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Novartis: Hunter Of Novel Medicines.

Novartis To Pay $9.7bn For The Medicines Company

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Rumours that Novartis AG was in talks to acquire The Medicines Company were confirmed on 24 November with the announcement of a $9.7bn agreed deal. The acquisition brings it a soon-to-be-filed novel PCSK9 inhibitor that is poised to take on the incumbent drugs on the market with claims of greater convenience, excellent safety and comparable efficacy.

The Swiss major will pay $85.00 per share in cash, representing a premium of about 41% over the 30-day average of the NASDAQ-listed firm's share price. It hopes to complete the transaction in the first quarter of 2020.

The deal gives Novartis inclisiran, a first-in-class small-interfering RNA (siRNA) drug that is in late-stage trials to reduce low-density lipoprotein C (LDL-C). Results from two Phase III trials of inclisiran in different patient populations impressed at the recent American Heart Association conference, and The Medicines Company expects to file for US approval before the end of the year, and for European approval in the first quarter of 2020.

BAD NEWS FOR AMGEN, SANOFI, REGENERON

Inclisiran is expected to offer an attractive treatment alternative to the underperforming PCSK9 inhibitors Praluent (alirocumab, Sanofi/Regeneron Pharmaceuticals Inc.) and Repatha (evolocumab, Amgen Inc.). Those drugs are monoclonal antibodies that must be administered every two or four weeks, whereas inclisiran is dosed twice a year. The former products have failed to live up to early expectations since their launch in 2015, and have had their prices slashed. The Medicines Company has previously indicated that it would price its product lower than Praluent and Repatha.

Inclisiran was licensed from RNA specialist Alnylam Pharmaceuticals Inc. (which will retain a right to royalties on sales of the product). It targets mRNA to silence genes that lead to the production of PCSK9 (proprotein convertase subtilisin-kexin type 9) in the liver.

The subcutaneous drug's efficacy looks to be on a par with Repatha and Praluent and it has a safety profile comparable to placebo. In one trial, ORION-9, it achieved 50% LDL-C lowering sustained over 18 months of treatments in patients with heterozygous familial hypercholesterolemia. In the other, ORION-10, it achieved 58% LDL-C lowering over 18 months in patients with atherosclerotic cardiovascular disease. According to Novartis there are more than 50 million patients "across key markets" with atherosclerotic cardiovascular disease or familial hypercholesterolemia on current standard of care who are not at goal.

With twice-yearly subcutaneous dosing, it is expected to be administered during patients' routine visits to their healthcare professionals, which Novartis says should help improve patient adherence. In the trials, it was given to patients at baseline, at three months and every six months thereafter for 18 months.

"We now have utter conviction inclisiran can disrupt cholesterol therapy," wrote Baird Equity Research analyst Madhu Ku-

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Novel Drug Approvals
Novartis's sickle cell crises treatment among raft of new products (p13-20)

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Sir Andrew on the US system after PBM move (p10)

RNAi Rainfall
Alnylam gets second approval and Novo Nordisk enters the fray (p4 & 13-14)

from the editor

eleanor.malone@informa.com

The approval of givosiran means there are now two small interfering RNA (siRNA) molecules available on the market, both for rare diseases and both from Alnylam (see p13).

RNA-targeting therapeutics are not new: the FDA has actually approved nine products in the class, the first in 1998. However, whereas the pioneers in the field used antisense oligonucleotide technology, the new wave of excitement centers on siRNA.

Alnylam is the biggest source of siRNA clinical candidates, including the one that Novartis has just agreed to buy, inclisiran (see cover story). It hasn't all been plain sailing for the company. Just three years ago, the termination of Phase III trials of revusiran following patient deaths cast a pall over Alnylam and the wider field. A few years before that, big pharma had largely reversed its prior enthusiasm for RNAi and its subsequent exodus from the space exacted a heavy toll. However, Alnylam has hung in there and others have entered the fray, and advances have been made. Now, pharma is flocking back.

The nearly $10bn that Novartis is prepared to lay out for a yet-to-be-approved product demonstrates the attractiveness of a long-lasting siRNA therapeutic with strong safety and efficacy data that targets a large patient population. And with Dicerna securing a broad deal with Novo Nordisk just days before (see p4), it looks like RNAi is not only back in favor, but also limbering up to go beyond rare disease indications into more common cardiometabolic disorders and other diseases. Watch this space as siRNAs spread their wings.

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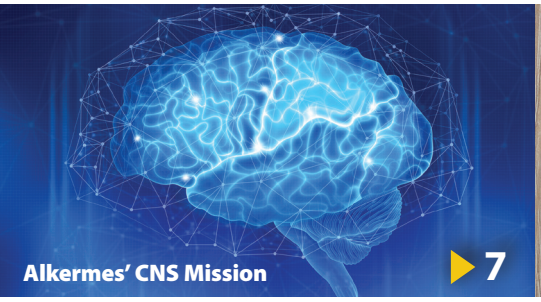

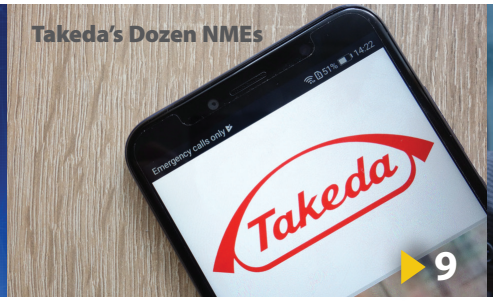

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Catch It While You Can: Smaller Firms Flock To China As Value Takes Center Stage

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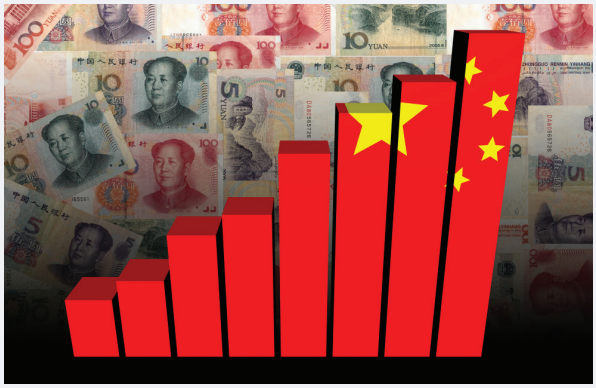

As China rolls out a massive centralized procurement program to slash prices for many widely-used off-patented drugs, some are seeing market opportunities.

Up to now, the generic drug sector in the country - which accounts for over 70% of the world's second-largest single pharma market - has been dominated by multinationals, which charge a premium for their branded generics, and domestic companies that mainly use lower prices to compete in lower-tier segments.

But since 2018, the sector has been transformed. The Chinese government issued a policy mandating bioequivalence testing for 75 generics, starting from widely prescribed oral tablets. Only manufacturers who cleared the requirement could enter bids for all levels of public procurement.

Another catalyst to the transformation has come from an unexpected quarter. In 2018, one of the blockbusters that caught nationwide attention was not a drug but a film. "Dying to Survive" ("I'm No Medicines God" in Chinese) quickly became a national sensation, depicting a group of cancer patients in Shanghai who formed a buyers club and risked being detained for illegally bringing in life-saving generic drugs from India. Many saw the film's success as a sign that the government is paying close attention to patient access and drug affordability issues.

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mar in an 18 November note following the ORION-9 and -10 data presentations at AHA, where he also highlighted previously presented data from the European ORION-11 trial also in atherosclerotic cardiovascular disease.

"Unlike PCSK9 mAbs […] we believe inclisiran could potentially see widespread uptake for the treatment and prevention of hypercholesteremia much like a yearly flu vaccine," wrote SVB Leerink analysts, also on 18 November.

Not everyone was so enthusiastic. Wolfe Research's Tim Anderson, Richard Law and Wai-Tsing Chan listed three reasons for caution over inclisiran."First, as is well known, there is no data yet from clinical trials "proving" definitively that inclisiran improves clinical outcomes," they said in a 24 November note. Results of the 15,000-patient ORION-4 cardiovascular outcomes trial are not expected until 2024. (Both Praluent and Repatha had their labels updated with cardiovascular risk reduction claims following post-approval CVOT data.) Jefferies analysts also underlined this point, warning in a 25 November that its survey of doctors indicated most would want to see cardiovascular outcomes data and longer term safety before prescribing inclisiran.

Second on the Wolfe Research list of warnings, the acquisition "only brings to Novartis a single product and not a broader R&D platform or other meaningful assets – for an outlay of $9B, it would be nice to have the latter."

Third, they noted that "Novartis may not have an extended monopoly with inclisiran": CiVi Biopharma in taking a similarly acting product, CiVi007, into Phase II development.

COMPLEX THERAPIES

Separately, one key point that Kumar underlined in his 18 November note was "the unique manufacturing costs associated with mass production of a RNAi drug like inclisiran for CV disease, and whether a big Pharma firm would be willing to commit the CapEx necessary to generate inclisiran as a solo asset."

Novartis is no stranger to taking on advanced therapies with complex manufacturing, however, with recent launches including the gene therapy for spinal muscular atrophy, Zolgensma (onasemnogene abeparvovec, acquired with AveXis Inc. in 2018), and the CAR-T therapy Kymriah (tisagenlecleucel). Nor is it a stranger to developing RNA-targeting lipid-lowering candidates: only this year, it took up an option to license the antisense oligonucleotide TQJ230 (AKCEA-APO(a)-LRx) from Ionis Pharmaceuticals Inc. affiliate Akcea Therapeutics Inc., paying $150m for development and commercialization rights and planning a Phase III trial for cardiovascular risk reduction in patients with elevated lipoprotein(a).

BLOCKBUSTER INTENTIONS

Meanwhile, inclisiran would put its existing cardiovascular field force to good use. The latter has been focused on bringing heart failure drug Entresto (sacubitril/valsartan)'s annual sales beyond $1bn following a slow launch after approval in 2015, and following the patent expiry of one-time growth driver Diovan (valsartan). Novartis said it would only require a few hundred more reps to support inclisiran's launch in the US, while its existing Entresto sales force would be able to meet 90% of the requirements to launch inclisiran in the five major EU markets, Japan and China.

Novartis expects that, assuming completion in the first quarter of 2020, inclisiran will begin contributing to group sales from 2021 "with the potential to become one of the largest products by sales in the Novartis portfolio." It cited four brokers who had estimated future revenues for the product ranging from $4bn to more than $8bn by 2029.

Novartis's top selling drug in 2018 was Gilenya (fingolimod) for multiple sclerosis, with sales of $3.3bn. Entresto, its best-selling cardiovascular medicine, was 10th best overall on $1.0bn.

With sales of Repatha and Praluent amounting to $550m and $307m in 2018, Amgen and Sanofi/Regeneron now face the unappealing prospect of needing to lower their prices further in the near future to compete with an unwelcome upstart newly in the hands of commercial giant.

Nevertheless, according to a survey of 20 payers covering 152 million lives published by Jefferies in October, inclisiran could still face reimbursement hurdles as several indicated they would impose similar restrictions as they impose on the MAb PCSK9 inhibitors. However, they would be willing to remove restrictions on PCSK9 inhibitors should they cost less than a median price point of $2,500 a year (which Jefferies notes is less than half of the current list price of Praluent and Repatha).

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The Medicines Company Rises On Novartis Takeover Rumors: **https://bit.ly/37CEVUs**

Novo Nordisk Enters Its First Strategic RNAi Pact

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Novo Nordisk AS's pact with Dicerna Pharmaceuticals Inc. to discover and develop RNA-blocking therapies for conditions such as heart disease, type 2 diabetes and NASH should generate clinical candidates within three years, the Danish company's head of global drug development said. The collaboration provides Novo Nordisk with the capability to inhibit hepatocyte targets involved in disease regulation and has the potential to generate a number of clinical development candidates, Marcus Schindler told *Scrip* in an interview.

