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Therapeutic delivery: industry update covering June 2019

Iain Simpson^{*,1}

¹Director, Front End Innovation, Phillips Medisize, Cambridge, UK

*Author for correspondence: iain.simpson@phillipsmedisize.com

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Acquisitions, licensing deals & other commercial news

GSK completes consumer healthcare buyout

GlaxoSmithKline plc announced that it has completed the buyout of Novartis' stake in their consumer healthcare joint venture [1]. The venture was formed back in 2014 as part of a larger \$20 billion transaction between the two companies that saw Novartis take some therapeutic assets from GSK in return for transferring its vaccine business to GSK, also putting their consumer health assets into the joint ventures with the option for GSK to take full ownership of this at a later date. The purchase of Novartis' 36.5% stake, for a consideration of \$13 billion was then announced in March 2018 and has now completed.

Meanwhile, in a related transaction announced in December 2018, GSK and Pfizer Inc (NY, USA) agreed to combine their consumer health businesses to form a new world-leading consumer healthcare joint venture with annual sales of around \$13 billion and in which GSK will have a 68% controlling stake.

The combined business will have a leading position in several disease areas including in vitamin and mineral supplements, pain relief, respiratory, skin health, digestive health and therapeutic oral health. It will be the global leader in over the counter products with a market share of 7.3% with a leading position in most key markets including the US and China.

Having integrated the activities in the joint venture and made some divestments, the aim is to float the business off as a separate listed business in 3 years' time, leaving the rest of GSK as a focused prescription pharmaceutical company.

AbbVie to acquire Allergan

This month, a proposed deal was announced in which AbbVie (IL, USA) will acquire Allergan (Dublin, Ireland) in a deal worth \$63 billion [2]. With sales of Humira, the world's largest selling drug by value under threat from biosimilar entry in Europe and some other markets and accounting for well over 50% of AbbVie revenues in 2018, the need to diversify its business has been apparent ever since the business split from Abbott in 2011. Its attempt to acquire Shire was scuppered in 2014 by changes in US tax regulations and other smaller acquisitions have yet to reduce its dependence on Humira.

With a market value of around \$140 billion, this is a significant acquisition for AbbVie and will result in a business with globally competitive franchises in several areas including immunology, hematologic oncology, neuroscience, women's health, eye care and virology, medical aesthetics; the latter built upon Allergan's leading position in Botox treatment, for which the company is best known. The transaction is expected to close in early 2020, subject to regulatory approvals.

Amgen & the University of Washington's Institute for Protein Design announce a strategic research partnership in protein development

Amgen (CA, USA) and the Institute for Protein Design (IPD) announced a collaboration in the application of protein technology to the development of new medicines [3]. Initial funding has been provided by Amgen to support three research projects seeking to apply IPD's expertise and improve traditional protein-based medicine with the

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intention to expand the collaboration into the design of new proteins and to create approaches that can be broadly applied across a large suite of problems in the development of new medicines. David Baker, founder and director of IPD, noted that at present, protein engineering has tended to focus on modifying natural proteins but emerging technology now allows proteins to be of a custom design from first principles, in order to meet specific requirements for drugs and in other areas.

The IPD is a not-for-profit research center focused on the custom design of proteins to improve human health as well as to address challenges in energy, industry and technology. It was founded in 2012 as part of UW Medicine in Seattle.

Merck to acquire Tilos Therapeutics

Merck and Co (MA, USA) announced that it is to buy the privately held biopharmaceutical company, Tilos Therapeutics (MA, USA), in a deal with a potential value of up to \$773 million, including an upfront payment as well as contingent milestone payments [4].

Tilos is focused on the developing therapeutics for the treatment of cancer, fibrosis and autoimmune diseases through the targeting of the latent TGF- β complex. TGF- β is a cytokine that has tumor-suppressive mechanisms that cancer cells need to combat for survival. But significantly, it also modulates processes that cancer cells can potentially exploit for survival and proliferation such as cell invasion, regulation of immune response and microenvironment modification. TGF- β is secreted as a complex with two other polypeptides, latent TGF- β binding protein and latency-associated peptide (LAP) in many cell types, including macrophages. These complexes keep the TGF- β inert until it is activated by biochemical process. Tilos has focused on the potential of anti-LAP antibodies that can block the release of TGF- β and hence regulate its availability to promote tumor development and immune regulation. A benefit of anti-LAP antibodies is that they leave the TGF- β complexes intact, which means they can be designed to target pathological processes and still ensure that TGF- β can be utilized to support normal cellular functions.

