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Industry update: the latest developments in the field of therapeutic delivery, April 2019

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April 2019 was perhaps remarkable for the amount of industry news about gene therapy, and notably the announcement by a global contract development and manufacturing organization, Catalent, that it was creating a capability in gene therapy product development and manufacturing through its acquisition of Paragon Bioservices, Inc (MD, USA). This move followed just a few weeks after another similar major contract development and manufacturing organization gene therapy acquisition. There was other encouraging gene and cell therapy news reported from AveXis (IL, USA), Ajinomoto Bio-Pharma (CA, USA), Kiadis Pharma (Amsterdam, The Netherlands), Fibrocell (PA, USA), Autolus Therapeutics plc (London, UK), ReNeuron (Surrey, England) and Kite Pharma (CA, USA). Also, there was plenty of therapeutic delivery technology innovation announced, including Calixar's (Lyon, France) membrane protein stabilization drug discovery technology, the Eli Lilly (IN, USA)/Avidity Biosciences LLC (CA, USA) deal around antibody oligonucleotide conjugates, ViiV Healthcare's regulatory filing for its long-acting anti-HIV-1 intramuscular injection, Marinomed Biotech's (Vienna, Austria) solubilization technology and an EU approval filing for Novo Nordisk's (Bagsværd, Denmark) oral delivery formulation of glucagon-like peptide-1 analog semaglutide. Diseases and treatment approaches that currently figure strongly in many biotech and big pharma pipelines and portfolios, notably nonalcoholic steatohepatitis and immuno-oncology, were as ever in the news, along with a number of rare disease therapies. As always, information sources employed to provide the materials used in compiling this update included company press releases, conference news and other news websites.

First draft submitted: 31 May 2019; Accepted for publication: 8 July 2019; Published online: 13 August 2019

Keywords: clinical trials • drug delivery • gene therapy • immuno-oncology • mergers and acquisitions • NASH • product approvals • rare diseases

Business news

Acquisitions, mergers & licensing

Catalent & Paragon Bioservices

That gene therapies are going to carve out a significant space in the treatment of serious diseases is underscored by the fact that contract development and manufacturing organizations are now building their capabilities in this rapidly growing area through acquisitions. Following on from the acquisition of viral vector manufacturer Brammer Bio (MA, USA) by Thermo Fisher Scientific (MA, USA) in late March 2019 [1], Somerset NJ-based Catalent has announced that it has agreed to acquire viral vector development and manufacturing business Paragon Bioservices, Inc (MD, USA) [2]. This will add to Catalent's expertise in adeno-associated virus vector, lentivirus vector and plasmid gene delivery, as well as capability in next-generation vaccines, oncolytic viruses and complex biologics to the services Catalent already offers to pharma and biotech companies.

Ajinomoto Bio-Pharma & GeneDesign

Continuing the gene therapy theme, it was announced that a wholly owned Ajinomoto (Tokyo, Japan) company, GeneDesign (Osaka, Japan), is being rolled into the global Ajinomoto organization. This allows Ajinomoto Bio-Pharma (CA, USA) to offer high quality, scalable process, custom oligonucleotides to the contract development and

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manufacturing organization's customers worldwide. Ajinomoto recently opened a new development center and will have the world's largest solid-phase oligonucleotide synthesizer, able to deliver batches of product of up to 10 kg [3].

Novartis & IFM Therapeutics

Novartis (Basle, Switzerland) announced that it is expanding its portfolio of immunomodulatory medicines through the acquisition of IFM Tre. IFM Tre is a subsidiary of Boston, US-based IFM Therapeutics and is focused on developing agents that target the NLRP3 pathway, a key component of the innate immune system [4]. NLRP3 triggers an inflammatory response through the assembly of a multiprotein complex, the inflammasome. The NLRP3 inflammasome enables the innate immune system fight pathogens but inappropriate, chronic activation is associated with several metabolic, fibrotic, autoimmune and neurological diseases. Fine tuning of aspects of the immune system via NLRP3 modulation may offer a novel therapeutic approach to the treatment of gout, atherosclerosis, nonalcoholic steatohepatitis (NASH), inflammatory bowel disease and diseases of the CNS that may be inflammation mediated. Two preclinical and one clinical stage asset currently in the IFM Tre pipeline will now be advanced by Novartis.