Under their partnership, Novo Nordisk and Dicerna will pursue joint exploration of over 30 targets in chronic liver disease, NASH, type 2 diabetes, obesity and rare diseases. Both companies retain opt in rights for candidates discovered under the collaboration. Schindler, who leads Novo Nordisk's early-stage drug research in cardiovascular disease, NASH, kidney, hemophilia, diabetes and obesity, said his side will lead programs targeting cardio-metabolic disorders, with Dicerna

having opt-in rights to two programs during clinical development.

The pact also gives Dicerna, which uses ribonucleic acid (RNA) interference (RNAi) to develop medicines that silence genes that cause disease, the right to initiate two new orphan liver disease programs, where Novo Nordisk has opt-in rights.

The Copenhagen-based group best known for metabolic disease products in diabetes and obesity has been trying to refocus its underperforming biopharm business in recent years.

It's collaboration with Dicerna reflects that, and follows Novo Nordisk's move earlier in November into non-alcoholic steatohepatitis (NASH) R&D with the licensing of exclusive worldwide rights to preclinical UD-014 from Japan's UBE Industries Ltd.

In April, Novo signed an alliance with Gilead Sciences Inc.to test its GLP1 analog Ozempic (semaglutide) with a pair of Phase II candidates from Gilead in NASH combination therapy.

Its discovery and development commitment with US-based Dicerna is a first for the Denmark-based company and aims to develop next-generation RNAi-based therapies to silence disease-driving genes in the liver and other tissues.

"This is our first strategic collaboration in the space of RNAi-based therapies, and reflects our strategy to expand our technology base from what we have traditionally been good at, protein and peptide chemistry in particular, to give us access to a technology that lends itself to hepatocytes and intracellular targeting in particular," Schindler told *Scrip*.

"We are particularly keen to nominate and validate targets in cardiovascular,

Novo Nordisk's global drug development head Marcus Schindler.

NASH, diabetes and obesity. Our efforts will be especially on target identification and a level of target validation. Dicerna will contribute using their technology and molecules as well as the disease understanding that they have in house."

RNAi therapies have been a long time in coming, with the first finally arriving in August when Alnylam's small interfering RNA (siRNA) therapeutic Onpattro (patisiran) won US Food and Drug Administration (FDA) approval for polyneuropathy in adults with hATTR, a genetic, life-threatening disease caused by mutations in the TTR gene.

Analysts view Dicerna's deal with Novo Nordisk is viewed as a good one, and follows its agreement earlier this month with Swiss drug maker Roche for use of its GalXC platform technology in developing Dicerna's RNAi-based drug for chronic hepatitis B.

Schindler said Novo Nordisk was also impressed by Dicerna's proprietary RNAi technology platform.

Its liver-targeted GalXC-based compounds enable subcutaneous delivery of RNAi therapies that are designed to bind specifically to receptors on liver cells, leading to internalization and access to the RNAi machinery within the cells. Compounds produced via GalXC are intended to be broadly applicable across multiple therapeutic areas, including both liver and non-liver indications.

"Dicerna's technology is well validated. They have an efficient and fast-moving operation so we can expect to see a significant number of targets progressing and we're confident that Dicerna can generate molecules to most if not all targets that we move forward," Schindler told *Scrip*.

Novo Nordisk's scientific work for the collaboration will be done in the Danish company's facilities in Oxford, England as well as in Beijing, China. "We will also leverage our capabilities in Denmark at our larger disease area biology unit to validate and progress those targets," he added.

"We anticipate that we will have the first clinical candidates within two to three years. We have no specific number in mind at this point but aim to identify a significant number of clinical candidates," Schindler said.

Under the pact Dicerna will receive an upfront payment of $175m and a $50m equity investment in Dicerna as well as $25m annually during each of the first three years of the collaboration, contingent on Dicerna delivering RNAi molecules for a defined number of targets. It also stands to receive up to $357.5m per target in development, regulatory and commercialization milestone payments, plus tiered royalties on product sales ranging from the mid-single-digits to mid-teens.

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With Celgene Acquisition Closed, Bristol Faces Major Milestones

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Now that Bristol-Myers Squibb Co. has closed its purchase of Celgene Corp. for nearly $76bn in cash and stock, the big pharma will have to keep up the momentum within its newly acquired pipeline to achieve the value it promised at the start of 2019 when the deal was announced.

The transaction, which initially was valued at $74bn, ended up giving Celgene shareholders an almost $2bn additional return on their investment, thanks to Bristol's recently rising stock price. The buyer gave Celgene investors $50 in cash and one share of Bristol stock for each share of Celgene that they owned. However, the acquisition is just the beginning of a long-term investment in a large pipe-

line of hematology, oncology, inflammation and immunology drugs. The mega-merger closed on 20 November, followed by the 21 November closing of Amgen Inc.'s purchase of Celgene's blockbuster Otezla (apremilast), which is approved for adults with moderate to severe psoriasis, active psoriatic arthritis and mouth ulcers due to Behcet's disease.

Disposition of the oral drug was needed to get US Federal Trade Commission clearance of Bristol's Celgene acquisition, due to overlapping indications for Otezla and Bristol's oral TYK2 inhibitor BMS-986165, which is in Phase III for psoriasis and Phase II for psoriatic arthritis, systemic lupus erythematosus, Crohn's disease and ulcerative colitis.

SIX NEAR-TERM LAUNCHES; TWO ALREADY APPROVED

The TYK2 program is one of six near-term launches from the merged companies' pipelines that Bristol highlighted back in January when it announced the purchase of Celgene. The other five all come from Celgene, including the JAK2 inhibitor Inrebic (fedratinib) that was approved in the US in August and the erythroid maturation agent Reblozyl (luspatercept), developed in partnership with Acceleron Pharma Inc. and approved for transfusion-dependent beta-thalassemia earlier this month.

Bristol unveiled its purchase of Celgene at a time when the big biotech's stock was suffering from several R&D setbacks, including the discontinuation of development for Otezla in inflammatory bowel diseases and the failure of mongersen (GED-0301) in Crohn's disease.

Celgene management made notable efforts to turn the pipeline around while it was waiting for its acquisition by Bristol to close. In addition to the Inrebic and Reblozyl approvals, in March Celgene resubmitted the new drug application (NDA) for its S1P receptor modulator ozanimod in the treatment of multiple sclerosis. The US FDA issued a refuse-to-file letter in response to the original NDA filing 11 months earlier – one of the many milestone misses that sank Celgene's stock ahead of the buyout offer from Bristol.

Ozanimod also is one of the five Celgene assets highlighted by Bristol to justify its acquisition of the biotech company. The other two are the CD19-targeting chimeric antigen receptor T-cell (CAR-T) therapy JCAR017 (lisocabtagene maraleucel, or liso-cel) and the B-cell maturation antigen (BCMA)-targeting CAR-T therapy bb2121, which is being developed in partnership with bluebird bio Inc.

Updated pivotal trial data for JCAR017 in relapsed or refractory non-Hodgkin lymphoma will be presented at the American Society of Hematology (ASH) meeting 7-10 December in Orlando, along with updated early clinical trial results for bb21217, another Celgene/bluebird BCMA-targeting CAR-T therapy for relapsed or refractory multiple myeloma.

As part of the merger deal, Bristol issued Celgene investors a $9 per share contingent value right (CVR) that will pay out based on FDA approval of ozanimod for MS and JCAR017 for lymphoma by 31 December 2020 and bb2121 in multiple myeloma by 31 March 2021.

Celgene said at the end of October that it will submit a biologic license application for JCAR017 in the third-line-plus treatment of relapsed or refractory large B-cell lymphoma during the fourth quarter of this year and that a BLA submission for bb2121 in fourth-line-plus multiple myeloma is expected during the first half of 2020.

Other notable Celgene programs now in Bristol's R&D pipeline include:

- Ozanimod's Phase III studies in Crohn's disease and ulcerative colitis;
- An oral version of the now-generic hypomethylating agent Vidaza (azacitidine) that's in Phase III for multiple indications, including myelodysplastic syndrome and acute myelogenous leukemia (Phase III results in AML will be presented in a 10 December late-breaker session at ASH after a top-line disclosure in September; regulatory submissions are planned during the first half of 2020);
- The next-generation proteasome inhibitor marizomib in Phase III for newly-diagnosed glioblastoma via Triphase Accelerator Corp.; and
- The Phase II immunomodulatory agent iberdomide (CC-220), the most advanced of Celgene's multiple cereblon modulator (CELMoD) compounds in development as next-generation therapies for multiple myeloma and other diseases.

Now Celgene, as a wholly-owned subsidiary of Bristol, will have to keep up its positive momentum for the last three of its five big near-term approvals to add to Bristol's commercial portfolio and fulfill the CVR commitment.

DIVERSIFICATION BEYOND CURRENT BLOCKBUSTERS

Both companies were in search of diversification at the time their merger was announced and will continue to face the same big challenge as a single entity.

The pressure was on Celgene to meet its R&D pipeline milestones, because it needed products to diversify its commercial portfolio beyond the multiple myeloma blockbuster Revlimid (lenalidomide), which provides about two thirds of its revenue and will begin to face generic competition in 2022. The company began to make progress before Bristol stepped in.

Meanwhile, Bristol is fighting to maintain significant market share for its PD-1 inhibitor Opdivo (nivolumab), which has been losing ground in key indications to Merck & Co. Inc.'s Keytruda (pembrolizumab). Bristol is under pressure to diversify beyond Opdivo and the anticoagulant Eliquis (apixaban), which together generated about two-thirds of its $6bn in third quarter 2019 sales.

The Bristol-Celgene merger also provides much needed diversification for Amgen. The purchase of Otezla gives Amgen a drug with about $2bn in annual sales at a time when its commercial portfolio is seeing significant sales declines from multiple products facing biosimilar or generic competitors, while growth from newer drugs has yet to fill the revenue gap.

Amgen raised its 2019 sales and earnings guidance based on the closing of the Otezla deal, noting that it now anticipates total revenues of $23.1bn-$23.3bn versus earlier guidance of $22.8bn-$23bn with non-GAAP earnings per share expected to reach $14.50-$14.70 versus $14.20-$14.45 previously.

Its newly acquired drug should see sales continue to grow in its post-topical, pre-biologic indications. A supplemental new drug application (sNDA) for Otezla is under review at the US Food and Drug Administration for the treatment of scalp psoriasis.

