their focus.

▽ 2019

▽ KEY

AI-ML Scope

Artificial Intelligence/Machine Learning (AI-ML) Inputs Into The Traditional R&D Process

1 Target Identification



HOW AI-ML IS USED: Using systems biology to understand disease etiology

BENEFITS: Associating existing targets with new diseases

2 Lead Optimization



HOW AI-ML IS USED: High-volume *in silico* classification of drugs via computational chemistry

BENEFITS: Better drugs progressing faster to clinical stage

3 Clinical Trial Design



HOW AI-ML IS USED: Understanding patients and prognostic biomarkers

BENEFITS: Prospective trial stratification and enrichment to increase trial success rates

4 Patient Engagement



HOW AI-ML IS USED: Personalizing the patient experience using data and technology

BENEFITS: Improved adherence and outcomes



ALLIANCE DEALS

Upfront Value
(Maximum Deal Value)

APRIL



AstraZeneca/
BenevolentAI

Long-term collaboration to understand mechanisms of chronic kidney disease and idiopathic pulmonary fibrosis and identify new targets.

AI-ML
Scope:
1

Not disclosed

APRIL



Gilead/insitro

Using ML, human genetics and functional genomics to generate and optimize *in vitro* disease models for non-alcoholic steatohepatitis (NASH) and drive drug discovery.

AI-ML
Scope:
1

\$15m
(\$1,050m)

JANUARY



Pfizer/
CytoReason

Using data and ML to reconstruct cellular information from bulk tissue, train an immune-specific NLP engine, and integrate multi-omics data.

AI-ML
Scope:
1

\$29m

JANUARY



Otsuka/Click
Therapeutics

Licensing deal for the digital therapeutic CT152, which encompasses an AI-powered patient engagement platform to be regulated as an SaMD.

AI-ML
Scope:
4

\$20m
(\$302m)

JANUARY

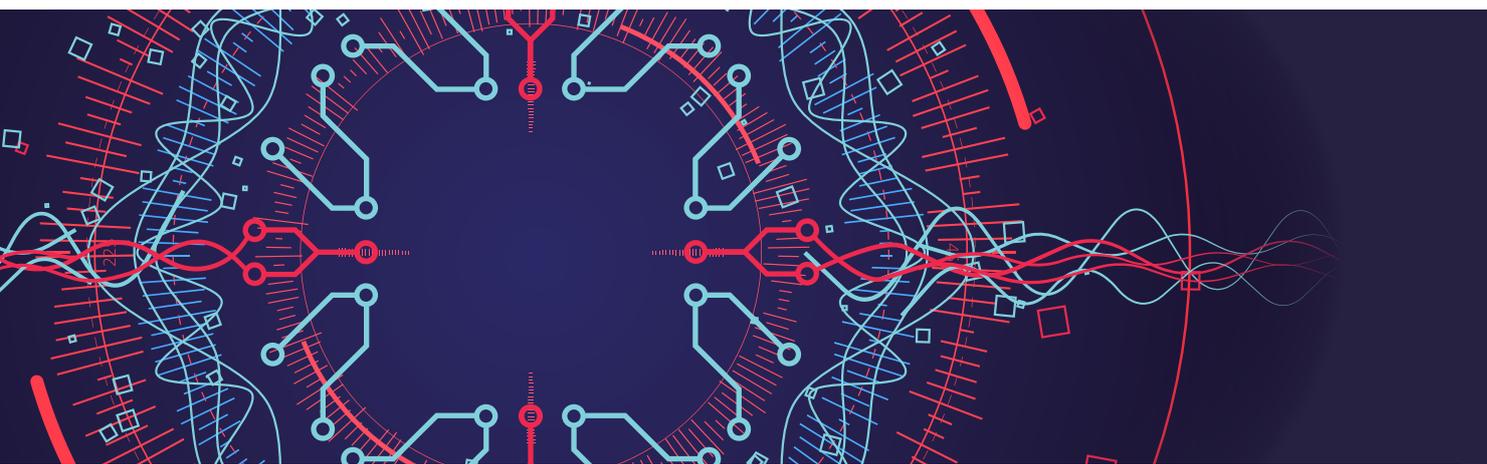


Roche/
Exscientia

Using AI capabilities to design preclinical drug candidates to meet prespecified potency, selectivity, and pharmacokinetic criteria.

AI-ML
Scope:
2

Not disclosed
(\$68m)



JANUARY

**Lundbeck/
Numerate**

Multi-target collaboration to identify small molecule candidates with ideal ADMET properties for psychiatric and neurological indications.

AI-ML
Scope:
2

Not disclosed

MAY

**Boehringer Ingelheim/
Bactevo**

Identifying small molecule therapies matched to human samples in neurodegenerative and mitochondrial disorders.

AI-ML
Scope:
2

Not disclosed

▽ 2018

AUGUST

**bluebird bio/
Gritstone**

Uses Gritstone's EDGE AI platform and biopsy sequencing data to identify mutations and tumor-specific antigens amenable to targeting via T-cell receptors.

AI-ML
Scope:
1, 2

\$20m
(\$1,220m)

FEBRUARY

**Bristol-Myers
Squibb/Sirenas**

Identifying drug candidates using an AI tool to mine large data sets to find small molecule metabolites derived from microbiome libraries.

AI-ML
Scope:
2

Not disclosed

▽ 2017

AUGUST

**Vertex/
Genomics plc**

Vertex gains access to ML platform to discover new targets; Genomics plc has developed an analysis engine linking genetic variation to disease outcomes.