Puma Biotechnology & Pierre Fabre

An exclusive agreement between Puma Biotechnology (CA, USA) and Pierre Fabre (Castres, France) provides the development and marketing of Puma's neratinib (Nerlynx®) in Europe and part of Africa by Pierre Fabre [5]. Pierre Fabre expects to start providing neratinib from late 2019 into 2020. Neratinib, also known as PB272, is a potent, irreversible tyrosine kinase inhibitor acting against the EGF receptors HER1, HER2 and HER4. It has shown favorable Phase II trial outcomes when employed as a single agent in the treatment of HER2⁺ metastatic breast cancer in patients having no prior treatment and in those previously treated with trastuzumab (Herceptin®, Roche [Basel, Switzerland]) [6]. Neratinib gained EU approval in late 2018 as an extended adjuvant therapy of early-stage hormone positive, HER2⁺ breast cancer in patients who are less than 1 year from the completion of prior adjuvant trastuzumab-based treatment.

Kiadis Pharma & CytoSen Therapeutics

A leader in cell-based cancer immunotherapy has been created through the acquisition of Cytosene Therapeutics (FL, USA) by Kiadis Pharma (Amsterdam, The Netherlands). The transaction will bring together CytoSen's *ex vivo* nanoparticle-processing technology to expand and activate natural killer (NK) cells with a T-cell therapy platform developed by Kiadis that has already advanced to Phase III clinical trial and has an EU registration in progress. Used in combination, the complementary cell therapies have potential in patients undergoing hematopoietic stem cell transplants for acute myeloid leukemia to make such treatment safer and more effective [7].

Fulcrum & GlaxoSmithKline

Losmapimod is a p38α/β MAPK inhibitor that decreases *DUX4* expression. Reducing expression of this gene, root cause of one of the most common muscular dystrophies facioscapulohumeral muscular dystrophy, may offer an approach to treatment of this disabling disorder, which currently has no approved treatments. Fulcrum Therapeutics (MA, USA) has acquired an exclusive worldwide license to losmapimod from its discoverer, GlaxoSmithKline (London, UK) and will advance the compound into a Phase IIb trial in mid-2019. GlaxoSmithKline had studied losmapimod in two dozen clinical trials in acute coronary syndrome, but it was not further advanced in that indication on efficacy grounds. Preclinical testing by Fulcrum suggested that losmapimod may be able to effectively target *DUX4* expression and potentially be of value in treatment of facioscapulohumeral muscular dystrophy [8].

Salix Pharmaceuticals & University of California

Bausch Health (Laval, Canada) subsidiary Salix Pharmaceuticals (NJ, USA) has announced that it had entered into a license agreement with the University of California (CA, USA) for certain intellectual property relating to an investigational compound targeting the pituitary adenylate cyclase receptor 1 for treatment of nonalcoholic fatty liver disease, NASH and other liver and gastrointestinal diseases. Pituitary adenylate cyclase receptor-1 activation by the University of California-discovered fusion proteins in preclinical animal studies showed increase in safety and lean mass, appetite suppression and reduced fat accumulation, suggesting potential in the treatment of the liver diseases [9].

Salix Pharmaceuticals & Mitsubishi Tanabe Pharma

Also in April 2019, Salix announced an exclusive license agreement with Mitsubishi Tanabe Pharma (Osaka, Japan) to develop and commercialize amiselimod (MT-1303), a sphingosine-1-phosphate (SIP) receptor antagonist with activity against SIP1, SIP4 and SIP5 receptor subtypes, and hence has potential in treatment of autoimmune diseases. The compound is in late-stage development at Mitsubishi Tanabe Pharma, being studied for multiple sclerosis, psoriasis, Crohn's disease and systemic lupus erythematosus. Salix has acquired rights to develop the compound in all fields except neurology, rheumatology and certain rare dermatology diseases and has commercialization rights in all countries except Japan and specified countries in Asia. Aligned with its existing activities in gastroenterology, Salix intends to progress development of amiselimod in inflammatory bowel disease as an alternative to biologics and other available therapies [10].

Regeneron & Calixar

Calixar SAS (Lyon, France) has licensed rights to its native membrane protein stabilization technology to Regeneron (NY, USA) to allow the latter to pursue research and discovery of antibodies against an undisclosed target in various therapeutic fields [11]. Calixar technology allows isolation of full-length membrane protein therapeutic targets of high purity, including ion channels, G-protein-coupled receptors. Contrary to conventional membrane protein approaches, Calixar's patented nondenaturing detergent/surfactant technology does not require protein refolding, any deletions, point mutation, truncation or fusion to enable isolation and so maintains functional and structural integrity. This approach is intended to enhance the success of downstream proteomics and drug discovery [12].

Bristol-Myers Squibb & Celgene

The proposed acquisition of Celgene (NJ, USA) by Bristol-Myers Squibb (NY, USA) was announced at the beginning of the year and despite concerns by some, the majority of shareholders of both companies have now voted to approve the combination, which is expected to close in the third quarter. This very significant transaction (US \$74 billion) has the potential to create global top ten players in oncology, cardiology, immunology and inflammation [13,14].

