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Industry update for May 2019

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This industry update features a round-up of pharmaceutical news in May 2019 based on press releases and websites. The month was characterized by the achievement of significant milestones in gene therapy. The biggest of these was the US FDA's approval of Zolgensma[®]. This medicine sums up the promise and price of genetic medicine. On one hand the clinical results show Zolgensma can dramatically improve the prognosis for infants with spinal muscular atrophy after just one administration, while on the other, it has been priced at around US\$2.1 million. With more such therapies likely to reach the market, the debate on Zolgensma goes beyond cost, to overall affordability, the true meaning of cost-effectiveness and how to reward companies for effective, innovative medicines.

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Acquisitions

Merck bolsters oncology portfolio with Peloton purchase

Merck (NJ, USA) (also known as MSD) and Peloton Therapeutics, Inc. (TX, USA) made public on 21 May that they had signed an agreement which will result in the purchase of Peloton via a Merck subsidiary [1]. The privately-owned Peloton is developing novel, orally-bioavailable small molecules targeting the transcription factor, hypoxia-inducible factor-2 α . This factor is abnormally high in 90% of cases of clear cell renal cell carcinoma (RCC) [2], the most common cause of kidney cancer. The high levels are a direct result of the von Hippel Lindau tumor suppressor being inactivated. Peloton's lead candidate, PT2977, is currently being evaluated in a Phase II study in von Hippel Lindau disease patients and in combination with cabozantinib, a VEGFR inhibitor, in a Phase II trial involving subjects suffering from metastatic kidney cancer. It is also being tested in metastatic RCC in a Phase I/II dose-escalation and dose-expansion study in patients with metastatic RCC and, as part of an expansion arm, in patients suffering from glioblastoma multiforme. In the Phase I/II study PT2977 has been shown to have a favorable safety profile and there are indications of antitumor activity when administered as monotherapy in advanced or metastatic RCC. The firm also has a second hypoxia-inducible factor-2 α inhibitor, PT2567, which it is initially assessing in pulmonary arterial hypertension [1,2].

The deal is worth \$1.05 billion dollars upfront in cash in return for all remaining Peloton shares. Shareholders may also qualify for a further \$1.15 billion if regulatory and sales milestones are met for selected candidates. The deal comes shortly after Peloton, which had intended to go public, had priced its shares at \$15–17 per share in preparation for its initial public offering. As \$17 per share would value the company around \$900 million [3], the agreement with Merck represents a significantly better return for investors both in terms of upfront cash, and opportunity for future revenue if the agreed milestones are achieved.

Spin-outs

Nektar launches Inheris Biopharma, Inc.

On 23 May, Nektar Therapeutics (CA, USA) launched its new subsidiary, Inheris Biopharma, Inc., focused on Nektar's CNS portfolio [4,5]. In particular, it will be responsible for the launch and commercialization of NKTR-181, Nektar's first-in-class, investigational opioid molecule. The new subsidiary, head-quartered in New Jersey, USA, will also be in charge of the development of several preclinical compounds in Nektar's CNS pipeline.

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NKTR-181 is a potent, selective, long-acting mu-opioid agonist which has been clinically evaluated for the treatment of moderate to severe chronic low back pain. It is designed to have poor permeability into brain tissue, reducing its rate of entry. This, in turn, blunts the dopamine release that is responsible for the euphoria associated with the administration of opiates and other opioid drugs. In clinical studies NKTR-181 has been shown to reduce CNS side effects, such as euphoria and sedation, which are associated with this class of compound, while providing pain relief over a 12-h period.

Against the background of the current opioid crisis in USA, the US FDA has given NKTR-181 Fast Track designation and a Prescription Drug User Fee Act target action date of 29 August 2019. With regulatory approval potentially imminent, the creation of Inheris will enable greater focus on the future commercialization of NKTR-181, while allowing Nektar to concentrate on its immunology and immuno-oncology assets.

Licensing & collaboration agreements

Vertex collaborates with Kymera on targeted protein degradation

Vertex Pharmaceuticals Inc. (MA, USA) and Kymera Therapeutics Inc. (MA, USA) announced on 15 May that they will collaborate over a 4-year period to research and develop small molecule protein degrader compounds with clinical promise, identified through Kymera's PegasusTM drug discovery platform [6]. The collaboration relates to the discovery of compounds to multiple targets.