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Alkermes Invests In Novel CNS Targets With Rodin Acquisition

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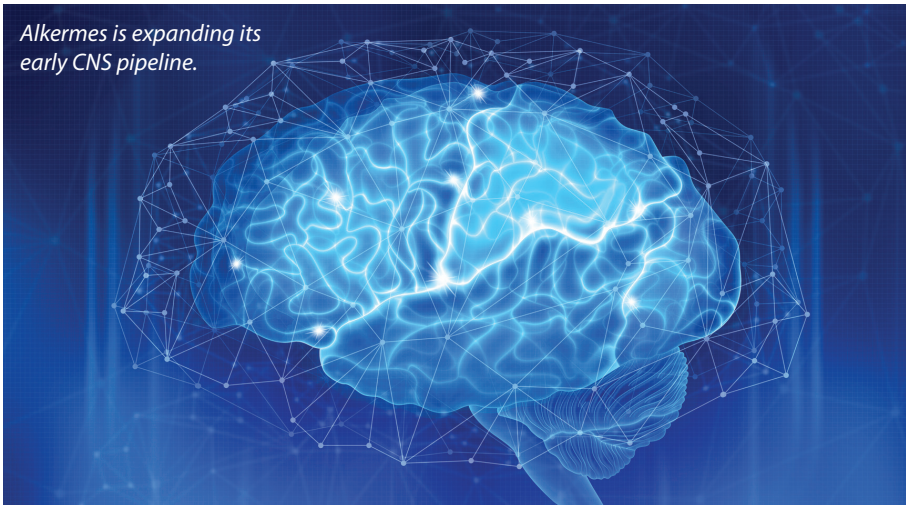
Alkermes PLC is building out its strategy to become a CNS drug developer with the acquisition of Rodin Therapeutics Inc. for $100m upfront. The company announced an agreement to buy privately-held Rodin on 18 November, gaining a platform for developing small molecule drugs for synaptopathies. In addition to the upfront, Alkermes could also pay future payments of $850m tied to certain clinical and regulatory milestones and certain sales thresholds.



Alkermes is expanding its early CNS pipeline.

Rodin is developing first-in-class, orally-available, brain-permeable therapeutics for neurodegenerative diseases like Alzheimer's, Huntington's and dementia that target specific histone deacetylase (HDAC) complexes. Selective inhibition of HDAC-co-repressor of repressor element-1 silencing transcription factor (CoREST) complex is believed to reactivate neuronal gene expression, strengthen existing synapses and promote the creation of new synapses, according to the companies.

"The reason [Rodin] fits with us so well is if you look at a lot of what we look at, whether it is major depressive disorder, the schizophrenia approaches we've been taking, we are really going after symptoms associated with an underlying disease," senior VP-corporate planning Blair Jackson said in an interview. "That is what the treatment of synaptopathies will allow us to do, whether it is in Alzheimer's, Huntington's disease, PTSD, wherever, and it's regardless of the pathology associated with the disease."

Alkermes has been keeping an eye on Rodin's works for some time, at least a couple of years, according to Jackson. That research coincided with some internal research Alkermes has been pursuing around synaptopathies. Alkermes was impressed with the chemistry Rodin has done developing brain-penetrant HDAC modulators – without effecting hematological properties.

While HDAC proteins have been shown to regulate synaptogenesis and synaptic plasticity, currently available ones are associated with dose-limiting hematological toxicities, which has limited their use for chronic treatment. Rodin's lead HDAC CoREST inhibitor, which has been tested in healthy humans, is the first reported brain-penetrant, complex-selective HDAC inhibitor that shows no signs of hematological toxicity.

BRINGING IN MORE NOVEL SCIENCE

Alkermes has been working in CNS for a long time, but its early focus was on drug delivery. The Rodin acquisition brings a novel high-science platform to a company that is better recognized for developing next-generation versions of mature medicines.

Alkermes markets the opioid antagonist Vivitrol (naltrexone) and the long-acting antipsychotic Aristada (aripiprazole) for schizophrenia. It is partnered with Johnson & Johnson on the long-acting forms of the antipsychotics Risperdal and Invega.

More recently, the company has been building out its pipeline – but with moderate success. ALKS 3831, which could potentially be filed with the US Food and Drug Administration shortly, is a combination of generically-available olanzapine with the novel opioid receptor antagonist samidorphan that is intended to minimize the weight gain side effect associated with the widely-used schizophrenia drug. A recently approved drug, Vumerity (diroximel fumarate), partnered with Biogen Inc., is next-generation oral fumarate similar to Biogen's blockbuster multiple sclerosis treatment Tecfidera (dimethyl fumarate), with an improved gastrointestinal tolerability. *(Also see "Biogen Vumerity Receives Full US Approval, But GI Comparison With Tecfidera Must Wait " - Pink Sheet, 31 Oct, 2019.)*

In more recent years, Alkermes has embarked on a strategy to develop novel mechanisms. In October, the company announced a business restructuring, including plans to cut 160 jobs, to save $150m and prioritize CNS and oncology research. *(Also see "Alkermes Restructures, Prioritizing CNS And Oncology And Cutting 160 Employees" - Scrip, 23 Oct, 2019.)*

Jackson said Alkermes has been making progress in the early pipeline. "What we have been very quiet on is the large amount of research we have been doing preclinically in a number of areas, both in CNS, as well as the cytokine space in oncology," he said. "Those products are starting to pull through on the early stage and what this deal will do is really allow us to augment that."

Rodin was founded in 2013 in Cambridge, Mass. to develop novel therapeutics for neurological conditions, funded by Atlas Ventures and Johnson & Johnson

Development Corporation. In January 2016, Rodin signed a research collaboration with Biogen, including an option for Biogen to acquire Rodin for a total of $485m. Biogen backed out of the deal a short time later after making just an $8m investment, and Rodin moved forward with another $27m financing in 2017. *(Also see "Venture Funding Deals: Spin-Offs Gain Their Own Footing" - Scrip, 4 Oct, 2017.)*

The company's lead candidate, a HDAC Co-REST inhibitor, RDN-929, successfully completed Phase I testing in healthy volunteers earlier this year. The randomized, double-blind, placebo-controlled study confirmed target engagement and showed RDN-929 was safe and well tolerated at multiple doses, and drug concentrations were measurable in cerebrospinal fluid.

Alkermes, however, said it may potentially prioritize other preclinical assets ahead of RDN-929, and will advance investigational new drug (IND)-enabling activities for preclinical assets. The company said it will also continue Rodin's preclinical work focused on a subset of patients with frontotemporal dementia with an inherited mutation of the progranulin gene (FTD-GRN) and exploratory work in hematological disorders and oncology.

"Some of their lead preclinical assets tended to have characteristics we felt were more suitable for a number of areas we were pursuing," Jackson explained. "Our feeling was this would be the perfect time to move those forward and continue to rely on the data they've learned with their lead asset, but we think some of these have a longer road ahead of them."

Alkermes expects to incur around $20m in incremental R&D expenses in 2020 related to the advancement of Rodin's development candidates. The company said it will fund the acquisition using available cash with most of the upfront payment recorded as R&D expense. The company benefited from receipt of the $150m milestone payment from Biogen in November, triggered by the US Food and Drug Administration approval of Vumerity for multiple sclerosis.

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Harpoon Finds A Blood Cancer Partner In AbbVie

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Harpoon Therapeutics Inc. has expanded an immuno-oncology drug discovery collaboration with AbbVie to include an option license for a B-cell maturation antigen (BCMA)-targeting T-cell engager poised to enter the clinic in 2020 for multiple myeloma.

The option deal is part of an expanded collaboration between the two partners that was announced on 21 November. AbbVie first partnered with Harpoon in October 2017 in a drug discovery collaboration to use Harpoon's Tri-specific T-cell Activating Construct (TRiTAC) platform with two of AbbVie's immuno-oncology targets to develop novel cancer drugs. Harpoon's TRiTAC platform produces novel T-cell engagers, engineered proteins that direct a patient's T-cells to kill cancer cells, targeting solid tumors and hematological malignancies.

That research went well, and AbbVie wanted to expand the partnership to include another six targets, as well as Harpoon's internally developed BCMA drug. Harpoon has four internally developed drugs, two of which are in the clinic and two of which are approaching the clinic. One of those is HPN217, the BCMA-targeting drug, which is poised to start clinical trials in multiple myeloma in 2020.

"We recognized that the other three programs we have are in solid-tumor indications whereas the BCMA program is a hematologic malignancy," CEO Jerry McMahon said in an interview. "We recognized from the very beginning that we would need a commercial/late-stage development partner for the program, given that multiple myeloma is a particularly complicated space to navigate."

AbbVie's experience in blood cancer makes it a strong partner for HPN217. AbbVie markets two drugs for hematological cancer, Imbruvica (ibrutinib) for B-cell driven cancers, and Venclexta (venetoclax) for certain leukemia.

The multiple myeloma treatment market is a competitive one, however, and it is poised to become even more crowded before HPN217 would have a chance to reach the market. In particular, several drug companies are close to filing BCMA-targeted drugs with the US Food and Drug Administration, including GlaxoSmithKline PLC, Bristol-Myers Squibb Co. (via the Celgene Corp. acquisition) and Johnson & Johnson.

Under the expanded deal, AbbVie agreed to pay $50m upfront plus another near-term $50m milestone payment for an option to license worldwide exclusive rights to HPN217 after completion of Phase I/II clinical testing. The milestone payment is due after the first patient is dosed in the clinical trial, which Harpoon will be responsible for. AbbVie could pay up to $510m in upfront, option and milestone payments, plus royalties on commercial sales. It would need to pay $200m to Harpoon to exercise the option.

Meanwhile, under the expanded discovery agreement, Harpoon could receive up to $310m in upfront and potential development, regulatory and commercial milestone payments, plus royalties on sales.

With the two $50m near-term payments from AbbVie, McMahon said the company will have the funding to operate into the second half of 2022, by which time it should have proof-of-concept data available on all four programs. "That really puts us in a nice position," he said. The company had cash and equivalents of $121.2m at the end of the third quarter. Harpoon had secured $70.7m in net proceeds from an initial public offering that was completed in February 2019.

Harpoon is moving forward its other internal candidates already in clinical testing, including HPN424 for prostate cancer and HPN536 for ovarian cancer and pancreatic cancer. The company plans to present interim results from the Phase I trial testing HPN424 in the first half of 2020 and expects to present proof-of-concept data from the Phase I/II trial for HPN536 in 2020.

The third solid tumor program, still in preclinical testing, is HPN328, potentially for small-cell lung cancer in patients with DLL3-expressing malignancies.

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Takeda: 12 NMEs Poised To Launch In Five Years, And Deliver $10bn In Peak Sales

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Takeda Pharmaceutical Co. Ltd.' efforts over the last five years to reshape its pipeline – including the merger with Shire PLC – are now poised to deliver. The Japanese pharma held its first ever investor day in New York on 14 November, coming after the company's stock was listed on the New York Stock Exchange in 2018 and the merger with Shire was completed in January.

With the integration of Shire largely completed, Takeda CEO Cristophe Weber, R&D president Andy Plump and other R&D leaders set out to showcase the Takeda's progress in reenergizing the pipeline with a focus in four core areas: oncology, rare diseases, gastroenterology and neuroscience.

"It's a very special moment because it's not just a pipeline update," Weber told investors. "It's how the R&D strategy that we developed five years ago is coming together."

Weber took over as CEO of Takeda in 2014 as the first non-Japanese executive to hold the top leadership spot at the company, and with big ambitions to globalize the company. He brought in new leaders like Plump, who previously worked at Sanofi, to streamline and revitalize R&D. With the $61bn acquisition of Shire, Takeda built out the commercial portfolio and R&D pipeline in rare diseases and established itself as a top 10 pharmaceutical player, based on pharmaceutical revenues, with revenues of more than $31bn.

Takeda revealed 12 potential new molecular entities that could launch in the next five years, through its fiscal year 2024, which could together deliver $10bn in peak sales. Takeda is calling these 12 NMEs "Wave 1," which will be followed by "Wave 2," made up of 26 earlier-stage NMEs that could launch in fiscal year 2025 and beyond.

"Reflecting back on five years from when I came, if I were to look at Takeda then and Takeda now, with the exception of the values and this iconic, rich history that lives with us every day, it's an unrecognizable company," Plump said.

For one thing, Takeda has greatly diversified the types of drug modalities in its R&D engine, from what was largely all small molecules to what is now 70% diversified modalities, including biologics, cell therapy, gene therapy, peptides and microbiome-targeted therapies.