AI-ML
Scope:
1

Not disclosed

JULY

**GlaxoSmithKline/
Exscientia**

Agreement spanning up to 10 targets across multiple therapy areas for the AI-guided discovery of novel selective small molecules.

AI-ML
Scope:
2

Not disclosed
(\$42.6m)

JUNE

**Genentech/
Microbiotica**

Using AI, Microbiotica's microbiome platform can identify gut bacteria tied to disease phenotypes. Genentech has various licensing options in IBD.

AI-ML
Scope:
1, 2, 3

Not disclosed
(\$534m)

MAY

**Sanofi/
Exscientia**

AI approach to analyze synergies of target combinations and design small molecules that can be used as bi-specific agents for metabolic diseases.

AI-ML
Scope:
2

Not disclosed
(\$274m)

Sources: Scrip, Strategic Transactions

Design: Jean Marie Smith / Informa Pharma Intelligence Design Team

CONTINUED FROM PAGE 11

time and the less attractive for a buyer," he said. Santhera has made no secret that it has been hamstrung by its financial limitations and Meier noted that "everybody was saying how do you fund it and here we have a solution," that avoids having to tap the markets for more cash. The money raised will last for at least 12 months, "until we reach our important inflection points."

Chief among those will be an application for marketing authorization in Europe for Puldysa. The path to possible approval has been a tortuous as the European Medicines Agency's Committee for Medicinal Products for Human Use initially rejected Santhera's request for the DMD indication for idebenone in September 2017, followed by a second thumbs-down in January 2018. (Also see "Santhera Confident Of

Raxone DMD Success Despite Setbacks" - Scrip, 4 Sep, 2018.)

Despite those knockbacks, the company has continued to be upbeat about the prospects for Puldysa and in March presented an update from the SYROS study which showed that long-term treatment with idebenone consistently reduced the rate of respiratory function loss in patients with DMD for up to six years in a real-world setting. Meier confirmed that the filing would be before the end of the second quarter this year. [UPDATE: Santhera filed Puldysa with the EMA on 27 May]

Further back, pivotal study data for vamorolone as treatment of younger, still ambulatory DMD patients is expected in 2020, while Santhera is looking to advance the promising clinical-

stage asset POL6014, acquired last year from Polyphor, which has the potential to treat cystic fibrosis and other pulmonary diseases.

Meier said that the Chiesi deal, which is currently expected to close in the third quarter, "gives clarity to all stakeholders, particular our shareholders, that the company now has the financial means to execute on our plans." He added that the summer months would involve working with Chiesi to ensure a smooth handover of Raxone (Santhera will continue to commercialize Raxone for LHON in France until ongoing pricing and reimbursement negotiations have been finalized) and "from the back end of this year onwards, our entire team will be able to focus on the launch preparations for Puldysa." ▶

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ElevateBio Announces AlloVir As First Spoke In Its Cell And Gene Therapy Hub

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ElevateBio LLC Chairman and CEO David Hallal said when the company unveiled its hub-and-spoke model for cell and gene therapy development, manufacturing and commercialization that it would reveal the first spokes in its hub in the coming weeks and months. Nine days later, on 22 May, ElevateBio announced its affiliation with AlloVir, as well as a \$120m series B venture capital round for the virus-specific T-cell therapy developer formerly known as ViraCyte LLC.

Linking up with AlloVir, founded in 2013 by researchers at Baylor College of Medicine's Center for Cell and Gene Therapy in Texas, aligns with what Hallal previously described as a benefit for small companies that are spun out of academia. By becoming ElevateBio subsidiaries, he said, the companies' scientific founders can focus on their research programs while relying on ElevateBio's centralized facilities and experts – including former executives from Alexion Pharmaceuticals Inc., like Hallal, and bluebird bio Inc. – to advance their cell and gene therapy candidates.

AlloVir co-founder and chief scientific officer Ann Leen, a professor of pediatrics at Baylor, told *Scrip* that was part of the appeal of engaging in a partnership with ElevateBio. Now, with \$120m in venture capital and a partner to focus on late-stage clinical development of lead product candidate Viralym-M, Leen and her colleagues at Baylor and AlloVir will be able to focus on developing additional T-cell therapies.

"What we really wanted to do was partner now with an entity that has the wherewithal to be able to develop this product and move it through Phase III and subsequently, hopefully, to commercialization," she said.

AlloVir considered partnering with a large pharmaceutical company or another biotechnology firm, but its co-founders were familiar with some of ElevateBio's employees based on their prior work in the cell therapy field. In addition to the collective expertise ElevateBio has and the development, manufacturing and commercialization infrastructure that it is building, Leen said she appreciated the venture's entrepreneurial spirit and flexible mindset that isn't so apparent at a big pharma company.

"In general, with large pharma there's a little bit more bureaucracy involved – they're not as nimble, they're not as quick," she said. "With AlloVir being a small group and with Elevate growing, but very nimble, I think we can get a lot of work done in a short period of time."

VIRALYM-M MOVING INTO MULTIPLE PHASE III STUDIES

Hallal, who is serving as AlloVir's CEO, told *Scrip* that "the clinical development, quality manufacturing and eventually commercialization expertise really complement quite nicely what the team at Baylor has done to bring this super innovation platform through a positive proof-of-concept Phase II study and really on the doorstep for multiple registration trials."

Viralym-M is an off-the-shelf T-cell therapy manufactured using donor T-cells to restore natural immunity to up to six viruses that commonly develop in immune-compromised patients, particularly people who have undergone an allogeneic stem cell transplant or solid organ transplant.