The Pegasus system is an integrated degradation platform which exploits informatics-driven target identification, novel E3 ligases, in-house ternary predictive modelling capabilities and degradation tools to discover hetero bifunctional compounds capable of causing targeted disease-associated protein degradation [7]. The molecules identified using Pegasus promote protein degradation by harnessing the ubiquitin-proteasome system, which is the body's natural mechanism for protein degradation and recycling. It involves two main steps: covalent binding of the protein to ubiquitin which marks it for subsequent degradation by the 26S proteasome [8]. The first step requires activation of ubiquitin, a 76-amino acid protein, by ubiquitin-activating enzyme (E1), followed by transfer to ubiquitin conjugases (E2). Ubiquitin is conjugated to the protein targeted for degradation via an E3 ligase which forms a complex with both the substrate molecule and E2. Addition of further ubiquitin molecules to the first results flags the ubiquitinated protein for breakdown by the 26S proteasome. The protein degrader molecules found through Kymera's platform are designed to bind both to the target disease-related protein and a specific E3 ligase making the target susceptible to destruction by the ubiquitin-proteasome system.

As a result of the agreement, Kymera will receive \$70 million upfront, with Vertex taking an equity stake in the company [6]. Kymera will then carry out research into protein degraders to multiple targets with Vertex having the right to exclusively license clinical candidates against the designated targets once identified. In addition, to the upfront payment, the deal could be potentially worth over \$1 billion in milestone payments, if Kymera successful achieves certain research, development, regulatory and commercial goals on up to six programs optioned as part of the collaboration. The deal also foresees Vertex paying tiered royalties on future net sales on any products commercialized.

Parvus & Genetech collaborate on autoimmune therapy development

In the middle of the month, Parvus Therapeutics (CA, USA) made public that it will work together with Genetech (CA, USA) as part of a global collaboration and license agreement to develop, manufacture and commercialize selected candidates in Parvus's novel NavacimTM pipeline for the therapy of inflammatory bowel disease, autoimmune liver diseases and celiac disease [9,10].

Navacims are based on the research of Pere Santamaria, a professor at the University of Calgary, Canada and founder and Chief Scientific Officer of Parvus. Navacims are disease-specific or tissue-specific and exploit an immunoregulatory mechanism which protects mammalian cells from being attacked by their own immune system. Navacims are surface-coated, nanoparticulate systems designed to present an autoimmune disease-relevant peptide-major histocompatibility complex to cognate T cell receptors on the T cells responsible for the autoimmune activity. The Navacim system enables the presentation of the complex to the target cells at a significantly higher density than found physiologically. The interaction of the disease-relevant Navacim triggers T-cell differentiation in response to prolonged assembly of T-cell receptor microclusters and associated cell signaling. As a result, disease-specific T effector cells are converted into disease-specific Type 1 regulatory cells which, in turn, undergo extensive systemic expansion. It is this large population of disease-specific Type 1 regulatory cells induced by the Navacim technology

which modulates the immune response to minimize the activity of polyclonal inflammatory cells involved in the autoimmune disease.

The Navacim technology offers the potential for specific, targeted, self-limiting modulation of the immune system as it requires autoimmune cells to be present, in order to exert its activity. The specificity of its activity has been demonstrated in preclinical disease models such as those for diabetes, multiple sclerosis, autoimmune liver disease and irritable bowel disease, where it has been shown to impact on the autoimmune response without affecting the ability of the model to withstand challenge by viruses, microbes and tumors.

The collaboration agreement foresees Parvus conducting preclinical and clinical development activities to Phase I, with Genentech, which is part of Roche (Basel, Switzerland), conducting the clinical program from Phase II onwards and taking responsibility for regulatory submissions and product commercialization [9].

The detailed terms of the agreement remain undisclosed. However, they include an upfront payment and milestone-based research, development and commercialization payments for each disease area within the collaboration. Parvus may also be entitled to remuneration for achieving certain milestones in other disease areas, plus royalties on net sales of products that arise from the collaboration.

Lilly licenses novel investigational analgesic from Centrexion

On 28 May, Eli Lilly and Company (IN, USA) announced that it had signed an exclusive, global licensing agreement with the Centrexion Therapeutics Corporation (MA, USA) for the Boston company's small molecule somatostatin receptor type 4 (SSTR4) agonist, CNTX-0290, which is being developed as a potential painkiller in chronic inflammatory, neuropathic and mixed pain conditions [11,12]. The molecule, which is currently being evaluated in a Phase I study, differs in its mode of action from traditional approaches for pain therapy such as opioid drugs, prostacyclins and steroids, in that it activates the somatostatin type 4 receptor. This receptor is found within the brain and spinal cord and has been found to modulate the analgesic effects of somatostatin, a growth hormone inhibitory peptide [13,14]. The activation of somatostatin receptor type 4 may offer a more effective pain relief strategy than existing medication options, which are not particularly effective in certain types of pain and may be accompanied by dose-limiting side effects and/or the potential for addiction.