Of the 12 NMEs included in Wave 1, half are expected to launch further out in the cycle, in 2023 or 2024, however.

Among the nearer-term pipeline candidates that could launch in fiscal 2020 or 2021 are two that came via Shire: TAK-721 (budesonide oral suspension) for eosinophilic esophagitis (EOE), an immune-mediated rare disease effecting the esophagus for which there are no treatments, and TAK-620 (maribavir) for cytomegalovirus infection following a transplant. The acquisition of Shire added 18 new NMEs to the pipeline.

The first of two Phase III studies studying TAK-721 read out positively in October. Two pivotal studies testing TAK-620 are ongoing, with Phase III data in patients receiving a solid organ transplant or hemopoietic stem cell transplant expected to read out in the second half of 2020.

PROGRESS IN ONCOLOGY

In oncology, Takeda has made notable strides. The company has a strong foundation in cancer, stemming from the acquisition of Millennium BioTherapeutics Inc. in 2008, which gave the company the backbone multiple myeloma therapy Velcade (bortezomib), now available generically. Takeda currently markets the follow-on proteasome inhibitor Ninlaro (ixaxomib) for multiple myeloma, and it further expanded the commercial portfolio with the 2017 acquisition of Ariad Pharmaceuticals Inc. for $5.2bn, which added Iclusig (ponatinib) and Alunbrig (brigatinib). *(Also see "Takeda Acquires Ariad In $5.2bn Deal – US Infrastructure A Key Component?" - Scrip, 9 Jan, 2017.)*

Nonetheless, Takeda missed out on the first wave of immuno-oncology drugs – the checkpoint inhibitors and cell therapies.

The head of Takeda's oncology drug discovery unit Chris Arendt outlined how the company has pivoted to assemble a pipeline with a core focus on immuno-oncology with curative intent, and has particularly built a novel cell therapy platform. A big component of the strategy has been partnering externally.

"We've been able to leapfrog into new modalities and leapfrog into exciting new mechanisms," Arendt said. "We are working on differentiated oncology concepts and a big theme across our portfolio is leveraging very powerful cells of the immune system, which are the innate immune cells that really orchestrate everything that happens in an immune response."

Some of the results of that work, however, are part of Wave 2, which is expected to reach the market after fiscal 2024, including the first-in-class SUMO inhibitor TAK-981, based on an internal SUMOylation platform, and TAK-573, based on the Attenukine platform that elicits both direct tumor kill and immune activation, using a engineered version of type 1 interferon targeted to tumor cells via a CD38 antibody.

Jefferies analyst Stephen Barker applauded the company's efforts in oncology. "Takeda's adoption of an outward-facing innovation model has enabled Takeda to make a great leap forward to the forefront of cell-based immuno-oncology," he said in a 15 November research note. "Rather than follow the crowd into checkpoint inhibitors and CAR-T cell therapies, Takeda has blazed a new path."

COMMITMENT TO CELL THERAPY

The company's emerging cell therapy pipeline got a lot of attention during the overview, with Arendt highlighting Takeda's focus on gamma delta T-cells and natural killer (NK) cells. The company expects

to have five cell therapy programs in clinical testing by the end of fiscal 2020.

The company formed a cell therapy translational team in July 2018 under the leadership of Stefan Wildt, who helped deliver Novartis AG's CAR-T therapy Kymriah to market. *(Also see "New Takeda R&D Collabs Aim To Boost IO Pipeline" - Scrip, 4 Jan, 2019.)*

"He's put together a best-in-industry team and opened a GMP manufacturing suite now in our Cambridge campus and will be helping us not only accelerate these cell therapies to that early clinical setting, but to make sure that we capture and leverage those incredible translational learnings that will inform the many iterations that are possible in this space," Arendt said.

Takeda announced earlier in November an exclusive licensing agreement with MD Anderson Cancer Center to develop cord blood-derived CAR-directed NK cell therapies, engineered with IL-15, for the treatment of B-cell malignancies and other cancers. *(Also see "Asia Deal Watch: Ambrx, NovoCodex Partner On Second ADC Candidate, For CD70-Positive Cancers" - Scrip, 6 Nov, 2019.)*

The first of the programs, TAK-007, is already in the clinic and will be going forward in CD19-positive malignancies, with an eye toward entering pivotal studies in 2021. In a patient with diffuse large B-cell lymphoma (DLBCL) who had failed three lines of prior therapy, after being treated with TAK-007 he achieved a complete response after just one dose.

"Our vision for this product is to be able to provide patients with a highly efficacious CAR NK immunotherapy that has a safety profile allowing it to be administered in an outpatient and community setting," Arendt said. The first CAR-T cell therapies are associated with serious adverse events, including cytokine release syndrome, and require administration in a hospital setting.

Despite the excitement over cell therapy, Takeda has two assets that are significantly closer to commercialization: TAK-788 for patients with EGFR non-small cell lung cancer with exon 20 insertion mutations and the NEDD8 inhibitor TAK-924 (pevonedistat) for myelodysplastic syndrome. Both are anticipated to reach the market in the 2021 timeframe. *Published online 19 November 2019*

The Healthcare World According To Andrew Witty

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Two and a half years after stepping down as CEO of GlaxoSmithKline PLC, Sir Andrew Witty returned to London to talk about life after big pharma and his views on the US healthcare system where he has become a leading figure as head of UnitedHealth Group Co.'s pharmacy benefit management and health services arm Optum.

Eyebrows were raised when Witty, an advocate of the need to change pricing models when at the helm at GSK, switched sides in July last year to run Optum. In addition, last week, he was named as the new president of UnitedHealth, the largest private payer in the US which reported whopping revenues of $60.4bn (+7%) in the third quarter.

Speaking at the Pharma Integrates conference in London on 18 November, Witty told attendees that the US was spending almost 20% of its gross domestic product on healthcare and patients are becoming more exposed to higher premiums and out-of-pocket expenses. "This has driven anxiety about affordability," he said, claiming that Optum is leading the charge in pushing for a simpler and more cost effective health system.

This involves aligning pharmacy, medical and behavioral health needs, using data to enable end-to-end management of care, according to Witty. The key element of this involves moving much care out of hugely-expensive hospitals and he spoke about the convenience of patients getting treatment at retail stores in shopping malls rather than travelling to out-of-town centers.

"I got my Shingrix in Target," Witty revealed, referring to GSK's shingles vaccine and the US retail major. Shifting the site of care cannot just lower costs but can also improve clinical outcomes, he noted, with the likes of home infusion services.

Witty said that the digital space in healthcare was clearly of interest: "The key is not to get lost in the noise [and] we keep declaring victory extremely prematurely." He stated that he was "very sceptical" when he hears "digital solves" but is "a big fan" of a digital element adding value.

Witty believes there is a place for behavioral health apps, including those based on 'nudge' theory, that propose subtle changes to the patient's environment that can boost compliance. He noted that Optum has spent over $1bn on incentives, "so if you get a flu shot or you lose weight, you have a reward."

The digital revolution, be it through wearables or insideables, needs to be led by clinical informers, Witty stressed, adding that the personal touch is still vital. He said that targeted human intelligence complemented with artificial intelligence is both a challenge and an opportunity.

By using data personalized to a patient, analytics will help determine not only a "best action" but also it needs to predict what the individual's next best action will be, Witty said. Using these analytical tools works better when the patient is inspired to invest in their own wellness, he added, noting that behavioral health programs run by Optum with some of the poorest communities in the US with mental health problems who had considerable compliance issues have seen a marked in adherence to medicines.

When it comes to the role of digital technology in healthcare, Witty said that "the UK is a phenomenal position," given its single-payor status where all citizens are provided with access to treatment. Having all the data in a common source makes sustainable and systemic chance more likely to succeed in the UK than most countries, he pointed out.

The attendance of Witty, who abandoned the suit and tie of his GSK days for a half-zip sweater for his fireside chat with well-known pharma figure Trevor Jones, caused a stir at Pharma Integrates. His time at GSK was regarded overall as a success, especially for his policy of lower drug prices for poorer countries, limiting doctor payments and spearheading data transparency on clinical trials.

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Biopharma Should Copy Our Gilead Deal, Says Rising Star Galapagos

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Galapagos chief executive Onno van de Stolpe said he and Gilead's Daniel O'Day toasted their $5.1bn "transformative" research deal with a glass of champagne in New York before they unveiled it to the biopharma world in July.

The alliance was based on their co-developed filgotinib for rheumatoid arthritis, which could claim best-in-class status in the oral JAK inhibitor class, and is set for FDA filing by the end of 2019.

Van de Stolpe was in London on 20 November to present to investors at the Jefferies conference, and was in an ebullient mood as he presented the company's plans for pipeline expansion, which on the whole impressed analysts.

The deal marked a highly novel approach to big pharma-biotech tie-ups, and provided the Belgium/Netherlands-based firm with billions of dollars in the bank, an unheard of situation for a European biotech.

It comprised a $3.95bn upfront payment, a $1.1bn equity investment stake in Galapagos (22% of the company) plus opt-in payments covering six molecules currently in clinical trials, more than 20 preclinical programs.

The deal gives Galapagos financial security, an opportunity to scale up its R&D and to launch its own commercial operations, starting in Europe.

Importantly, the agreement also includes a "standstill" guarantee that Gilead will not move to acquire it over a 10-year period.

From Gilead's perspective, the deal looks like a wiser use of money than an all-out acquisition, allowing it to keep its options open on Galapagos promising but still risky antibody pipeline.

Van de Stolpe said the deal gave Galapagos three things: the capital to invest in its pipeline; freedom, by putting very few restrictions on it in terms of the targets and disease areas it must focus on; and independence, which he says its employees and leadership values highly.

"I hope this model is followed more in the industry, rather than the outright acquisitions that we've seen in the past, where innovation is sort of secondary. Nothing good comes out of these big pharma acquisitions."

Galapagos CEO Onno van de Stolpe at the Jefferies conference in London.

> "I hope this model is followed more in the industry, rather than the outright acquisitions that we've seen in the past, where innovation is sort of secondary." – Onno van de Stolpe

He also underscored Galapagos' ambition to become a fully fledged commercial biopharma company – it will co-market filgotinib with Gilead in the big five European markets, and retaining exclusive commercial rights in the Benelux nations.

"I hope companies listen and take lessons out of this, and hopefully we can show that together, we can create true value and get it [Galapagos] to move up in the ranks of the successful companies in the world."

For Gilead, O'Day's number one priority is to find new blockbuster medicines to help replace the dwindling revenues from its hepatitis C portfolio, and the more modest growth expected in its HIV franchise.

Gilead is acquiring rights to GLPG1690, an oral, once-daily autotaxin inhibitor in Phase III for idiopathic pulmonary fibrosis (IPF), and GLPG1972, an ADAMTS-5 blocker in Phase IIb for osteoarthritis in the US.

2020 will be a big year for read-outs from Galapagos, including from its Toledo drug platform. This is against a novel, as yet undisclosed target but which has a dual action on inflammation.

There will be top-line data for filgotinib in ulcerative colitis, as well as its first-generation Toledo molecule '3312 and multiple proof-of-concept trial initiations for '3970, the second generation Toledo candidate.

All the same, analysts say it is too early to judge just how significant the Toledo pipeline will be, and say Gilead still needs to do more M&A to help restore its fortunes.

A recent note by Credit Suisse said filgotinib would not be enough to change the firm's "revenue trajectory" and predicted it would face competition from AbbVie an "inflammation marketing powerhouse".