In a Phase II proof-of-concept study, 93% of ASCT patients, who previously failed treatment with conventional antiviral therapies,

“With AlloVir being a small group and with Elevate growing, but very nimble, I think we can get a lot of work done in a short period of time.”

– Ann Lean

responded to Viralym-M. The responses included complete responses and partial clinical responses, but most of the responders had complete elimination of detectable virus in their blood and resolution of major clinical symptoms.

ElevateBio, based on these data published in the *Journal of Clinical Oncology* in 2017, will move Viralym-M into multiple Phase III pivotal trials and additional proof-of-concept studies for various virus-associated diseases.

“We’re anticipating that hemorrhagic cystitis – often associated with BK virus, but also can be associated with [cytomegalovirus (CMV)] or adenovirus – is likely to be our first pivotal study,” Hallal said. “It’s a high percentage of patients that receive an allogeneic stem cell transplant that suffer from hemorrhagic cystitis. And what we’ve learned from the transplant community is that, given the fact that all conventional therapies are highly ineffective and patients are really devastated by the condition, we’re going to move forward with that as our initial pivotal study.”

Three additional pivotal studies may test Viralym-M in adenovirus, antiviral-resistant CMV and Epstein-Barr virus (EBV)-associated malignancies or lymphoproliferative diseases. Proof-of-concept (POC) studies in the solid organ transplant setting also are anticipated. Those studies, as well as the first clinical trials for AlloVir’s preclinical product candidate ALVR106, a T-cell therapy targeting four community-acquired respiratory diseases (respiratory syncytial virus, influenza, parainfluenza virus and human metapneumovirus), are expected to begin within the next 12 months.

FUNDING, PARTNERING OPPORTUNITIES AS PROGRAMS ADVANCE

Hallal said AlloVir’s \$120m series B financing should fund its clinical development programs for the next few years. Beyond that, he said, “we’ll evaluate our capital needs and be thoughtful about using the [series B] proceeds and raising additional capital, up to and including an IPO, given the late-stage nature of the platform, in a very opportunistic way.”

The recent financing was led by Fidelity Management and Research Co. with participation from Gilead Sciences Inc., F2 Ventures, Redmile Group, Invus, EcoR1 Capital, Samsara BioCapital and Leerink Partners Co-Investment Fund LLC.

In terms of seeking partners going forward for AlloVir’s T-cell therapies, Hallal said ElevateBio feels confident it has the expertise to take Viralym-M – as well as additional assets from AlloVir and other ElevateBio subsidiaries – all the way from development through commercialization on its own.

“We see allogeneic stem cell transplants growing on an annual basis and being a sizeable patient population, and then when you add on to this solid organ transplants, namely renal transplants,

we see this as an extremely large, underserved opportunity for us to serve patients,” he said. “In aggregate, across a 50-country platform [in which] we have a lot of experience commercializing therapies worldwide, we see it as a very significant opportunity.”

DIFFERENTIATED PRODUCT IN A GROWING CELL THERAPY FIELD

Lean noted that AlloVir is addressing that opportunity with a product that is differentiated from other T-cell therapies, including chimeric antigen receptor T-cell (CAR-T) therapies.

For instance, it’s an allogeneic product manufactured from donor cells, which means that Viralym-M is an off-the-shelf therapy available for use when needed as opposed to autologous CAR-T therapies made from a patient’s own cells and administered back to the patient weeks after the decision to treat. It also means that cells from a single person can be used to treat thousands of patients.

In addition, Viralym-M is not a genetically-modified product, Lean explained. AlloVir uses natural immune stimulant proteins (cytokines) combined with non-harmful fragments of viruses to activate and expand T-cells that work against the targeted viruses.

“We’re growing these cells *ex vivo*; we add all of the ingredients together to our culture on day zero and then the device that we grow ourselves is left untouched for approximately two weeks while the T-cells specific to the viruses that we’re targeting expand appropriately through the culture process,” she said. “And then after two weeks we just harvest the product and then cryopreserve, or freeze, the cells down in multiple aliquots that are essentially then ready for administration to patients off the shelf.”

“To me, it looks more like a conventional drug than any other cell therapy,” Lean said. ▶

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Cipla Claims Pricing Advantage For Albuterol In US

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After a strong fourth quarter, Cipla Ltd. has entered fiscal 2020 on an “optimistic note”, gearing for a ramp-up in markets like the US, where it hopes to introduce its first respiratory inhalation generic, albuterol, later this year.

The Indian firm has been expanding its respiratory franchise globally, and management commentary was upbeat on the prospects for its generic albuterol in the US, despite the competitive landscape and arrival of authorized generics.

Cipla’s managing director and global CEO, Umang Vohra, said that the market for the product had just formed recently with three authorized generics, but suggested that there still exists significant opportunity for Cipla to price right and make a significant impact.

“We think that as long as you’re albuterol you can take share from any of the other three brands that are available. The launch of these three authorized generics has actually helped doing that, somewhat,” Vohra said on the Q4 earnings call on 22 May.

Albuterol sulfate authorized generic versions of GlaxoSmithKline PLC’s *Ventolin HFA* inhalation aerosol and Teva Pharmaceutical Industries Ltd.’s *ProAir HFA* became available in January this year, while in April Par Pharmaceutical said that it had begun shipping an authorized generic of Merck & Co. Inc.’s *Proventil HFA* inhalation aerosol.

COST COMPETITIVENESS

Cipla indicated that the current market for albuterol is estimated at around 55 million units, with the unit price of the generics significantly higher than \$20.