Tilos was founded in 2016 and based on research from Galina Gabriely and Howard Weiner at the Brigham and Women's Hospital (MA, USA) and with funding from Boehringer Ingelheim Venture Fund and Partners Innovation Fund.

Updates on clinical research

Study confirms no safety or efficacy issues in switching to adalimumab biosimilar

With the approval in Europe of five biosimilars of adalimumab, the market is watching closely how this impacts sales on the innovator version, AbbVie's Humira, which is currently the world's most valuable drug by annual sales [5]. In the UK, the NHS has already indicated that it plans to start new patients on the biosimilars and to switch existing users from Humira within 12 months. But there have been concerns that the biosimilars are not identical to the innovator and that there could be risks such as immunogenicity, which might mean clinicians are reluctant to switch stable patients. But now data published by Sandoz (Holzkirchen, Germany, a Novartis subsidiary), one of the companies with an approved biosimilar of adalimumab, suggests there are no safety or efficacy-related issues in switching [6]. In a double-blind study involving 353 patients with a diagnosis of moderate to severe rheumatoid arthritis (RA), patients were initially treated with a fortnightly injection of either Humira or Hyrimoz (Sandoz' biosimilar). After 22 weeks, those on Humira were switched to Hyrimoz for the remaining 24 weeks of the study. The primary study end point was a change in Disease Activity Score-28 (a measure of severity of RA) from the baseline at week 12 in both references and Hyrimoz treatment arms. Secondary end points included measurement of laboratory markers of disease activity as well as measurement of safety, local tolerability and immunogenicity. The study demonstrated no impact on safety or immunogenicity associated with switching compared with the control group treated on Humira alone for the duration of the study. The study supported a review of more than 90 publications that concluded switching from reference biologics to biosimilars does not impact safety, efficacy or immunogenicity [7].

Clinical research suggests developmental drug icalimab (CFZ533) can improve longevity of transplanted organs

Novartis presented data at the American Transplant Congress [8,9] that demonstrated its investigational drug, icalimab (CFZ533), can improve the durability of transplanted kidneys and potentially the long-term outcomes for individuals receiving kidney transplants.

Preliminary results from an on-going multicenter, randomized control trial demonstrated noninferiority on a composite clinical end point for kidney transplant patients receiving iscalimab therapy, compared with those in the control arm treated with tacrolimus, an immunosuppressant commonly used to reduce organ rejection after transplant. Those in the experimental study arm also demonstrated improved renal function, reduced risk for new onset diabetes and similar safety compared with the control arm. The data demonstrated that three out of five iscalimab-treated transplant patients had normal kidney histology at least 1 year after transplant, compared with none of those treated with tacrolimus (N = 7).

Durability of implanted kidneys is a significant issue with less than half of the last 10 years and in the USA, more than 100,000 individuals are on a waiting list for a transplant and estimated 3.2 million individuals in the world are currently suffering with end-stage renal disease. The quality of transplanted organs is an issue, especially given the shortage of donors and it's estimated that more damaged organs may only have an implant life of 3 years or less, so means of preserving durability has a significant benefit.

The study, from which these preliminary results were presented (Cirrus I NCT03663335), is targeting recruitment of 325 patients with a target study completion date of 2025. It includes both patients who have just had a kidney transplant at the time of enrolment to the study as well as those who have had a transplant 6–24 months earlier.

CFZ533 is a novel monoclonal antibody that selectively blocks the CD40–CD40L interaction, an important pathway in generating an immune response. As well as being a promising treatment of organ rejection, it also has potential in treating a range of autoimmune diseases.

Intec Pharma report results for the treatment of Parkinson's disease with carbidopa/levodopa delivered using a smart pill

Treatment of patients with Parkinson's disease using levodopa can be very effective in managing disease symptoms, such as akinesia (loss of movement) and rigidity, caused by a loss of dopamine due to the death of neurons in the substantia nigra region of the brain. There is an On–Off Phenomenon for levodopa treatment, characterized by periods when it is effective (ON) followed times when its effect rapidly diminishes and akinesia occurs (OFF). However long-term levodopa use is also complicated by the appearance of dyskinesia (involuntary movement) in the ON periods. As the therapeutic window that avoids akinesia and dyskinesia narrows it makes it difficult to control and the duration of 'ON' states becomes shorter and the wearing 'OFF' happens sooner. The situation is complicated by the short (1.5 h) half-life of levodopa, which makes it difficult to maintain a consistent and effective dose. Levodopa is commonly administered with carbidopa to inhibit peripheral metabolism of Levodopa before it crosses the protective blood–brain barrier to enter the brain, where it can be transformed into dopamine.