AbbVie's own JAK inhibitor Rinvoq (upadacitinib) gained US approval in August for rheumatoid arthritis, and will maintain its domination of the US market with Humira until its patent expiry in 2023.

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Hemophilia A Gene Therapy: BioMarin In Lead, Sangamo 'Prays' For Superior Results

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BioMarin Pharmaceutical Inc. is just days away from filing its ground-breaking hemophilia gene therapy with the FDA, and looks odds-on to gain approval by mid-2020.

Valoctocogene roxaparvovec (valrox for short) is at the head of a wave of new gene therapies for the inherited condition and has demonstrated the ability to virtually eliminate all bleeds and the need to inject blood clotting Factor VIII (FVIII) in trial patients.

But doubts about its long-term efficacy and durability mean that its rivals in pursuit may have a chance to overhaul its first-to-market advantage.

Sangamo Therapeutics Inc. (which is partnering with Pfizer Inc.) remains hopeful on signs that its SB-525 product could demonstrate superior results.

Meanwhile a third contender is Spark's SPK-8011, though the company has gone quiet on its development over the last 12 months, complicated by a much-delayed acquisition by Roche.

There is much to play for in the hemophilia A market, as it represents a much bigger commercial opportunity than any existing gene therapy fields.

At the same time, hemophilia patients are already well served by existing therapies, including Roche's new entrant Hemlibra, which makes the need for a gene therapy less pressing than in life-limiting rare diseases such as spinal muscular atrophy (SMA).

All these factors will be important for BioMarin when it comes to set its price for valrox – which it says could be anywhere between $1m and $3m.

Speaking at the Jefferies conference in London on 21 November, BioMarin's chief executive Jean-Jacques Bienaimé said this would nevertheless represent a saving for payers, as treating hemophilia patients in the US typically costs $400,000-600,000 a year throughout their lifetime.

EUROPEAN FILING FIRST

The company has in fact filed with the European Medicines Agency first, announcing the European regulator's acceptance of its accelerated assessment request on 22 November.

This submission is based on an interim analysis of study participants treated in an ongoing Phase III study, with material from the to-be-commercialized process and updated three-year Phase I/II data.

These interim Phase III data have shown a drop-off in blood clotting FVIII three years after treatment, though BioMarin says this could be down to a later use of steroids compared to the earlier trial.

While valrox looks certain to gain FDA approval, what is not so clear is what kind of claims to efficacy and durability the regulator will approve, a key point when BioMarin has rivals in pursuit.

Speaking shortly after Bienaimé at the Jefferies conference, Sangamo's chief executive Sandy Macrae said he was sure BioMarin would gain approval, but that questions remained about valrox's long-term efficacy. Its Phase III data shows valrox helped patients stay virtually bleed free and not needing FVIII replacement, but some have dipped well below the 50% factor levels, normally considered a hemophilia diagnosis.

Sangamo is set to present data at the ASH congress next month which could suggest greater efficacy than its rival, but it won't provide longer term data until mid-2020.

"If we can show [Factor VIII] levels of 100-150% and keep that consistent, we would hope to offer patients a greater benefit," said Macrae. "We won't be able to declare that until the end of this year at ASH and then into the middle of next year, when we can demonstrate 12 to 18 months of consistency."

He added wryly: "I keep my fingers crossed, I pray in the shower every morning, but until we see the data, the roulette wheel is spinning."

Sangamo is now in the process of handing over to Pfizer for the final pivotal trial, a big pharma partner which the biotech believes will give it an advantage in late-stage trial execution, regulatory approval and commercialisation.

Many analysts believe that BioMarin will still have a first-mover advantage, and at a year or two's head start on Sangamo/Pfizer and Spark/Roche.

Asked about valrox's revenue prospects in 2021, which would be its first full year on the market, Bienaimé was confident that valrox would exceed analyst forecasts of $150m.

He pointed to 300 patients who had wanted to enrol in its Phase III trials, but had not been able to take part.

Bienaimé said that even using conservative figures of a $1.5m price for valrox, and 200 patients treated in a year would deliver $300m revenues.

He added that its manufacturing plant in California could easily provide enough gene therapy for 400-500 patients, with plans for a second plant, probably in Ireland, also advancing.

Lastly, the company is developing a next-generation AAV vector which would allow re-treatment of gene therapy. This is not possible with the first generation of therapies, as they produce an immune response in the body and neutralising antibodies which would block their action.

This means patients currently taking a first generation product have to weigh up its risks and benefits carefully, a dynamic which would change if re-treatment became available.

"But if you tell them that they can take valrox and in five, six seven years it doesn't work anymore, you can be treated again- and we'll have data way before that – that's a much easier decision, either with our product or another product," says Bienaimé.

BioMarin says this second-generation vector would also open up a gene therapy treatment and re-treatment paradigm in rare childhood diseases such as Duchenne muscular dystrophy.

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Alnylam Wins FDA Approval For Givlaari, Its Second RNAi Drug

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Alnylam Pharmaceuticals Inc. is on its way to becoming a multi-product drug maker, having secured approval for a second RNAi-based therapeutic from the US Food and Drug Administration. That means the company is poised to meet the goal of having multiple commercial products before 2020 previously set by CEO John Maraganore.

"We believe the FDA's approval of Givlaari further establishes RNAi therapeutics as a whole new class of medicines, which has the potential to deliver significant impact to patients across diseases, both rare and common," Maraganore said during a same-day conference call.

The FDA announced the approval of Givlaari (givosiran) for acute hepatic porphyria (AHP) on 20 November, three months ahead of the priority review user fee date for givosiran of 4 February. The quick approval came despite safety concerns around liver and kidney toxicity, including some cases of chronic kidney disease. The drug is the first treatment approved for the rare genetic disease and had received breakthrough therapy designation from the agency. It was also approved with a broad label, without any requirements around the number of attacks a patient must have to support treatment.

Acute hepatic porphyria results in the build-up of toxic porphyrin molecules, which form during the production of heme, which helps bind oxygen in the blood, and causes acute attacks that can lead to severe pain, paralysis, respiratory failure and mental problems. The attacks can occur suddenly and produce permanent neurological damage and death. Givosiran targets aminolevulinic acid synthase 1 and is administered as a monthly subcutaneous therapy.

The approval was based on the results of the ENHANCE clinical trial of 94 patients with acute hepatic porphyria; patients who received Givlaari experienced 70% fewer porphyria attacks compared to patients taking placebo.

The ENVISION trial also achieved statistically significant positive results on five of nine secondary endpoints, including urinary ALA levels at three and six months in AHP patients, annualized attack rate in AHP patients and annualized days of administered hemin doses in AHP patients. Hemin is one option currently used to treat patients but has drawbacks, including renal insufficiency and iron overload, which can cause liver cancer.

Serious adverse events were also reported with givosiran, including more cases of chronic kidney disease versus placebo, as well as nausea, injection-site reactions and fatigue. CKD was reported in five givosiran-treated patients, but all the cases were in patients with renal dysfunction at baseline. FDA recommends physicians monitor patients for renal function and for anaphylactic reaction. The agency also recommended patients should have their liver function tested before and periodically during treatment.

FOCUSING ON DIAGNOSIS

Only a few thousand patients in the US and Europe are believed to have AHP, and Alnylam will price the drug accordingly at roughly $575,000-per-patient-per-year, before discounts. Management, during a same-day conference call, said the drug's net price will be more like $425,000. The company also outlined a value-based reimbursement agreement for payers, including a novel prevalence-based adjustment feature that will trigger rebates to participating payers if the number of diagnosed patients they cover exceeds current epidemiologic estimates for AHP.

> "We believe the FDA's approval of Givlaari further establishes RNAi therapeutics as a whole new class of medicines."
> – John Maraganore

In August, Alnylam signed a non-exclusive, three-year commercial agreement with Ironwood Pharmaceuticals Inc. to help increase physician awareness of AHP and givosiran. Ironwood will help commercialize the product to gastroenterologists and other physicians who prescribe its irritable bowel syndrome drug Linzess (linaclotide). In exchange, Ironwood will receive fixed payments and mid-teen royalties on net sales of givosiran prescriptions or referrals.

Alnylam has also ramped up education initiatives around diagnosis. There are only about 1,000 patients in the US and EU who have recurrent attacks, but the company believes it also could target another 5,000 patients in the two regions who experience sporadic attacks and chronic manifestations. *(Also see "Alnylam Ramps Up Commercial Planning For Givosiran Based On Phase III Data " - Scrip, 6 Mar, 2019.)* The company guided analysts to forecast about 3,000 patients in both regions initially.

The diagnosis rate for the disease is low at around 20%, so successfully commercializing Givlaari will require improving diagnosis rates.

The drug will be Alnylam's second commercial product and only the second RNAi-based therapy to reach the market. Alnylam's Onpattro (patisiran) launched last year as the first RNAi therapeutic approved in the US and the first drug for hereditary transthyretin-mediated amyloidosis (hATTR), another rare genetic disease. *(Also see "Alnylam Offers Flexible Value-Based Deals For Breakthrough RNAi Drug Onpattro" - Scrip, 11 Aug, 2018.)* The company reported that Onpattro generated $46.1m in third quarter revenues, with more than 600 patients worldwide on treatment since its launch.

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For An Ultra-High-Priced Drug, Alnylam Brings A New Idea

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Alnylam Pharmaceuticals Inc. is introducing a novel prevalence-based pricing adjustment for payers to support the launch of its newly approved Givlaari (givosiran), which will come with a high price tag.

Givlaari was approved by the US Food and Drug Administration on 20 November for the rare genetic disorder acute hepatic porphyria (AHP), which affects just a few thousand patients in the US and Europe.

The drug will launch with an ultra-high price tag as well: $575,000-per-patient-per-year before discounts. The company told investors to expect a net price more in the range of $425,000 after discounts and rebates.

> The company's pricing decision was driven by the ultra-orphan nature of the disease and the high cost of helping patients currently.

In a proactive move to counter potential pushback from payers, Alnylam said it will offer a prevalence-based adjustment feature that will trigger rebates to participating payers if the number of diagnosed patients they cover exceeds current epidemiologic estimates for AHP.

There are only about 1,000 patients in the US and EU who have recurrent attacks, which can result in severe pain, neurological damage and death. The company believes it could target another 5,000 patients in the two regions who experience sporadic attacks and chronic manifestations. The company guided analysts to forecast about 3,000 patients in both regions initially.

As is frequently the case with drugs for rare diseases, the prevalence rates aren't always fully understood, and diagnosis rates are low until there is a new treatment to spur diagnosis. Often, in such cases, drug makers base their pricing on the initially low prevalence figures only to find the number of patients is higher than expected, which then becomes an issue for payers.

During a same-day conference call, Alnylam president Barry Greene said it is the first drug company to introduce a prevalence-based adjustment feature to payers, as far as it is aware. The company said the decision was driven by a desire to be "proactive" and bring a new idea to the negotiating table.

"This innovative approach offers greater certainty to payers that their overall financial risk will be adjusted if a substantially larger number of patients than currently estimated are identified," Alnylam said. In addition, CEO John Maraganore said the new feature is part of a risk-sharing arrangement with payers. "We do require the payer to also reimburse the product for the label, not to restrict reimbursement to some clinical trial components," he pointed out.

The launch will also be supported by a more traditional value-based reimbursement agreement for both government and commercial payers in which they will pay the full value for Givlaari only when it delivers patient outcomes similar to what was demonstrated in the ENVISION clinical trial supporting FDA approval. In the 94-patient ENVISION trial, patients who received Givlaari experienced 70% fewer porphyria attacks compared to patients taking placebo.