“Right now the three authorized generics are by themselves and they are priced higher than the \$20 mark, and our math says that we have cost competitiveness to price this significantly lower than that and possibly take a fair share of the market,” Vohra said in response to an analyst’s query on the potential for worsening pricing dynamics.

At the time of announcing the availability of the authorized generic of *Ventolin HFA*, GSK said that the products will have a wholesale acquisition cost (WAC) of less

“We expect biosimilars to become an important growth driver for the business in the near to medium term.”
– Umang Vohra

than \$36. “This represents at least a 35% reduction to the current WAC price of branded *Ventolin* and potentially a lower cost alternative to the patient, depending on a patient’s insurance coverage,” GSK said.

GENERIC SENSIPAR DRIVES US GROWTH

Meanwhile, Cipla indicated that it expects to file two respiratory products in FY2020 – trials for its generic *Advair* (fluticasone/salmeterol) are underway. Cipla had earlier maintained that it was targeting one “sizeable” respiratory inhalation launch in the US every year, starting with albuterol.

For the fourth quarter ended March 2019, Cipla’s North America business grew 41% year-on-year and 38% on a sequential basis to \$163m, driven by a ramp-up of existing products and the launch of generic *Sensipar* (cinacalcet). Overall revenues for the quarter stood at INR44.04bn (+19%; \$632m), with net profits at INR3.67bn.

Jefferies said that Cipla’s results were “far ahead” of expectations. “Revenue +6% and margins +670bps versus estimates. The beat though was largely driven by high sales of at-risk generic *Sensipar* launch. Ex of this, revenues were in line with expectation and margins c100bps ahead,” Jefferies equity analyst Piyush Nahar said in a note dated 22 May.

A US federal judge recently denied Amgen Inc.’s request to block Cipla’s sales of a generic version of *Sensipar*, ruling that Amgen is not likely to succeed on the merits of its breach of contract claim against the Indian firm.

BIOSIMILARS OPPORTUNITY

Cipla also expects to continue to invest in expanding its biosimilars franchise. During the quarter, the company added pegfilgrastim into its portfolio for the markets of Australia, New Zealand, Colombia, and Malaysia. “We expect biosimilars to become an important growth driver for the business in the near to medium term,” Vohra said.

Cipla, which in 2017 recalibrated investments in the “resource-intensive” biosimilars segment, shifting more towards an in-licensed approach, believes it is competitive in the sector in rest of world markets because “it’s not solely about price it’s also about your reach in the market and what you can do with the product.” (Also see “*Cipla Cuts Down In-House Biosimilars Plans*” - *Scrip*, 26 May, 2017.)

“We’ve seen that in India. We’re likely to see that in several of the other markets where we made these filings. So, I think that we stand competitive,” CEO Vohra said, adding that the company was currently focusing on completing its portfolio offering for emerging markets.

In January, Cipla struck an in-licensing deal with China’s Bio-Thera Solutions Ltd. for its late-stage bevacizumab biosimilar (BAT1706).

The Indian firm also has a similar deal with Singapore-based Prestige BioPharma for its biosimilar version of Roche’s *Herceptin* (trastuzumab). In India, Cipla has a partnership with Roche for a second brand of *Avastin* (bevacizumab) and the IL-6 inhibitor tocilizumab (*Actemra*).

Separately, Cipla also said that it had recently entered into a partnership with Korean group LG Life Sciences Ltd. and in-licensed its portfolio in India. The partnership marks Cipla’s foray in the high growth and specialty segments of infertility and the human growth hormone business, it said on the Q4 earnings call. ▶

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Syncona CEO On Why Its 10th Start-Up Focuses On T-Regulatory Cell Therapies

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With the founding of Quell Therapeutics via a £35m series A financing, **Syncona Ltd** has created its tenth biotech start-up since its own foundation in 2012 and the investment group says other novel corporate launches can still be expected.

Quell Therapeutics, a new cell therapy company, was founded on 20 May with £34m provided by Syncona and a further £1m contributed by UCL Technology Fund.

Quell's aim is to develop engineered T regulatory (Treg) cell therapies for a range of conditions such as solid organ transplant rejection, and autoimmune and inflammatory diseases.

Tregs are a subset of T-cells with the potential to downregulate the immune system.

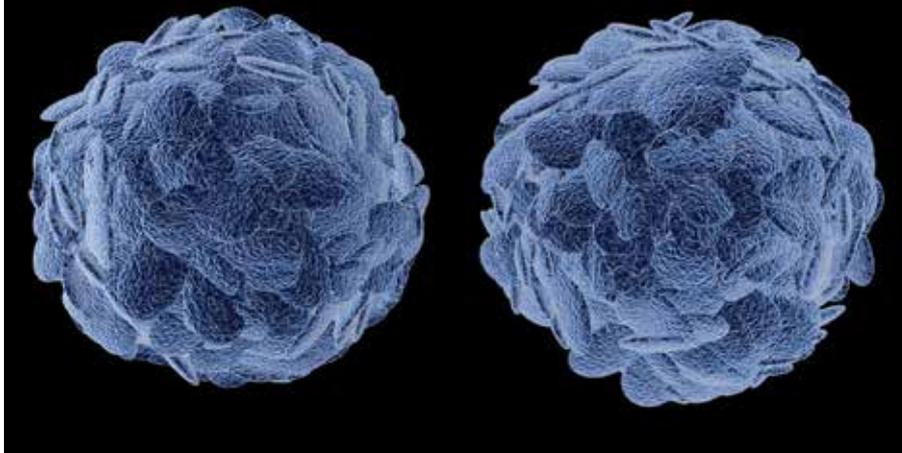
"There has been exceptional progress commercially in the T-cell space over the past five years. And much of those principles of cell engineering that have been applied, and are now being very deeply applied, to effector T-cells, which are the killing arm of the immune system, and could in principle also be applied to a different arm of the T-cell family called the T regulatory cell space," Martin Murphy, chief executive of Syncona Investment Management Limited told *Scrip*.