The Accordion Pill (AP) [10] is a drug-delivery system being developed by Intec Pharma (Jerusalem, Israel) that uses biodegradable polymeric films, which are loaded with drugs and folded inside an oral capsule. On reaching the stomach, the AP capsule dissolves and the films are released so that they can unfold and be retained in the gastric region, where they can slowly release the drug providing a much longer and controlled delivery profile. The ability to control the drug release makes it an attractive solution to ensuring controlled dosing of carbidopa/levodopa (CD/LD).

Results published this month from a Phase II clinical study [11,12] in which CD/LD was administered to Parkinson's patients using the AP. The open-label, two-way randomized crossover study, evaluated multiple dose strengths of the pill given twice daily during part of the study and an active comparator given during the other part of the study. For the 18 patients who completed the trial, a reduction in mean daily OFF time by approximately 45% was observed compared with standard CD/LD treatment. Pharmacokinetic studies showed that CD/LD doses delivered by the AP (AP-CD/LD) demonstrated an increased stability of levodopa plasma concentrations than those for the standard treatment.

A Phase III clinical trial for the AP-CD/LD medication is already underway.

Regulatory news

Nucala™ (mepolizumab) gains US FDA approval for two new self-administration options

GlaxoSmithKline announced that the US FDA has approved two new delivery methods for Nucala™; an IL5 biologic indicated for the treatment of severe asthma [13]. The approval allows the drug to be administered at home by patients or caregivers every 4 weeks either by an autoinjector or prefilled syringe. This is the first time an anti-IL5

biologic has been approved for home use, giving healthcare professionals a choice as to how and where their patients receive treatment.

The approval was supported by data from two open-label, single-arm, Phase IIIa studies that demonstrated that patients were able to administer the drug successfully outside the clinic, utilizing either of the devices and showed a preference for this approach as opposed to attending a clinic. A further study showed no difference in pharmacokinetic and pharmacodynamic profiles for Nucala administered by this approach, compared with in-clinic administration of a lyophilic drug.

The convenience of being able to administer drugs at home is a major factor in improving medication adherence and is already the standard in other chronic diseases such as RA. Competition in the market for injectable drugs to treat severe or persistent asthma has been increasing, so this approval will provide a competitive advantage compared with other drugs that can only be provided in the clinic.

Roche's personalized medicine Rozlytrek® is approved in Japan for cancer treatment

Roche announced the approval of Rozlytrek® (entrectinib) in Japan for the treatment of *NTRK* fusion-positive advanced recurrent solid tumors [14]. As well as offering an effective treatment for a range of cancers, the significance of the approval is that it is claimed to be the first approval of a first tumor-agnostic medicine in Japan, a promising, emerging area in the evolution of cancer treatments.

Many current cancer treatments focus on the location in the body where the tumor originated. The significance of drugs such as Rozlytrek is that they provide tissue agnostic therapies with treatment based on a disease biomarker that can be associated with different tumors and tumor sites.

The process by which normal transition into cancerous cells is characterized is by changes at the cellular, genetic and epigenetic levels that result in abnormal cell division. In some situations, this can result in the dysregulation in signaling of receptor tyrosine kinases, which play an important role in a variety of cellular processes including growth, motility, differentiation and metabolism, triggering production of cancerous cells. When survival of the resulting tumors becomes dependent on signaling by this defective kinase pathway, targeted inhibition with small-molecule drugs creates a therapeutic route to their destruction, which is the mode of action for Rozlytrek.

Although <1% of patients with the more common cancer types have this genetic mutation, prevalence can be much higher in some rare cancers including salivary gland and some children's cancers, which can explain the effectiveness of the treatment seen in the reported studies.

Four clinical studies of Rozlytrek involving 54 participants showed a reduction in tumor size for 78% of patients with ROS1-positive and metastatic non-small-cell lung carcinoma (NSCLC) with complete remission for 5.9%. The duration of response ranged from approximately 2 months to more than 36 months. Tumor shrinkage persisted for at least 12 months in 55% of the 40 patients included in the analysis.

Reduction in tumor size was also observed in 57% of patients (N = 54) with *NTRK* gene fusion-positive, locally advanced or metastatic solid tumors, when treated with Rozlytrek. For approximately 60% of these responding patients, tumor shrinkage continued for 9 months or more. A total of 7.4% of the cohort showed total tumor elimination.