Greene said the company's pricing decision was driven by the ultra-orphan nature of the disease and the high cost of helping patients currently, which can reach $400,000 to $650,000 annually, including hospitalization and hemin administration.

Alnylam said it has already reached one coverage agreement with Harvard Pilgrim covering Givlaari and is working with others.

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Major Milestone For SK Biopharm As Anti-Epileptic Gets US Approval

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SK Biopharmaceuticals Co. Ltd. has received US FDA approval for its novel anti-epileptic drug Xcopri (cenobamate), for the treatment of partial onset seizures in adults, providing a new treatment option for refractory epileptic patients.

A new effective therapy for drug-resistant epilepsy has been seen as one of the most pressing unmet needs in this sector.

With the landmark regulatory clearance, the SK Group company has become the first South Korean firm to have independently brought a compound from discovery through to US approval. Through its US subsidiary SK Life Science, it will also independently market and sell the drug, with a goal to launch it in the second quarter of 2020, pending scheduling review by the US Drug Enforcement Administration (DEA).

"The approval of Xcopri is a significant milestone for SK Biopharmaceuticals and SK Life Science," Jeong Woo Cho, president and CEO of both companies, said in an interview with *Scrip*.

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Syneos Health's Best New Drug Award

Launching a successful new product launch marks the culmination of years of risky and expensive R&D; this Award recognizes excellence in drug development.

ALNYLAM PHARMACEUTICALS' ONPATTRO (PATISIRAN) FOR POLYNEUROPATHY OF HEREDITARY TRANSTHYRETIN-MEDIATED AMYLOIDOSIS

In August 2018, Alnylam Pharmaceuticals made history with the first FDA approval for an RNA interference (RNAi) therapeutic, Onpattro, for the treatment of the polyneuropathy of hereditary transthyretin-mediated amyloidosis in adults, a disease which previously had no FDA-approved therapies. The development and approval of Onpattro has opened the doors for RNAi to become a new way to develop medicines, as monoclonal antibodies once did in the 1990s.

ASTEX/JANSSEN PHARMACEUTICA'S BALVERSA (ERDAFITINIB) FOR METASTATIC UROTHELIAL CARCINOMA

The first-in-class FGFR inhibitor, Balversa, was approved in the US for adults with locally advanced or metastatic urothelial carcinoma that has susceptible fibroblast growth factor receptor (FGFR)3 or FGFR2 genetic alterations, alongside a companion diagnostic. This precision medicine provides new hope for patients who have a very poor prognosis, with less than 5% five-year survival from the time of metastatic diagnosis.

AVEXIS/NOVARTIS'S ZOLGENSMA (ONASEMNOGENE ABEPARVOVEC-XIOI) FOR SPINAL MUSCULAR ATROPHY

This gene therapy, administered via a one-time 60-minute intravenous infusion, is designed to halt disease progression in patients with SMA less than two years of age. As the first therapy to functionally replace the *SMN1* gene, Zolgensma is a potentially appropriate foundational therapy for pediatric patients with SMA, showing a transformative impact on survival and achievement of motor milestone developments.

EMD SERONO, THE BIOPHARMACEUTICAL BUSINESS OF MERCK KGAA'S MAVENCLAD (CLADRIBINE TABLETS) FOR MULTIPLE SCLEROSIS

Mavenclad was the first and only FDA-approved oral multiple sclerosis (MS) treatment to provide two years of proven efficacy with a maximum of 20 days of treatment for adult patients with relapsing-remitting disease (RRMS) and active secondary progressive disease (SPMS). The drug provides a new option for this heterogeneous disease where up to 43% of people do not use available disease-modifying drugs.

HUTCHISON CHINA MEDITECH/LILLY'S ELUNATE CAPSULES (FRUQUINTINIB) FOR COLORECTAL CANCER

Hutchison China MediTech Limited celebrated a landmark in September 2018 when its novel cancer drug fruquintinib became the first modern drug discovered and developed in China to be approved by the Chinese National Medical Products Administration. Fruquintinib, which is being marketed as Elunate by Lilly, is designed to be a global best-in-class VEGFR inhibitor for solid tumors and was approved for third-line colorectal cancer.

INSMED'S ARIKAYCE (AMIKACIN LIPOSOME INHALATION SUSPENSION) FOR MYCOBACTERIUM AVIUM COMPLEX LUNG DISEASE

Arikayce became the first and only therapy approved in the US for the treatment of refractory MAC lung disease as part of a combination antibacterial drug regimen for adults with limited or no alternative treatment options. The drug provides an option for patients unable to eradicate the disease with the current standard of care, fundamentally changing how MAC is managed in this difficult-to-treat segment.

SOBI'S GAMIFANT (EMAPALUMAB-LZSG) FOR PRIMARY HAEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS

In November 2018, the US FDA approved Gamifant – an interferon gamma blocking antibody – as the first and only treatment for patients with primary haemophagocytic lymphohistiocytosis (HLH) with refractory, recurrent or progressive disease or intolerance to conventional HLH therapy. Gamifant represents a new approach to treating primary HLH and helping very sick patients reach haematopoietic stem cell transplant.

Pharma Company of the Year

Scrip's Pharma Company of the Year Award honors outstanding achievement by pharmaceutical companies over the qualifying 12 months, 1 June 2018 and 31 May 2019.

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- Progress in the emerging markets.
- New product launches including line-extensions and formulations.
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CONTINUED FROM PAGE 14

The approval is set to accelerate the firm's plan to become a global pharma in the long-term, boost its plan to launch a huge initial public offering on the main Kospi market in South Korea next year and help the recovery of biotech/pharma sentiment in the country after a series of disappointing clinical trial news this year. *(Also see "Korean Biotech Sentiment Still Shaky But IPO Recovery Seen By Year-End" - Scrip, 12 Nov, 2019.)*

The company hasn't yet determined the US list price for Xcopri and plans to share more information at the time of launch.

CLOSER TO FULLY INTEGRATED GLOBAL OPERATIONS

The SK Group companies have focused on developing new treatments for CNS disorders since 1993, when they started research and development activities as SK Group's drug development business unit. They were successful in discovering and out-licensing a late-stage compound, solriamfetol, to Jazz Pharmaceuticals PLC, which received FDA approval earlier this year.

"Now, with the FDA approval of Xcopri, we are advancing our goal of becoming a fully-integrated global pharmaceutical company that can discover, develop and deliver new treatment options in CNS independently without partnering or licensing-out. We look forward to the launch of Xcopri and powering the next phase of our transformation," the CEO said.

SK Biopharmaceuticals has established physical R&D and commercial organizations in the US to progress a broad range of innovative CNS therapies from its pipeline, both in partnerships and alone.

"We are continuing to expand our US operations with a focus on our marketing and sales force, and we also plan to begin offering a patient support program at the time of launch," Cho said. "While SK Life Science is focused on the commercialization of Xcopri in the US, we've also entered an exclusive licensing agreement with Arvelle Therapeutics GmbH to commercialize Xcopri in Europe. *(Also see "Deal Watch: Roivant Spins Out Arvelle, Licenses Epilepsy Candidate From SK Biopharma" - Scrip, 15 Feb, 2019.)* We are also preparing to commercialize Xcopri in Asia including Korea."

CONVINCING CLINICAL RESULTS

The US approval was based on results from two global, placebo-controlled studies and a global open-label safety study that enrolled adults with uncontrolled partial-onset seizures, taking one to three concomitant anti-epileptic drug (AEDs). In the randomized studies (Study 013 and Study 017), Xcopri demonstrated significant reductions in seizure frequency compared to placebo at all doses studied.

"This is important because over the past two decades, overall treatment outcomes for people with epilepsy have not significantly changed, and many patients continue to have uncontrolled seizures. We're hopeful that Xcopri will be able to change this reality for some patients," the CEO said.

About three million adults live with epilepsy in the US and according to the Centers for Disease Control and Prevention, nearly 60% reported having seizures, even if they took an AED, said Beth Lewin Dean, CEO of Citizens United for Research in Epilepsy (CURE). "There is an urgent need to advance research and introduce new treatment options. The FDA approval of Xcopri for the treatment of partial-onset seizures is a welcome option for the epilepsy community."

In Study 013, which included a six-week titration phase followed by a six-week maintenance phase, a statistically significant 56% reduction in median seizure frequency was seen with Xcopri 200mg/day (n=113) versus a 22% reduction with placebo (n=108). In Study 017, which included a six-week titration phase followed by a 12-week maintenance phase, patients randomized to Xcopri 100mg/day (n=108), 200mg/day (n=109) or 400mg/day (n=111) had statistically significant 36%, 55% and 55% reductions in median seizure frequency, respectively, versus a 24% reduction with placebo (n=106).

During the maintenance phase of Study 013, a post-hoc analysis showed that 28% of patients receiving Xcopri had zero seizures, compared with 9% of placebo patients. During the maintenance phase of Study 017, 4% of patients in the Xcopri 100mg/day group, 11% of patients in the Xcopri 200mg/day group, 21% of patients in the Xcopri 400 mg/day group and 1% of patients in the placebo group reported zero seizures.

Serious reactions associated with Xcopri included drug reaction with eosinophilia and systemic symptoms (DRESS), QT shortening, suicidal behavior and ideation, and neurological adverse reactions. The most common (≥10% and greater than with placebo) treatment-emergent adverse events associated with Xcopri include somnolence (sleepiness), dizziness, fatigue, diplopia (double vision) and headache.

The long-term safety of Xcopri has been evaluated in ongoing open-label extensions of the randomized studies and the open-label safety study. Additional clinical trials are investigating the drug in other seizure types.

ACCESS PROGRAM

"The approval of Xcopri will provide clinicians with an effective medication for our patients who are continuing to have focal (partial-onset) seizures," said Michael Sperling, Professor of Neurology and Director of the Jefferson Comprehensive Epilepsy Center at the Vickie and Jack Farber Institute for Neuroscience – Jefferson Health in Philadelphia, and an investigator in the Xcopri clinical development program.

"It is very encouraging to see that patients receiving Xcopri saw significant reductions in frequency of seizures, with some even achieving zero seizures."

SK Life Science said it is committed to supporting patients taking Xcopri and will introduce a new access program to help patients get started and stay on track with their medicine. Xcopri should be initiated at 12.5mg once-daily and titrated every two weeks and will be available in six tablet strengths for once-daily dosing: 12.5mg, 25mg, 50mg, 100mg, 150mg and 200mg. Xcopri can also be combined with other AEDs or used alone.

While the precise mechanism by which cenobamate exerts its therapeutic effect is unknown, the molecule is believed to reduce repetitive neuronal firing by inhibiting voltage-gated sodium currents. It is also a positive allosteric modulator of the γ-aminobutyric acid (GABAA) ion channel.

SK Biopharmaceuticals' pipeline currently includes eight compounds in development for the treatment of CNS disorders including epilepsy, Lennox-Gastaut syndrome and attention-deficit/hyperactivity disorder. All eight molecules were discovered in-house.

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FDA Approval For Novartis's Sickle Cell Treatment Adakveo

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The US Food and Drug Administration approved on 15 November Novartis's Adakveo, a new treatment to reduce vaso-occlusive crises (VOCs), or pain crises in sickle cell disease.

Adakveo (crizanlizumab) is now licensed for adult and pediatric patients aged 16 years and older with sickle cell disease (SCD),and is one of a wave of new treatments for the condition.

Novartis confirmed that the drug would be priced between $84,852 and $113,136 per year for most US patients.

Around 100,000 people in the US have sickle cell disease, and people of African ancestry represent 90% of the population with sickle cell disease in the country, although it is also present in Hispanic, south Asian, southern European, and middle eastern populations as well.