The series A capital injection is Syncona's latest investment in Quell after an initial tranche of the series A commitment of £8.3m was paid in March 2019 and brings its stake in the Treg start-up to just over 69%.

TREG PROMISE

"Quell is very much consistent with our strategy and our portfolio of companies in that we identified an area that we

Syncona founded Quell Therapeutics with £35m Series A Financing



thought was going to be important. We identified world-class academics to act as founders of that business and we are then working in partnership with them," Murphy said.

Quell was founded in partnership with six leading experts in the Treg field, cell engineering, solid organ transplantation and autoimmune diseases from King's College London, UCL, and Hannover Medical School.

"We're now in active build-out mode for Quell and have a CEO lined up; we haven't yet announced who that individual is but we will in the near future," he said.

Syncona typically launch two or three innovative start-ups per year.

"We now have around £1.4bn of capital and use that to found businesses alongside exceptional founders, and then we write the plan for those businesses, provide operational resources and capital. That's our model and we'll be using that for Quell as well," Murphy said. He said the manufacture of Tregs

would be done in the UK for use in coming clinical studies.

Quell and Syncona would be engaging with the MHRA early on for regulatory guidance. "Early regulatory interaction is extremely worthwhile in these spaces. These are very innovative products with complex manufacturing and you do well to get very early regulatory input," he said.

Quell will probably add a US element in its operations and business plan fairly soon, Murphy added.

"We build our businesses with a global perspective and all of our businesses, if they're not based in the US then they look to the US very early in their development and our products have been developed for the global pharmaceutical market.

"We're currently in build out mode and it makes sense to build locally but there will be a US strategy for this company and it will be relatively early in the life of the company." ▶

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Penalty For Daiichi As It Falls Short In Japan Flu Vaccine Project

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Daiichi Sankyo Co. Ltd. will have to pay what it terms a “delinquency charge” after failing to meet its obligations under a national H5N1 flu vaccine supply project in Japan, although the broader financial impact this fiscal year is expected to be limited.

In a project overseen and financially supported by the country’s Ministry of Health, Labour and Welfare as part of a second phase scheme to build national production capacity for cell cultured flu vaccines, the company was selected as the major contractor in August 2011.

Its now dissolved Kitasato Daiichi Sankyo Vaccine subsidiary was then awarded around JPY30bn (\$272m) in grants to support the construction of new production facilities, with the aim of building capacity to supply doses sufficient for 40 million people within six months of any major outbreak.

The cell culturing method has the advantage of a much shorter lead time than the one to two years required for embryonated egg cultured vaccines, enabling a faster response and rapid production of vaccines targeting any precise strain of H5N1. However, Kitasato Daiichi Sankyo Vaccine first warned in April 2014 that it would miss the 40 million target, pointing to findings that higher than expected doses of the vaccine would be required, effectively upping the

required production output and prompting steps to improve yield.

Despite an extension of the deadline to this March, Daiichi said it “has been unable to fulfill its obligation to build a scheme to vaccines for 40 million people” on time. The program has so far only been able to build capacity sufficient for 23 million people, but the company and its Daiichi Sankyo Biotech operation will continue work toward meeting the capacity goal, although no new timing was given.

The Kitasato operation was dissolved from this April and its activities transferred to Daiichi Sankyo and the Biotech arm. The company has taken a number of steps over the past few years that signal a strategic shift away from vaccines, as it looks to focus effort and resources on building up its oncology R&D and portfolio.

In addition to the undisclosed penalty, Daiichi will return an unspecified amount of the original government grant, although the company said it expects only a minor financial impact in the current fiscal year, given that it “believes that assumed delinquency charges have been recorded in previous fiscal years.”

OLMESARTAN CLIFF HITS GROWTH

Daiichi Sankyo reported a 3% fall in group revenues to JPY929.7bn (\$8.44bn)

for the fiscal year ended 31 March, hit mainly by the genericization of its olmesartan antihypertensive products. North American sales of these plunged by half in the period to \$97m, and also fell in Europe, while the regular price in Japan in April 2018 also hit sales of some products at home.

The novel oral Factor Xa inhibitor anti-coagulant *Lixiana* (edoxaban) continued to grow strongly in Japan, however.

Operating profit was 10% higher at JPY83.7bn, helped by lower R&D and general expenses, while profit attributable to owners surged 55% to JPY33.1bn following an upfront component of the huge deal signed before year-end in March with AstraZeneca PLC, for Daiichi’s lead oncology antibody-drug conjugate trastuzumab deruxtecan. (Also see “Boost For Daiichi’s Oncology Ambitions As AZ Agrees Huge \$6.9bn Deal For Lead ADC Asset” - *Scrip*, 28 Mar, 2019.)

The Japanese firm expects total revenues to rise by only around 1% this fiscal year, to JPY940bn, although operating profit should rise by 20% to JPY100bn on property divestments and cost savings, while profit attributable to owners should slide by 23% to JPY72bn on the unfavorable comparison with last year.