Although very effective in studies, there have been concerns that the effect might be lost long term, as cancer cells mutate and develop resistance. However, cancer treatment is becoming increasingly personalized with treatment being adjusted based on diagnostic testing, to meet the changing characteristics of the disease. As such it can, in many cases, be effective for chronic long-term rather than a short-term acute disease.

Bluebird Bio announces gain EU approval for gene therapy treatment; Zynteglo

Bluebird Bio Inc (MA, USA) announced that it has received approval in Euro for the gene therapy treatment, Zynteglo, for the treatment of transfusion-dependent β -thalassemia, a severe genetic disease caused by mutations in the β -globin gene that results in reduced or absent hemoglobin [15]. At present, the only effective long-term treatment for transfusion-dependent β -thalassemia is usually via regular blood transfusions but this has the risk of long-term complications including organ failure. Hematopoietic stem cell (HSC) transplantation from a donor can be curative but has limitations due difficulties in finding and matching donors.

Zynteglo uses gene therapy to add functional copies of a modified form of the β -globin gene (β A-T87Q-globin) into a patient's HSCs. The process works by transduction of β A-T87Q-globin gene into HSCs taken from the patient, utilizing a Lentiviral vector. The modified HSCs are then infused back into the patient.

Clinical studies have shown that around 75–80% of patients (N = 11/14) have continued to maintain transfusion independence for durations of 21–56 months (up to the study cut-off).

The intention is that the one-off treatment will be curative with no further treatment of transfusions necessary. Patients will require long-term monitoring and the EU approval is conditional on the evaluation of further data from ongoing studies.

At an investor meeting, soon after the approval, Bluebird announced that the treatment will be priced at €1.575 million (\$1.77 million), which is higher than what was anticipated by analysts [16]. Payment is via a 5-year, results-driven instalment payment plan, with an initial payment of €315,000 at treatment and then four further annual instalments of the same amount that are only payable if the patient continues to respond to the therapy. This is a similar payment model to that adopted by Novartis for its gene therapy, Zolgensma.

Breztri Aerosphere (PT010) approved in Japan for patients with chronic obstructive pulmonary disease

AstraZeneca (AZ; Cambridge, UK) announced approval in Japan for its Breztri Aerosphere (budesonide/glycopyrronium/formoterol fumarate) [17]. The drug is as a triple-combination therapy indicated for the treatment of chronic obstructive pulmonary disease.

Japan is the first region in the world to approve the drug but it is also currently under regulatory review in the US and EU with a response expected in 2020. It is also claimed to be the first approval by the Japanese Ministry of Health, Labour and Welfare for a triple-combination drug in a pressurized metered-dose delivery system.

The drug has been granted a priority review in China, with an expected regulatory anticipated later in 2019.

Breztri Aerosphere is a single-inhaler, fixed-dose triple combination of budesonide, an inhaled corticosteroid, glycopyrronium, a long-acting muscarinic agonist, formoterol fumarate and a long-acting β_2 -agonist. Previously known as PT010, it was acquired by AZ with the purchase of Pearl Therapeutics (CA, USA) in 2013. Approval of the drug in the US will trigger a final \$150 million regulatory milestone by AZ to Pearl shareholders.

Triple LABA/LAMA/ICS combinations have been developed to allow three commonly used and effective respiratory medicines to be provided as a single dose from a single device. Although, there is currently not enough evidence to show that this outperforms the three individual components given in separate inhalers, the approach offers convenience for the patient, potentially leading to improved compliance and hence better healthcare outcomes. Compliance in respiratory medicine is a big issue with reported levels of adherence often as low as 30%.

Science & novel technologies

Remotely controlled nanofluidic implantable drug delivery device

Researchers from Alessandro Grattoni's laboratory located in Nanomedicine Department, Houston Methodist Research Institute (TX, USA), reported on the development and proof of concept testing of a novel implantable drug delivery device [18]. The device is intended to be implanted subcutaneously in a patient and provide sustained and remotely adjustable delivery of a drug stored in a reservoir in the device through a silicone membrane into the host patient.

The core to controlled drug delivery are nanochannels that are created in silicon membranes utilizing micro-fabrication techniques. Platinum electrodes are then added to both sides of the membrane either using metal foils or using vapor deposition. In a passive state with no voltage applied to the electrodes, differences in drug concentration between the device reservoir and the exterior of the device, drive diffusion of the drug molecules through the nanochannels. However, fluidic behavior of charged particles at a nanoscale level is different from that at micro and macroscale levels due to interaction with the electrical double layer in the nanochannels. Adjustment of channel properties can then result in saturated diffusive transport in the absence of an electric field that is quasi-independent from the concentration gradient. The drug transfer rate can then be regulated by changing the voltage on the electrodes, which varies the electric field across the membrane.