Adakveo was approved based on data from the SUSTAIN trial, which showed Adakveo reduced the annual rate of sickle cell pain crises by 45% compared to placebo (1.63 vs 2.98) and the annual rate of days hospitalized (4 vs 6.87) in a 52-week study.

Adakveo is a monoclonal antibody that binds to the P-selectin protein, a major driver of the vaso-occlusive process, on the surface of platelets and endothelial cells in the blood vessels.

The primary efficacy outcome was the annual rate of VOCs leading to a healthcare visit, defined as an acute episode of pain with no cause other than a vaso-occlusive event that required a medical facility visit and treatment with oral or parenteral opioids, or parenteral NSAIDs.

Key secondary and other efficacy endpoints include annual rate of days hospitalized, time to first VOC leading to healthcare visit, and number of patients that did not experience a VOC.

AHEAD OF VOXELOTOR

Adakveo is not the first new SCD treatment in recent years – that claim went to Emmaus's Endari (L-glutamine), launched in 2018. That made it the first new treatment for SCD in 20 years - however its sales have been slow to build, and is unlikely to pose a major challenge to Novartis.

> The timing of the approval is a coup for Novartis, allowing it to reach the market ahead of Global Blood Therapeutics.

The timing of the approval is a coup for Novartis, allowing it to reach the market ahead of Global Blood Therapeutics (GBT) which also has its candidate voxelotor awaiting US approval.

Analysts predict Adakveo will hit peak annual sales in excess of $1bn. Meanwhile voxelotor, a once daily oral treatment, is expected to gain FDA approval by 26 February 2020 or earlier, and is expected to reach similar revenues. Abrams is the chair of the oversight committee for the American Society of Hematology's Research Collaborative Clinical Trials Network on Sickle Cell Disease, an initiative started by ASH last year to accelerate treatments and cures. The goal is to connect patients to clinical trial sponsors and facilitate faster clinical trial education. The therapy area is one that has faced clinical trial hurdles, partly because of the patient demographic, which has a higher level of mistrust of the medical community and drug companies and unique socio-economic challenges.

The current standard treatment for SCD is hydroxyurea, a daily oral medication, but compliance levels are estimated to be around 50%.

Adakveo is administered once a month by intravenous infusion, and Novartis hopes to build its case for the treatment around its efficacy, although it has not yet produced data comparing its drug to standard therapy.

Drugs Advancing For Sickle Cell Disease

A look at some of the drugs in mid- to late-stage development for the rare inherited blood disorder.

DRUG MAKER	DRUG	MECHANISM OF ACTION	DEVELOPMENT STATUS
Novartis	Crizanlizumab	P-selectin antibody	Approved
Global Blood Therapeutics	Voxelotor	Hemoglobin polymerization inhibitor	Filed
Micelle Biopharma	Docosahexaenoic acid	Unspecified	Phase III
AstraZeneca	Ticagrelor	P2Y12 receptor antagonist	Phase III
Roivant	RVT-1801	Non-viral gene therapy	Phase II
Imara	IMR-687	PDE9 inhibitor	Phase II
Cyclerion	Olinciguat	Guanylate cyclase stimulators	Phase II
Sanofi	BIVV-003	ZFN gene editing	Phase I/II
CRISPR/Vertex	CTX-001	CRISPR/Cas9 gene-edited stem cell therapy	Phase I/II
bluebird bio	Lentiglobin	Gene therapy	Phase I/II

Sources: Datamonitor Healthcare and company filings

Adakveo and voxelotor have different mechanisms of action and address different issues, which suggest both could establish new niches in the market.

GBT's voxelotor targets the polymerization of the sickle hemoglobin, a fundamental mechanism of the disease, and the company believes it can eventually demonstrate that this will reduce incidence of stroke, organ damage and pain crises.

However GBT's Phase III Hope study's primary endpoints were hemolysis (destruction of red blood cells) and hemaglobin levels, which do not yet challenge Novartis's focus on the more clinically meaningful VOCs.

OTHER COMPETITORS

There are numerous other companies looking to enter the market, including AstraZeneca and Micelle Biopharma, which both have candidates in Phase III.

Also in the pipeline are gene therapies which could cure patients of the condition. These include bluebird's LentiGlobin gene therapy for sickle cell disease and CRISPR Therapeutics and Vertex's CTX001, which are both in Phase I/II studies.

Adakveo is Novartis' sixth FDA approval this year, likely to be the highest tally of any big pharma company in 2019. Its other approvals were Beovu, Piqray, Zolgensma, Mayzent and Egaten.

By far the greatest burden of sickle cell disease is in Africa, and Novartis has undertaken a major program to address the current lack of basic treatment available to hundreds of thousands of patients on the continent.

Novartis has delivered more than 20,000 hydroxyurea treatments to Ghana, with plans to deliver a total of 60,000 treatments by the end of the year. It is also developing a child-friendly formulation of hydroxyurea and will carry out two clinical trials with Adakveo in Ghana and Kenya, which are expected to start in 2020.

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After US Approval, BeiGene Set To Gain Sixth PD-1 Green Light In China

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The recent US approval of BeiGene Ltd.'s BTK inhibitor Brukinsa (zanubrutinib; BGB-3111) for mantle cell lymphoma signaled the arrival of a new era when "Made in China" pharma innovation is able to take on the world, declared an executive for the company.

The clearance, hailed as the first ever for a novel oncology drug in the US for a Chinese drug firm and also BeiGene's first ever approval anywhere, has excited many in the pharma industry at a time when innovation is seen as increasingly vital to a company's continued growth.

"We believe that nothing is enough to say about this approval," said BeiGene China general manager Xiaobin Wu in a press briefing, quoted by local Chinese media. The approval indicates that innovative new drugs are now following China's leading positions in manufacturing and information technology to take their place on the world stage.

The FDA approval, for second-line use in adults, was based on data showing efficacy in terms of tumor shrinkage. "Clinical trials showed that 84% of patients saw tumor shrinkage with this therapy. For patients whose disease relapses or becomes refractory, secondary therapies may be successful in providing another remission, and today's approval will provide patients with another treatment option." said the US agency in a statement.

Notably, the approval is based on a multi-center study conducted in 86 Chinese patients, which showed 84% had tumor shrinkage with a median duration of response (time between initial response to therapy and subsequent disease progression or relapse) of 19.5 months, noted the agency.

Additionally, a Phase I study conducted in Australia showed efficacy to be similar across Chinese and Caucasian patients, noted BeiGene.

PRICING, OTHER INDICATIONS

The Beijing firm plans to supply the BTK inhibitor to the US market through its contract manufacturing partner Catalent in Kansas City, MO. Wu said the US market launch for Brukinsa is expected in the coming weeks and that the wholesale acquisition price of a 30-day supply would be $12,935.

In China, BeiGene is awaiting the approval of zanubrutinib in two new drug applications that are under priority review, one in relapsed/refractory (R/R) mantle cell lymphoma (MCL) and the other in R/R chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL).

"We expect to receive approval in China for the treatment of patients with R/R MCL and R/R CLL/SLL in the first half of 2020. BeiGene is also planning to file a supplemental new drug application of Brukinsa in China for WM [Waldenstrom's macroglobulinemia] in the first half of 2020," a company spokesperson told *Scrip*.

The molecule joins AbbVie Inc.'s Imbruvica (ibrutinib) as a second-line BTK inhibitor and this drug is already approved for adult patients with chronic CLL or SLL.

SIXTH PD-1 COMING

The breakthrough FDA approval came ahead of a pending Chinese approval for another novel BeiGene drug, the PD-1 inhibitor tislelizumab. Records show that a technical review of this by China's Center for Drug Evaluation (CDE) has already been completed and that a formal final approval is now pending from the National Medical Products Administration (NMPA).

Upon approval, tislelizumab will join Merck & Co. Inc.'s Keytruda (prembrolizumab), Ono Pharmaceutical Co. Ltd./Bristol-Myers Squibb Co.'s Opdivo (nivolumab), and three anti-PD-1s from domestic developers Junshi Pharma (Tuoyi (toripalimab)), Innovent Biologics Inc. (Tyvyt (xintilimab)) and Jiangsu Hengrui Medicine Co. Ltd. (SHR1210) to become

the sixth such immuno-oncology drug to be approved in China. *(Also see "Fifth PD-1, Zavicefta, Novel Psoriasis Ointment Among Latest China Approvals" - Pink Sheet, 4 Jun, 2019.)*

Others including AstraZeneca PLC's Imfinzi (durvalumab) are also in late development in the country.

Although China is potentially the largest market globally for cancer therapies given its huge population, the intense development activity around PD-1s has some wondering if there will be enough room for each to grow and compete, given how low some domestic firms are willing to price.

So far, Junshi has priced its PD-1 at the lowest level, roughly CNY100,000 ($14,300) annually after considering patent assistance programs, while both Opdivo and Keytruda are priced in the range of CNY200,000 to CNY300,000. Innovent's product is priced at the middle, at CNY170,000.

Ongoing national drug pricing negotiations are expected to cover high-priced immuno-oncology drugs for the first time ever and it has been reported that Keytruda's price may be drastically lowered in order to get the coverage, while Opdivo may be out of the process. Both Junshi and Innovent have reportedly lowered their prices slightly to receive coverage while Hengrui, which recently gained approval for its product, has yet enter the negotiations.

Anti-PD-1 Agents Approved Or Pending Approval in China

COMPANY	PRODUCT	INDICATIONS	APPROVAL DATE
BMS	Opdivo	Non-small cell lung cancer (NSCLC)	2018/06
Merck & Co	Keytruda	Melanoma, NSCLC	2018/07, 2019/04
Junshi	Tuoyi	melanoma	2018/12
Innovent Bio	Tyvyt	Hodgkin's lymphoma	2018/12
Hengrui	Iruituo	Hodgkin's lymphoma	2019/05
BeiGene	tislelizumab	Hodgkin's lymphoma	pending

(Source: Pink Sheet, NMPA)

INDICATIONS THE MAIN BATTLEGROUND?

There are an estimated further 18 PD-1 inhibitors in ongoing clinical trials in China, for which a total of 156 studies are underway, noted Haitong Securities, citing CDE data.

The development activity is also highly concentrated on a few cancer types - for instance, 16 of the 18 molecules are being studied in lung cancer, followed by gastric cancer, hepatic cell carcinoma and lymphoma. The developers include biosimilar specialist Shanghai Henlius Biotech Inc., Akeso Pharmaceuticals, AlphaMab and CStone Pharmaceuticals Co. Ltd., the so-called second-tier PD-1 companies.

But many will face fierce competition despite efforts to differentiate through indications or combination strategies. Akeso for one is hoping its PD-1/CTLA-4 molecule can be easily used in combination with other chemotherapies. *(Also see "China's Akeso Bets On IO Antibody Combo With First US IND" - Scrip, 3 May, 2019.)*

Only a few of these second-tier firms are likely to make it to market, predicted analysts from one securities firm.

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AstraZeneca's Calquence Catches Up With Imbruvica's CLL Claim

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FDA's broad approval for AstraZeneca PLC PLC's Calquence (acalabrutinib) for chronic lymphocytic leukemia and small lymphocytic leukemia for any line of treatment gives the company the best shot possible at gaining share from AbbVie Inc./Johnson & Johnson's market leading Imbruvica (ibrutinib).