The company late last October made major cuts to its mid-term business targets as it invests more in oncology R&D as part of the strategic pivot to this sector. (Also see “Daiichi Sankyo Hauls Back Mid-Term Profit Outlook As It Builds Oncology” - *Scrip*, 2 Nov, 2018.) ▶

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Reneo Reveals \$50m Series A, Mitochondrial Disease Development Plans

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Reneo Pharmaceuticals Inc. has been developing REN001 for rare genetic mitochondrial diseases for more than a year. But now that it has two clinical trials under way and a third planned to start later this year, the firm came out of stealth mode on 20 May to announce its \$50m series A venture capital financing.

San Diego-based Reneo is run by former Lumena Pharmaceuticals Inc. executives, including president and CEO Niall O’Donnell, who was Lumena’s interim chief medical officer when it was sold

to Shire PLC for \$260m in 2014. (Also see “Shire buys repurposed Pfizer/Sanofi drugs through \$260m Lumena acquisition” - *Scrip*, 12 May, 2014.) O’Donnell – now also a managing partner at the VC firm RiverVest Venture Partners, a Reneo investor – told *Scrip* that the start-up ticked all of RiverVest’s boxes: a good team, a good drug and good investors.

Ex-Lumena executives and board members also involved in Reneo include chief medical officer Alejandro Dorenbaum (a for-

mer Lumena CMO); board member Ed Mathers, a partner at the VC firm New Enterprise Associates (NEA), which also invested in Lumena; and executive chairman Mike Grey, who was Lumena's president and CEO and now serves as chairman and CEO of Mirum Pharmaceuticals. Mirum reacquired Lumena's drugs from Shire and launched last year with \$120m in Series A financing. (Also see "Newly Hatched Mirum To Focus On Rare Liver Disease Candidates Shelved By Shire" - *Scrip*, 7 Nov, 2018.)

Reneo licensed its sole drug candidate from vTv Therapeutics Inc., which acquired rights to the PPAR delta agonist from Novo Nordisk AS. O'Donnell explained that Reneo was looking for a PPAR agonist to treat mitochondrial diseases and vTv was a small cap public company with several programs on its plate and limited capacity to pursue them all. The two firms came to terms that allowed Reneo to focus its resources exclusively on REN001, moving it past several already concluded Phase I toxicology studies.

"We have been working on this actively for 15 to 20 months," he said. Reneo funded the work with its series A round, with the first tranche of financing that closed about 18 months ago. NEA led the series A, which also was backed by RiverVest, Lundbeckfonden Ventures and Pappas Capital.

Reneo might have stayed in stealth mode a while longer, but once the company initiated its first two Phase Ib trials for REN001 nearly two months ago – one in fatty acid oxidation disorders (FAOD) and another in primary mitochondrial myopathies (PMM) – its activities entered the public domain via clinicaltrials.gov.

"We've been getting incoming interest from patients and physicians around our approach to treat patients with myopathies," O'Donnell said.

The FAOD study conducted in the US is enrolling patients who have a genetic defect that means they cannot metabolize fat as an energy source, causing severe energy deficiencies, especially in their skeletal muscles.

"Using the mechanism of action of our drug, we think we can improve their day-to-day functioning, allow them to walk up the stairs and do things that you and I can do as a normal, functioning

human being," O'Donnell said.

PPAR delta antagonism increases fatty acid metabolism, which should increase the amount of adenosine triphosphate (ATP) within cells to improve symptoms associated with FAOD and PMM.

Reneo's PMM study is under way in the UK, enrolling patients with genetic defects in their mitochondria that causes them to have an energy deficiency in their skeletal muscles, which leads to severe activity and exercise intolerance.

"These are orphan indications, so one of the things you can do in the orphan space is do extended open-label studies, 1) to really understand the disease, 2) to test the safety of the drug in a very rigorous fashion, and 3) start to look at clinically relevant endpoints for these patients," O'Donnell said. "And so, by Q1 2020, with both studies we should have clear go/no-go decisions based on both the safety and efficacy of the drug in both patient populations. We've also got a third indication that we haven't disclosed yet and that will read out later in 2020."

He noted that Reneo is entirely focused on REN001 "for the moment and probably for the bulk of the Series A. The thing we like about it is this drug's mechanism of action aligns well with multiple genetic myopathies. ... There's the potential to treat numerous orphan diseases with one compound, which is intriguing and compelling, from an investment perspective".

The drug also has the advantage of being an oral pill, which is rare in the rare disease space, he added.

As for whether Reneo will take REN001 all the way through development and approval to commercialization on its own, O'Donnell said all options are on the table – staying private or going public to keep it entirely in-house or seeking a partner for later-stage development and beyond.

"The \$50m series A allows us to go, in a calendar timeframe, to the end of 2020, by which stage we would have finished [the Phase Ib studies in] the three indications – the fatty acid oxidation, the primary mitochondrial myopathy and the third yet unnamed indication," he said. ▶

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EXECUTIVE INTERVIEW

Sanofi Genzyme's Sibold On Investing In Blood Disorders And Fending Off Rivals

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Sanofi is in the midst of building out a new blood disorder franchise after completing its acquisition of Bioverativ Inc. in 2018 and launching the rare blood disease treatment Cablivi this year. The business area is expected to be a big growth driver for the company, but it's also a competitive field that Sanofi will have to navigate.

Sanofi Genzyme exec VP Bill Sibold talked to *Scrip* in an interview in New York

on 14 May about building a new franchise, the launch of Cablivi (caplacizumab-yhpd) for acquired thrombotic thrombocytopenic purpura (aTTP), and defending its hemophilia franchise against new competition from Roche.