A printed board circuit (PCB) assembly incorporated into the device, costs of a system-on-chip to control the device and a Bluetooth low energy radio is utilized to facilitate external control. The device is powered by a commonly used commercial battery.

The device was tested *in vitro* with methotrexate (a drug commonly used to treat rheumatic diseases) and enalapril (a drug commonly used to treat hypertension). Changing the voltage applied to the electrodes was seen to change the rate of the drug release from the reservoir. Power consumption of the device was calculated and shown to give an operating life of 20 days, which can be potentially increased to several months through design optimization.

In vivo studies were also conducted in rats and primates. After 21 days of implantation, no active inflammatory reactions were observed as well as initial development of fibrosis (which is typically a later stage of response to a foreign body), which indicates good biocompatibility tolerability of the implant.

The authors see the main potential of the device in the management of chronic diseases, such as hypertension, RA and heart failure. They argue that some diseases benefit from intermittent rather than continuous administration of medication and treatment at night time, for example might reduce drug side effects. Also, note that optimal doses might vary from patient to patient and their device dosage would also be potentially optimized on a personalized basis.

New stable nanoemulsions could offer novel drug-delivery approach

Nanoemulsions offer a range of benefits that makes them suitable for drug delivery. These include good stability, improved solubility, protection of the incorporated drug from chemical or enzymatic degradation and controlled drug release. However, production of emulsions often requires high input of energy that can make them costly and hard to scale. A team of engineers from Massachusetts Institute of Technology (MA, USA) led by Patrick Doyle have been working on manufacturing nanoemulsions using a low-energy process. This month these engineers published work [19] on the development of a method of creating stable nanoemulsions, which has the potential to be used in novel drug delivery approaches. As well as offering the benefit of easy and cost-effective scale up, the liquid nanoemulsions can be engineered to transform into gels at elevated temperatures, including body temperature (37°C). These gel properties can ensure that fluid can remain in place and deliver, for example, a drug payload.

The process works by the incorporation of heat-sensitive polymers called poloxamers, or Pluronics, into the system. At room temperature, these molecules dissolve in water but do not significantly interfere with the formation of the emulsion. However, at elevated temperatures, the hydrophobic regions of the polymers attach to the emulsion droplets, binding them together to create a jelly-like solid [20].

The team is now exploring approaches to incorporate active pharmaceutical ingredients into the gel. They suggest that the approach might be applicable to topical medications to treat burns or other injuries and could also be injected to form a solidified 'drug depot', which is able to release drugs over an extended period. The droplet size could also be ideal for in nasal drug delivery.

Summary

This Industry Update covers the period from 1 June to 30 June 2019 and is based on information sourced from company press releases, scientific literature, patents and various news websites. The month saw GlaxoSmithKline (GSK; Brentford, UK) complete its buyout of Novartis's (Basel, Switzerland) stake in their consumer health joint venture as well as an announcement by AbbVie (IL, USA) of its intention to acquire Allergan (Dublin, Ireland) and Merck and Co (NJ, USA) to acquire Tilius Therapeutics (MA, USA). Amgen (CA, USA) announced a partnership with the IPD (WA, USA) to apply protein technology to the development of new drugs. Sandoz (Holzkirchen, Germany) reported research that showed no safety or efficacy issues in switching to its adalimumab biosimilar from the innovator drug, Humira, and Novartis (Basel, Switzerland) presented data showing the potential of its investigational drug, iscalimab, to improve the durability of implanted kidneys. Intec (Jerusalem, Israel) reported results that showed that its smart pill can improve the treatment of Parkinson's disease with (CD/LD). Among the regulatory news announced during the month, GSK (Brentford, UK) announced approval by the FDA of two new delivery methods for Nucala to support home administration of a treatment for asthma; Roche (Basel, Switzerland) and AstraZeneca (Cambridge) each gained Japanese approval for new drugs. Bluebird Bio (MA, USA) gained approval in Europe for its gene therapy to treat a rare blood disease and announced its proposed risk-shared pricing. A group at Houston Methodist Research Institute (TX, USA) published work on a novel implant that can provide long-term and controllable drug delivery and a group from Massachusetts Institute of Technology (MA, USA) published work on nanoemulsion technology that has potential for topical, nasal and injectable drug delivery.