The US Food & Drug Administration cleared AstraZeneca's BTK inhibitor for the CLL/SLL indication on 21 November, a review expedited because it came under the agency's Project Orbis to collaborate on oncology reviews with international regulators. Calquence was originally approved for second-line treatment of mantle cell lymphoma (MCL), an aggressive type of non-Hodgkin lymphoma striking about 3,300 in the US each year. *(Also see "AstraZeneca's Calquence Steps Into Blood Cancer Ring With Mighty Imbruvica" - Scrip, 31 Oct, 2017.)*

The leukemia indication brings Calquence into direct competition with Imbruvica, which is indicated for CLL/SLL, MCL, Waldenstrom's macroglobulinemia, marginal zone lymphoma and graft versus host disease and brought in approximately $1.3bn in sales in the third quarter. CLL is the most common form of leukemia, diagnosed in 21,000 people each year, according to the US National Institutes of Health.

AstraZeneca has seen some off-label use of Calquence in CLL, following the release of the ASCEND trial showing a progression-free survival benefit in relapsed or refractory chronic lymphocytic leukemia (CLL) and its listing in the National Comprehensive Cancer Network compendium – but that was limited to second-line use. SC125177 The company reported in its third quarter earnings release that it was seeing equal proportions of Calquence prescriptions coming from "non-promoted" use in second-line CLL as from MCL. Calquence brought AstraZeneca sales of $108m in Q3, up from $38m in Q3 2018.

The FDA approved the CLL claim based on the ASCEND trial and a second Phase III study, ELEVATE TN. In that trial, Calquence combined with obinutuzumab and as monotherapy reduced the risk of disease progression or death by 90% and 80%, respectively, AZ reported. *(Also see "AZ's Calquence Hits Endpoint In Second CLL Phase III Study" - Scrip, 6 Jun, 2019.)*

"In the ELEVATE-TN and ASCEND trials comparing Calquence to commonly used treatment regimens, Calquence demonstrated a clinically meaningful improvement in progression-free survival in patients across multiple settings, while maintaining its favorable tolerability and safety profile," ELEVATE-TN lead author Jeff Sharman, medical director of hematology research for the US Oncology Network, said in AZ's statement on the approval. He noted that "tolerability remains an issue in the current treatment landscape of chronic lymphocytic leukemia, which may require ongoing therapy for many years."

COMPARATIVE DATA NEEDED

Imbruvica, the BTK inhibitor launched through Johnson & Johnson's partnership with AbbVie, currently leads the market. BGC analyst Eric Le Berrigaud said that Calquence's ultimate position versus its competitor depends on the results of a comparative trial, expected in the next two years.

"Physicians are used to Imbruvica and we do not expect a rapid and massive shift towards Calquence, but we do see it progressively taking market share from the leader," Berrigaud said in a 22 November note. "It is the head-to-head trial, which may report at the very end of 2020 or early in 2021, that will determine if Calquence can become new drug of choice in this setting."

Calquence could find a competitive edge over Imbruvica in its safety profile. Both drug labels warn of possible cardiac effects, bleeding, cytopenias, and secondary malignancies. But only Imbruvica warns of potential embryo-fetal toxicity and tumor lysis syndrome.

The initial approval in the less-common MCL gave AstraZeneca a quicker path to market, allowing it to establish the drug and position it for off-label uptake as the CLL trials reported. The new approval completes a strategy that AstraZeneca started several years ago, and will be the real test of its push into hematology. *(Also see "AstraZeneca Looks To Deliver On Its Promises In Oncology" - Scrip, 26 Jun, 2018.)*

Under CEO Pascal Soriot, AstraZeneca has built out its cancer program, seeking more indications and bigger markets for its existing cancer drugs as it worked to become an oncology leader. *(Also see "AstraZeneca Looks To Deliver On Its Promises In Oncology" - Scrip, 26 Jun, 2018.)*

The move into cancer is well on its way to securing significant gains for the company, Leerink analyst Andrew Berens commented in a 22 November note initiating coverage. He predicted that by 2025, oncology will represent over half of AZ's revenues, with growth in overall revenue and other indicators.

"With this shift towards high margin, high growth oncology assets, we forecast improving fundamentals for the company," Beren said. He added that AZ's shift "allows a more focused specialty sales force to support the portfolio, resulting in more efficient SGA allocation, from 39% of sales in 2015 to 30% by 2025."

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Astellas Beats Rivals To Japan HIF-PHI Market As Roxadustat Launched

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Following an approval in September, Astellas Pharma Inc. has launched in Japan the novel oral anemia drug roxadustat, making it the first in the hypoxia-inducible factor prolyl hydroxylase inhibitor (HIF-PHI) class to reach the market in the country.

Roxadustat Launches First Salvo In Japan HIF-PHI Battle.

The first-in-class molecule, discovered by and licensed from FibroGen Inc., was listed in the national health insurance system's reimbursement tariff on 19 November and launched the following day, as Evrenzo, for the treatment of renal anemia associated with chronic kidney disease (CKD) in patients on dialysis.

The launch positions Astellas well in a potentially large market. There are around 13 million people with chronic advanced CKD in Japan, with about 10% of those with Stage 3-5 CKD also having renal anemia, a situation that increases the rate of progression to renal failure and the likelihood of cardiovascular complications.

The number of patients on dialysis in Japan is increasing steadily, exceeding 330,000 in 2017.

Intravenously administered erythropoiesis-stimulating agents (ESAs) are currently the standard of care for anemia in CKD, and the HIF-PHIs will provide a new and more convenient once-daily oral option.

Datamonitor Healthcare is currently predicting sales of $564m for roxadustat in Japan in the 2024 and says that it "has the potential to become the new standard of care for anemia in CKD, on account of its superior safety, cost-efficiency, and reduced need for iron supplements compared to ESAs."

But multiple rivals are snapping at Evrenzo's heels, the closest of which look set to reach the market potentially within the next year. The nearest of these appears to be Mitsubishi Tanabe Pharma Corp.'s vadadustat (MT-6548; licensed from Akebia

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.

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

PIPELINE WATCH, 15–21 NOVEMBER 2019

Event Type	Lead Company/Partner	Drug Name	Indication	Comments	Change To LOA (%)	LOA (%)
Phase III Updated Results	AVEO Pharmaceuticals, Inc.	Tivopath (tivozanib)	Renal Cell Cancer, Refractory	TIVO-3; Improved PFS	0	27
Phase III Updated Results	Resverlogix Corporation	apabetalone	Acute Coronary Syndrome	BETonMACE; Encouraging Results	0	24
Phase III Updated Results	The Medicines Company/Alnylam	inclisiran	Atherosclerotic Cardiovascular Disease	ORION-10; Met Primary, Secondary Endpoints	0	60
Phase III Updated Results	The Medicines Company/Alnylam	inclisiran	Familial Hypercholesterolemia	ORION-9; Durable Responses	2	62
Phase III Top-Line Results	UCB SA	bimekizumab	Psoriasis	BE READY; Met Primary, Secondary Endpoints	4	67
Phase III Top-Line Results	Mezzion Pharma Co. Ltd.	udenafil	Single Ventricle Heart Disease	FUEL; Exercise Capacity Improved	0	47
Phase III Top-Line Results	Merck & Co/Bayer	vericiguat	Worsening Congestive Heart Failure	VICTORIA; Met Primary Endpoint	5	53
Phase III Top-Line Results	Diffusion Pharmaceuticals, Inc.	trans sodium crocetinate	Glioblastoma	INTACT; Encouraging Efficacy Signal	0	35
Phase III Top-Line Results	Myovant Sciences Ltd.	relugolix	Prostate Cancer	HERO; Met Primary, Secondary Endpoints	8	45
Phase III Top-Line Results	Sanofi	sutimlimab (BIVV009)	Cold Agglutinin Disease	CARDINAL; Met Primary Endpoint	0	60
Phase III Trial Initiation	Sierra Oncology/Gilead	momelotinib	Myelofibrosis	MOMENTUM; In 180 Patients	25	35
Phase III Trial Initiation	Tonix Pharmaceuticals	Tonmya (cyclobenzaprine)	Fibromyalgia	RELIEF; In 470 Patients	0	37

Source: Biomedtracker | Informa, 2019

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Therapeutics Inc.), for which the first approval filing globally was made in Japan in July. *(Also see "Vadadustat Emerges As Japan HIF-PHI Contender With First Filing Globally " - Scrip, 23 Jul, 2019.)*

Evrenzo has been launched in 20mg, 50mg and 100mg tablet formulations, reimbursed at JPY387.40 ($3.58), JPY819.20 and JPY1,443.50 per tablet respectively. For adult patients not receiving ESAs, the usual starting dosage is 50mg three times weekly. Thereafter, this should be adjusted according to the patient's condition but not exceeding 3.0mg/kg. In adult patients switching from ESAs, the usual starting dose is 70mg or 100mg three times weekly, adjusted according to the patient's condition but not exceeding 3.0mg/kg.

Outside Japan, Astellas's alliance with FibroGen extends to other markets including the EU, CIS and Middle East and South Africa. FibroGen is partnering with AstraZeneca PLC for China, the US and other selected markets and roxadustat received its first approval globally in China (for use in both dialysis-dependent and non-dependent CKD patients) earlier this year.

Multiple rivals are snapping at Evrenzo's heels.

JAPAN RIVALS

Elsewhere in the HIF-PHI sector in Japan and in addition to vadadustat, Japan Tobacco Inc. and commercial subsidiary Torii Pharmaceutical Co. Ltd. have said they are planning a Japanese filing for their candidate enarodustat following positive topline Phase III results, but the exact timing of this remains unclear.

GlaxoSmithKline PLC/Kyowa Hakko Kirin Co. Ltd.'s daprodustat is also in Phase III in Japan, with an approval application expected sometime this year.

Astellas is also conducting Phase III trials in Japan with roxadustat for the additional indication of renal anemia in patients not receiving dialysis, an approval that could significantly expand the potential market for the product. AstraZeneca and FibroGen recently reported positive data in this set of patients.

Globally, roxadustat is also in Phase III in the US and Europe and in Phase II/III in China for anemia associated with myelodysplastic syndromes and Phase II development is underway for chemotherapy-induced anemia.

Globally in all indications, analysts have predicted that expanded use in these settings could eventually generate blockbuster sales of $1.4bn for the molecule by 2024.

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APPOINTMENTS

Executive	To Company	New Role	From Company	Previous Role	Effective Date
George O. Elston	EyePoint Pharmaceuticals Inc	Chief Financial Officer and Head, Corporate Development	Enzyvant Therapeutics	Chief Financial Officer and Head, Corporate Development	14-Nov-19
Cheryl Keech	ILiAD Biotechnologies llc	Chief Medical Officer and Executive Vice President, Clinical Research	PPD	Executive Medical Director	19-Nov-19
Catherine Nester	Inozyme Pharma	Vice President, Physician and Patient Strategies	Incyte Pharmaceuticals	Senior Oncology Business Director	14-Nov-19
Pedro Huertas	Inozyme Pharma	Chief Medical Officer	Sentien Pharmaceuticals	Chief Medical Officer	14-Nov-19
Jason Tardio	Ovid Therapeutics Inc	Chief Commercial Officer	Novartis	Vice President and Head, Multiple Sclerosis Franchise	18-Nov-19
Badrul Chowdhury	Savara Inc	Chief Medical Officer	AstraZeneca	Senior Vice President, Chief Physician-Scientist, Respiratory, Inflammation and Autoimmunity	18-Nov-19
Brigitte Robertson	Yumanity Therapeutics	Chief Medical Officer	Takeda	Therapeutic Area Head, Neuroscience Global Clinical Development	18-Nov-19

Click here for all appointments: https://bit.ly/2oHWRYn

Source: Medtrack | Informa, 2019

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