The agreement includes an upfront payment of \$47.5 million to Centrexion. It also foresees Centrexion receiving up to \$575 million from Lilly contingent on the company achieving certain development and regulatory milestones. In addition, should CNTX-0290 reach the market, Centrexion will be eligible for up to \$375 million in potential sales milestones and tiered royalties, and the opportunity to co-promote the product with Lilly in USA in the future [11].

Boehringer-Ingelheim signs second deal with Gubra

Boehringer-Ingelheim (Ingelheim, Germany) and Gubra (Hørsholm, Denmark) issued a joint press release on 29 May that they plan to collaborate for the second time, with the new collaboration and licensing agreement focusing on the development of novel peptide poly-agonists for obesity and related conditions [15]. The first agreement, signed 2017, had the goal of identifying novel peptidic molecules capable of regulating food intake [16]. Gubra is a privately-owned research organization with proprietary early target and drug discovery programs and preclinical animal models in nonalcoholic steatohepatitis, obesity, diabetes and gastrointestinal diabetic complications [17]. The latter also forms the basis of the Danish company's contract research offering which, in addition to *in vivo* pharmacology, includes *ex vivo* assays, histology, stereology, RNA sequencing and bioinformatics.

Under the terms of the deal, Gubra will receive an upfront payment and be eligible for additional remuneration based on the successful achievement of development and commercialization milestones, with the total agreement being potentially worth €240 million to Gubra. In addition, if compounds resulting from the collaboration are commercialized, then it will benefit from a tiered royalty stream of up to double-digit figures on global net sales [15].

Funding

DeSiTech receives funding from the Bill & Melinda Gates Foundation

The Finnish drug delivery and development company, DeSiTech Ltd (Turku, Finland), announced on 21 May that it had received significant grant funding from the Bill & Melinda Gates Foundation [18]. The funding is targeted for the development of prolonged release injectable formulations for family planning and anti-HIV drugs for treatment of patients in low-and-middle income countries.

DelSiTech's biodegradable Silica Matrix technology enables encapsulated molecules to be released from the amorphous matrix through matrix erosion in a controlled manner over periods of 1 day to 1 year. The technology, which was developed at the University of Turku (Turku, Finland) and Åbo Akademi University (Turku, Finland), is manufactured by a sol-gel process involving the polymerization of alkoxysilanes, Si(OR). The resulting DelSiTech™ Silica matrix contains nanosized pores plus OH groups and water. Matrix erosion, and hence encapsulated molecule release, can be modified by altering the manufacturing parameters to change the number of hydroxyl groups and the specific surface area of the matrix. The technology is suitable for the encapsulation of small molecules, biologics and viral vectors [19].

Product approvals

Cyramza®'s fifth approval brings biomarker-driven therapy to hepatocellular cancer

Eli Lilly and Company (IN, USA) received good news on 13 May when the FDA approved a fifth indication for its Cyramza® product (ramucirumab injection, 10 mg/ml), the company's human VEGFR2 antagonist [20,21]. The new indication is for the second-line treatment of metastatic or advanced hepatocellular cancer (HCC) in patients with levels of the α -fetoprotein (AFP) equal to or in excess of 400 ng/ml, who have been previously been treated with the kinase inhibitor, sorafenib. AFP is a naturally occurring glycoprotein whose levels are elevated in HCC and in a number of other cancers. An AFP concentration of ≥ 400 ng/ml is thought to occur in around 40% of advanced HCC patients and has been shown to be associated with a poorer prognosis.

The effectiveness of Cyramza in the target group of patients was demonstrated in a multicenter, double-blind, placebo-controlled Phase III trial using overall survival as the primary end-point and progression-free survival as a secondary end-point.

Cyramza is also used in the treatment of gastric, non-small-cell lung and colorectal cancer and had sales of US \$821.4 million in 2018 [22]. The approval of the new indication will help expand these sales, as will the FDA's removal of the black box warning with respect to ramucirumab's serious potential side effects namely, increased risk of hemorrhage, including gastrointestinal bleeding, perforation of the gut and impaired wound healing. The removal of the black box warning, which draws specific attention to serious and life-threatening risks, was based on the latest safety data and occurred concurrently with approval of the new indication [20,21]. However, the labelling still contains warnings and precautions with respect to these possible ramucirumab-related adverse effects.