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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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References

1. GSK completes Consumer Healthcare buyout. www.gsk.com/en-gb/media/press-releases/gsk-completes-consumer-healthcare-buyout/
2. AbbVie to acquire Allergan in transformative move for both companies. <https://news.abbvie.com/news/press-releases/abbvie-to-acquire-allergan-in-transformative-move-for-both-companies.htm>
3. Amgen and the Institute For Protein Design (IPD) at University Of Washington announce unique strategic research partnership. www.amgen.com/media/news-releases/2019/06/amgen-and-the-institute-for-protein-design-ipd-at-university-of-washington-announce-unique-strategic-research-partnership/
4. Merck to acquire Tilos Therapeutics. www.mrknewsroom.com/news-release/research-and-development-news/merck-acquire-tilos-therapeutics
5. Simpson I. Industry update covering October. *Ther. Deliv.* 10(2), (2018). <https://doi.org/10.4155/tde-2018-0071>
6. www.novartis.com/news/media-releases/new-sandoz-biosimilar-adalimumab-data-confirm-switching-from-reference-biologic-has-no-impact-safety-or-efficacy
7. Cohen HP, Blauvelt A, Rifkin RM *et al.* *Drugs* 78, 463 (2018). <https://doi.org/10.1007/s40265-018-0881-y>
8. Novartis presents first-of-its-kind histology data with iscalimab (CFZ533) suggesting the extended survival of transplanted organs may be possible. www.novartis.com/news/media-releases/novartis-presents-first-its-kind-histology-data-iscalimab-cfz533-suggesting-extended-survival-transplanted-organs-may-be-possible
9. 632 - CNI-free therapy with iscalimab (anti-CD40 mAb) preserves allograft histology compared with standard of care after kidney transplantation. <https://eventpilotadmin.com/web/page.php?page=IntHtml&project=ATC19&id=2067>
10. Intec Pharma announces results from earlier Phase 2 clinical trial of Accordion Pill-Carbidopa/Levodopa in Advanced Parkinson's disease patients published in Parkinsonism and related disorders. www.intecpharma.com/technology/
11. <https://ir.intecpharma.com/news-releases/news-release-details/intec-pharma-announces-results-earlier-phase-2-clinical-trial>
12. Navon A. The Accordion Pill: unique oral delivery to enhance pharmacokinetics and therapeutic benefit of challenging drugs. *Ther. Deliv.* 10(7), (2018). <https://doi.org/10.4155/tde-2018-0067>
13. Nucala (mepolizumab) gains FDA approval for two new self-administration options. www.gsk.com/en-gb/media/press-releases/nucala-mepolizumab-gains-fda-approval-for-two-new-self-administration-options/
14. www.roche.com/media/releases/med-cor-2019-06-18.htm
15. bluebird bio announces EU conditional marketing authorization for ZYNTEGLO™ (autologous CD34+ cells encoding β A-T87Q-globin gene) gene therapy for patients 12 years and older with transfusion-dependent β -thalassemia who do not have β 0/ β 0 genotype. <http://investor.bluebirdbio.com/news-releases/news-release-details/bluebird-bio-announces-eu-conditional-marketing-authorization>
16. Bluebird prices gene therapy Zynteglo at €1.575M in Europe, to be paid over 5 years. www.fiercepharma.com/pharma/bluebird-prices-gene-therapy-zynteglo-at-eu1-575m-europe-to-be-paid-over-5-years
17. Breztri Aerosphere (PT010) approved in Japan for patients with chronic obstructive pulmonary disease. www.astrazeneca.com/content/astraz/media-centre/press-releases/2019/breztri-aerosphere-pt010-approved-in-japan-for-patients-with-chronic-obstructive-pulmonary-disease-19062019.html
18. Trani ND, Silvestri A, Bruno G *et al.* Remotely controlled nanofluidic implantable platform for tunable drug delivery. *Lab Chip* 19, 2192 (2019) doi:10.1039/C9LC00394K (Epub ahead of print).
19. Hashemnejad SM, Badruddoza AZM, Zarket B *et al.* Thermoresponsive nanoemulsion-based gel synthesized through a low-energy process. *Nat. Commun.* 10, 2749 (2019) doi:10.1038/s41467-019-10749-1 (Epub ahead of print).
20. 'Nanoemulsion' gels offer new way to deliver drugs through the skin. <http://news.mit.edu/2019/nanoemulsion-gels-skin-drugs-0621>