Sibold took over as the head of Sanofi's Genzyme unit in 2017, well prepared to oversee the company's expanding specialty medicines business after having previously overseen Genzyme's global multiple scler-

osis, oncology and immunology organizations. One year later, Sanofi added a new blood disorder business to the portfolio.

The business, based in Cambridge, Mass., is growing, generating €7.22bn (\$8.07bn) in 2018, growth of 31%, driven by the launch of Dupixent (dupilumab) for atopic dermatitis and severe asthma and the addition of the two Bioverativ brands. Sanofi's hallmark diabetes and cardiovascular business, meanwhile, is slowing, de-

clining 14% to €4.51bn (\$5.04bn) in 2018.

With its \$11.6bn purchase of Bioverativ, Sanofi gained two marketed drugs, Elocate (recombinant Factor VIII) for hemophilia A and Alprolix (recombinant Factor IX) for hemophilia B. Together, the two drugs generated €893m (\$999m) in 2018. Sanofi also gained pipeline drugs: sutimlimab (formerly BIVV009) in Phase III for the rare blood disease cold agglutinin disease (CAD); BIVV001 in Phase I in hemophilia A; ST-400, a gene-edited cell therapy for beta-thalassemia in Phase I/II with Sangamo Therapeutics Inc.; and a preclinical gene therapy for hemophilia. (Also see *"Sanofi Builds Blood Disorder Specialty With Bioverativ Buy"* - Scrip, 22 Jan, 2018.)

Sanofi also has its own late-stage asset fitusiran, a Phase III RNAi compound in development for hemophilia A and B that was discovered by partner Alnylam Pharmaceuticals Inc.

Sibold noted that BIVV001 is extending the half-life of Factor VIII, which he said would allow once a week dosing and allow for regular clotting to improve efficacy.

"We've got what we think are the best in class factors of the day, the next generation of factors, the next mechanism of action with fitusiran, and then gene therapy in the future," Sibold said.

HEMLIBRA: A TOUGH RIVAL

In the near term, however, Sanofi is facing fierce competition from Roche's Hemlibra (emicizumab-kxwh), which is currently the only prophylactic treatment for all people with hemophilia, with and without Factor VIII inhibitors. FDA approved Hemlibra for use in patients with Factor VIII inhibitors, a small subset of the market, in November 2017, and expanded the indication in October 2018. (Also see *"Roche's Hemlibra Wins Expanded FDA Approval, Opening The Door To Broad Hemophilia A Opportunity"* - Scrip, 4 Oct, 2018.)

Sibold acknowledged that Elocate has felt the heat from Hemlibra. First quarter sales of Elocate declined 4.2% to €174m (\$195m). But he is optimistic about the future.

"With any product, one quarter or two quarters do not make the future," he said. "We'll see how things unfold in the real world. What we are comfortable with is that we've got an incredible safety record with Elocate." In addition, he pointed to a



Bill Sibold, Sanofi Genzyme Exec VP

unique benefit of Elocate as differentiating – the 100% resolution of joint issues in some people.

"We are committed to hemophilia with the franchise. We've got alternate mechanisms of action that we're looking for and ultimately gene therapy as well," he said.

But gene therapy rivals are expected to be a big threat to Sanofi's hemophilia business. That's because companies like BioMarin Pharmaceutical Inc. and Spark Therapeutics Inc. (soon to be acquired by Roche) are much further ahead in development. Both companies are studying gene therapies in Phase III trials, and given the potential of gene therapy to be a one-time cure, being first to market could be a critical advantage. (Also see *"Spark Plots Rebound For Hemophilia A Gene Therapy, As Rival BioMarin Surges"* - Scrip, 12 Dec, 2017.)

BUILDING A MARKET FROM SCRATCH

On another front, Sanofi Genzyme is building a new market for Cablivi for the treatment of the rare blood clotting disorder aTTP. Sanofi acquired the product with its acquisition of Belgium's Ablynx NV last year for €3.9bn (\$4.4bn). (Also see *"Ablynx, Bioverativ Buys Drive Sanofi's Hematology Reign"* - Scrip, 29 Jan, 2018.) FDA approved Cablivi in February and Sanofi launched it in the US on April 2 at a price of \$270,000 per typical aTTP episode, before any rebates and discounts.

There were previously no approved therapies for aTTP, and the typical standard of care is plasma exchange therapy. Patients experience sudden onset of symptoms, with fever and sometimes bleeding and end up in hospital intensive care units. Cablivi almost immediately stops the clotting in blood vessels in the

body, Sibold said. The exact epidemiology of the disorder is unknown. "Our fear is that sometimes people don't live long enough to even get into the system, or they are not diagnosed," he said.

Sanofi has a dedicated commercial team to support the product. Unlike hemophilia, which is treated through hemophilia treatment centers, Cablivi is first used in hospital intensive care units.

"We have to build a market essentially from scratch," mapping out the hospitals that treat patients in each country, Sibold said. There are approximately 200 hospitals in the US that primarily treat patients with aTTP.

DIFFERENTIATING DUPIXENT IN ASTHMA

Sanofi is also facing tough markets in its other specialty care franchises. In the immunology area, Dupixent (dupilumab), an interleukin-4 (IL-4)/IL-13 inhibitor that Sanofi sells with partner Regeneron Pharmaceuticals Inc., had total sales of €329m (\$368m) in the first quarter of 2019, and €266m (\$297m) in the US. The FDA approved the biologic for atopic dermatitis in March 2017 and for asthma in October 2018.