FDA approves novel gene therapy for spinal muscular atrophy in children

On 24 May, the FDA granted approval for Zolgensma® (onasemnogene abeparvovec-xioi), for the treatment of spinal muscular atrophy (SMA) in children under 2 years [23–25] with bi-allelic mutations in the *SMN1* gene, including those who are presymptomatic at diagnosis. In SMA, the *SMN1* gene, which encodes the survival motor neuron (SMN) protein, is mutated. The lack of functional SMN leads to motor neurons cell death, severe muscle weakness and paralysis. Infantile-onset SMA is the most serious and common subset of this rare, genetic condition with annually around 450–500 babies being affected by SMA in the US alone. The genetic condition manifests itself in children having difficulties in holding their head up, swallowing and breathing with the infants either dying or requiring permanent ventilation before the age of 2. These symptoms can be apparent at birth or develop later when the child is around 6 months old.

Zolgensma is an adeno-associated (AAV9) virus vector-based gene therapy. Zolgensma was developed by AveXis, Inc. (IL, USA) which is now part of Novartis (Basel, Switzerland) [25]. It is designed to deliver one copy of the human *SMN1* gene into the target motor neuron cells to replace the missing or defective gene. The suspension is dosed intravenously based on weight (1.1×10^{14} vector genomes per kg of body weight) with one infusion being sufficient to result in expression of the SMN protein in the pediatric patient's motor neuron cells, thus, improving the infant's muscle strength and chances of survival.

FDA approval for Zolgensma, which had been previously granted Fast Track, Breakthrough Therapy and Priority Review designations, was based on the results of one ongoing Phase III and one completed Phase II clinical study in 36 children suffering from infantile-onset SMA. In the ongoing Phase III treatment with Zolgensma has enabled 19 out of the 21 children enrolled to survive significantly longer than would have been predicted based on the standard prognosis for children with this condition, with 13 of these 19 having reached at least 14 months of age. In addition, the genetic replacement therapy resulted in the pediatric patients having significantly improved motor function [23,24]. The main side effects of therapy are elevated aminotransferases and vomiting and, as a result, liver

function tests are needed prior to administration and monitoring afterwards. The product carries a boxed warning with respect to the development of acute, serious liver injury.

In addition to its fast-tracked approval by the FDA, AveXis received a rare pediatric disease priority review voucher from the agency, which it can use to obtain priority review on another compound. Elsewhere, the product is also undergoing accelerated review by the EMA who previously granted it PRIME (PRiority MEDicines) designation, and also has accelerated Sakigake designation in Japan [23].

It has, however, not been all positive press for Zolgensma. The gene therapy product has been dubbed the most expensive drug in the world based on its US \$2.1 million price tag for one administration [26]. Its approval has stimulated debate about the affordability of genetic therapies, especially for public health care systems, and their value in terms of cost-effectiveness for both the individual patient and society as a whole.

Clinical trials

Phase III trial of Tocagen's targeted brain cancer therapy on track

On 21 May, Tocagen Inc. (CA, USA) made public the outcome of a scheduled interim analysis of data from a Phase III trial of its novel investigational Toca 511 and Toca FC targeted brain cancer therapy for the treatment of high grade glioma [27,28]. The Toca 511 and Toca FA is an injected gene therapy and oral small molecule combination which works in tandem to target the activity of the well-established oncology compound, 5-fluorouracil (5-FU), to tumor cells, while minimizing healthy cell damage.

Toca 511 (vocimagene amiretrorepvec), a retroviral replicating vector, delivers a gene for the enzyme, cytosine deaminase (CD) to the rapidly dividing cancer cells, with the result that they express this enzyme. As CD is derived from yeast, it is not present in human cells. Toca FC is an oral, prolonged-release formulation of a prodrug of 5-FU, 5-fluorocytosine, which is converted into 5-FU by CD. Release of 5-FU results in the death of the transfected cells plus neighboring cells within the tumor including immune-suppressive myeloid cells. Cell death triggers a chain of reactions, which stimulates the immune system to further attack the tumor [27,28].

The Phase III multicenter trial, involving 403 patients, is designed to evaluate Toca 511 and Toca FC in patients with recurrent, high-grade glioma who are undergoing resection versus the current standard of care. The study primarily assesses the impact of administration of Toca 511 and Toca FC on overall survival of these patients whose prognosis is typically poor. The scheduled interim analysis of the data generated so far by an Independent Data Monitoring Committee was positive with the recommendation being for the trial to continue in its current form [27].