The drug joins a budding class of biologics for severe asthma, though three competitors are all IL-5 inhibitors approved for a narrower indication, severe eosinophilic asthma. Nonetheless, Sanofi/Regeneron are newcomers to the space going up against respiratory power players like GlaxoSmithKline PLC and AstraZeneca PLC.

Dupixent is not taking market share from competitors in the asthma space, Sibold said, but instead growing the market. He noted that there are 900,000 asthma patients in the US and only about 10% are treated with a biologic, and about 75% of patients starting Dupixent are biologic naïve.

Looking at new to brand prescriptions, "we've seen that we are performing better than other launches by biologics in asthma" despite being the fifth biologic to market, Sibold said. "I think that goes to the efficacy that we have with this product."

In addition, he said Dupixent works on other comorbidities that asthma patients have, including atopic dermatitis. "When

TURN TO PAGE 23

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



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PIPELINE WATCH, 17–23 MAY 2019

Event Type	Lead Company/Partner	Drug Name	Indication	Comments	Change To LOA (%)	LOA (%)
Phase III Updated Results	Array BioPharma, Inc.	Braftovi (encorafenib)/Mektovi (binimetinib), Erbitux (cetuximab)	Colorectal Cancer	BEACON CRC; Positive Results	4	43
Phase II/III Updated Results	Bellerophon Therapeutics	INOpulse	Pulmonary Hypertension	iNO-PF; Clinical Improvements	0	15
Phase III Top-Line Results	Ascendis Pharma A/S	TransCon growth hormone	Short Stature	fiGHt; Safe And Effective	0	68
Phase III Top-Line Results	Ocular Therapeutix, Inc.	OTX-TP	Glaucoma	Mixed Results	-2	50
Phase III Top-Line Results	Merck & Co., Inc.	Keytruda (pembrolizumab)	Breast Cancer, Triple-Negative	KEYNOTE-119; Missed OS Endpoint	-2	41
Phase III Top-Line Results	BioCryst Pharmaceuticals, Inc.	BCX7353	Hereditary Angioedema	APeX-2; Mixed Results	0	63
Phase III Trial Initiation	Arena Pharmaceuticals, Inc.	etrasimod	Ulcerative Colitis	ELEVATE UC; A S1P Receptor Modulator	39	65
Phase III Trial Initiation	Allergan Inc.	relamorelin	Diabetic Gastroparesis	RLM 3071-305-020 (OLE); A Ghrelin Agonist	0	63
Phase III Trial Initiation	SpringWorks Therapeutics, LLC	nirogacestat	Desmoid Tumors	In Adults	25	35
Phase III Trial Initiation	Novo Nordisk A/S	somapacitan	Short Stature	REAL 4 (Pediatric); Once Weekly	0	61
Phase III Trial Initiation	PCI Biotech AS	fimaCHEM	Biliary Tract Cancer	RELEASE; Inoperable Patients	25	35

Source: Biomedtracker | Informa, 2019

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CONTINUED FROM PAGE 21

you have a product that can help you not only with your primary [condition] but could help with some other issues, I think it becomes a differentiated product," Sibold said.

Sanofi is looking to expand Dupixent indications to nasal polyps and chronic rhinosinusitis. Sibold noted that many asthma patients have nasal polyps, and the most in need patients have the polyps return after surgery. About 50,000 patients are in this unmet need group.

NEXT ONCOLOGY PRODUCT

In the oncology space, Sanofi launched the PD-1/L1 inhibitor Libtayo (cemiplimab-rwlc) for cutaneous squamous cell carcinoma in collaboration with Regeneron last year. It is an initial indication that the companies plan to expand upon.

Next in line is the CD38-targeting antibody isatuximab for relapsed/refractory multiple myeloma (r/rMM). Sanofi plans to file applications with regulatory authorities in the US and Europe later this year.

The company is presenting the full re-

sults from its pivotal Phase III ICARIA-MM trial comparing isatuximab in combination with the current standard of care, Celgene Corp.'s Pomalyst (pomalidomide) and low-dose dexamethasone, to pomalidomide and dexamethasone alone at the American Society of Clinical Oncology annual meeting in June. Top line results reported earlier this year showed isatuximab extended progression-free survival.

The multiple myeloma market is among the most competitive in oncology and if approved, isatuximab will be competing with Johnson & Johnson/Genmab AS's Darzalex (daratumumab), which has a big jump start. Darzalex was approved in June 2016 as the first human anti-CD38 monoclonal antibody to treat r/rMM. Darzalex, which has been approved in combination with various regimens, generated \$2.03bn in 2018 sales.

Sibold said isatuximab targets a different epitope and Sanofi expects to differentiate it from Darzalex. One difference is isatuximab's shorter infusion time. Nonetheless, J&J has developed an updated subcutaneous formulation of Darzalex that it plans to file in the second half of

2019, which will reduce the administration time to five minutes.

"One of the advantages of not being first is you get a chance to look and see how the market unfolds and what are going to be the right combinations. We think we've done our next trials in combinations that are the most relevant combinations of today," Sibold said. He added that since not everyone responds to a drug the same way, having a second CD38 monoclonal antibody is going to be important.

Sanofi has had an oncology presence for years, largely in chemotherapy. It missed out with next-generation targeted therapies and the initial immuno-oncology wave. It is now looking to shift course under John Reed, who became head of R&D last year. Reed previously led early drug development at Roche. In February, the company gave an update on its R&D strategy, under which Sanofi is fast-tracking 17 programs, including eight in oncology. (Also see "Sanofi Prioritizes Cancer And Rare Diseases In Pipeline Shake-Up" - *Scrip*, 7 Feb, 2019.) ▶

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