Positive top-line results for valoctocogene roxaparvovec

At the end of the month, BioMarin Pharmaceutical Inc. (CA, USA) released positive summary data from its Phase III GENER8-1 clinical study of its gene therapy candidate, valoctocogene roxaparvovec, for the treatment of adults with severe hemophilia A [29]. This therapeutic candidate involves an AAV-factor VIII vector designed to deliver the clotting factor VIII gene which is mutated in patients with hemophilia. The gene therapy has been awarded Orphan Drug status from both the FDA and EMA for the treatment of this condition [29,30].

Valoctocogene roxaparvovec, as a treatment for severe hemophilia A, is being evaluated in a total of six studies including two Phase III trials, GENER8-1 and GENER8-2. The data released are from GENER8-1, an open-label, single arm study, which once recruitment is complete, will involve a total of 139 participants with residual factor VIII levels ≤ 1 IU/dl. It has been designed to evaluate superiority to the current standard of care using a dose of 6×10^{13} vg/kg valoctocogene roxaparvovec.

Data from a 20-patient cohort from GENER8-1 showed that as of 28 May, eight had achieved the preset goal of Factor VIII activity levels of 40 international units per deciliter (IU/dl), or more, at 23–26 weeks. In addition, at the cut-off point of the end April, 16 patients, who reached the 26-week time-point, had an estimated median annual bleed rate of zero and an estimated mean annual bleed rate of 1.5. This an 85% reduction in baseline levels where all patients were receiving prophylactic Factor VIII infusions. Treatment with valoctocogene roxaparvovec also resulted in an 84% decline in median annualized Factor VIII usage and a 94% reduction in mean FVIII usage annualized between week 5 and 26 and resulted a mean and median Factor VIII level of 36 (standard deviation [SD] = 28) IU/dl and 33 IU/dl in the 23–26 time-period, respectively [29].

Based on these positive results, Biomarin plan to meet with the FDA and the EMA to discuss the data and timing of the regulatory submissions. Valoctocogene roxaparvovec has Breakthrough Therapy designation from the FDA and Priority Medicines (PRIME) status from the EMA.

Patents

Hedgepath receives further protection for SUBA-Itraconazole

On 6 May, HedgePath Pharmaceuticals, Inc. (FL, USA) received good news from the U.S. Patent and Trademark Office (USPTO) with respect to the acceptance of 20 new claims pertaining to the use of itraconazole, formulated in its proprietary SUBA®–Itraconazole formulation, in the treatment of prostate cancer [31]. These claims relate to the oral administration of SUBA–Itraconazole for the therapy of nonmetastatic prostate cancer and metastatic castrate-resistant prostate cancer, including its administration together with the standard chemotherapy used in late-stage prostate cancer. The new patent also covers techniques for predicting and determining therapeutic success with itraconazole therapy based on prostate-specific antigen levels post-treatment.

This positive news was followed on 29 May with a Notice of Allowance from the USPTO for further protection (26 claims) regarding the product's use in lung cancer especially nonsquamous, non-small-cell lung cancer [32].

SUBA–Itraconazole is a solid dispersion of itraconazole first developed by Mayne Pharma (Salisbury, Australia) to improve the oral bioavailability of the regulatory-approved antifungal. It is licensed to Hedgepath [33]. The Florida company is repurposing itraconazole for the treatment of prostate and lung cancer based on the finding that it can interfere with the upregulation of the Hedgehog (Hh) regulatory pathway [34]. Upregulation of this pathway is thought to be involved in the development of resistance to androgen deprivation therapy in late-stage prostate cancer.

USPTO issues patent on novel intranasal anthrax vaccine

On 29 May, BlueWillow Biologics (MI, USA) announced that the USPTO had issued a patent protecting its intranasal NanoVax® anthrax vaccine [35]. This vaccine incorporates the company's novel oil-in-water nanoemulsion technology which is capable of stimulating both systemic and mucosal immunity when applied intranasally [35,36]. The patent entitled 'Compositions and methods for Bacillus anthracis vaccination' was issued to the University of Michigan (USA), on whose research the vaccine is based and is licensed exclusively to BlueWillow [37]. Work at the university demonstrated the vaccine's effectiveness after two intranasal doses in protecting mice and guinea-pigs to lethal challenge to anthrax [35].

The company is currently collaborating with Public Health England to develop an intra-nasal anthrax vaccine for the National Institute of Allergy and Infectious Diseases containing the Public Health England's recombinant protective (rPA) antigen and BlueWillow's Nanovax adjuvant with Phase I clinical studies anticipated to start this year [35].

Financial & competing interests disclosure

The author has no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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