Collaborations*Alnylam & Sanofi*

RNAi therapeutics innovator Alnylam Pharmaceuticals (MA, USA) has announced the conclusion of its research and option phase alliance in rare genetic diseases with Sanofi (Paris, France). Collaboration on commercialized and Phase III assets (patisiran, vutrisiran and fitusiran) will continue, and Alnylam will be able to refocus resources on the continued growth of its rare disease pipeline. Additionally, collaboration on a selected investigational RNAi asset in an undisclosed rare genetic disease will continue to progress to the conclusion of IND-enabling studies, whereupon Sanofi will then assume the responsibility for any further development and commercialization of the asset [15].

Alnylam & Regeneron

The same day that Alnylam announced the changes to its agreement with Sanofi, it also announced a new agreement with Regeneron to discover, develop and commercialize RNAi therapeutics for the treatment of ocular and CNS diseases [16]. The collaboration will also select RNAi therapeutic programs aimed at genes expressed in the liver and include the evaluation of a combination of Regeneron's pozelimab with Alnylam's cemdisiran. The previously announced collaboration between the two companies to identify RNAi therapeutics for NASH [17] will continue.

Gilead Sciences & NovoNordisk A/S

The search to identify effective and safe therapies for NASH continues apace, as items in this article and in previous recent Industry Update articles might indicate. It is a serious disease of the liver that often affects people with diabetes, with a risk of liver-related mortality and for which there are currently very limited treatment options. Gilead Sciences (CA, USA) have a number of active programs pursuing an indication in NASH and they have now announced a clinical collaboration with Novo Nordisk (Bagsværd, Denmark) to combine compounds from each of their pipelines in a proof-of-concept study in the disease. Combination therapy treatment with Novo's glucagon-like peptide (GLP-1) analog semaglutide added to Gilead's FXR agonist cilofexor, along with their ACC

inhibitor firsocostat, will be evaluated in patients with NASH. The companies are also looking to collaborate on preclinical research to help advance further understanding of the disease [18].

Gilead Sciences & insitro

Hot on the heels of their Novo Nordisk collaboration announcement, Gilead Sciences announced a further NASH strategic collaboration, this time with insitro (CA, USA). Machine learning is utilized by insitro to transform drug discovery and development, first, by generating high throughput, functional genomic datasets aligned with patient data and then applying novel analytical approaches. Then, insitro builds predictive models from this information to accelerate the creation of effective therapeutics. Under the 3-year collaboration, insitro will create disease models for NASH and use these models to discover targets that are expected to have an influence on clinical progression and regression of disease. Gilead can advance up to five targets identified through this collaboration and will be responsible for chemistry and development effort against the identified targets [19].

Fibrocell & Castle Creek

Fibrocell Science, Inc. (PA, USA) has announced a collaboration agreement with Castle Creek Pharmaceuticals (NJ, USA) to develop and commercialize Fibrocell's gene therapy candidate, FCX-007, for the treatment of recessive dystrophic epidermolysis bullosa. This is a rare, life-threatening genetic disorder that is diagnosed at infancy and currently has no approved treatment or cure. Fibrocell is a cell and gene therapy company working on autologous cell-based therapies for skin and connective tissue diseases. Its FCX-007, which is being developed with Intrexon Corporation, is *ex vivo* genetically modified autologous dermal fibroblasts containing the gene to enable them to express COL7 protein, which is missing or deficient in recessive dystrophic epidermolysis bullosa patients. It is applied locally by injection to provide generation of COL7 in the disease affected areas without creating systemic exposure. The collaboration with Castle Creek will add capability and funding to advance FCX-007 through to the biologics license application (BLA) filing with the US FDA. Castle Creek already has another investigational agent in clinical trials, CCP-020 being evaluated for the treatment of epidermolysis bullosa simplex, so the collaboration will expand the range of potential epidermolysis bullosa therapies the rare skin diseases company is pursuing [20].

Eli Lilly & Avidity Biosciences

A global licensing and research collaboration was announced between Eli Lilly (IN, USA) and Avidity Biosciences (CA, USA) to discover, develop and commercialize potential new medicines in immunology and other selected indications. The collaboration will seek to progress new therapeutic approaches based on the Antibody Oligonucleotide Conjugates (AOC™) technology developed by Avidity [21]. Their platform combines the selectivity of a monoclonal antibody and the specificity of oligonucleotide-based therapeutics in a single molecule, with the antibody scaffold carrying multiple oligonucleotides, to provide new RNA-based medicines. The technology can overcome the barriers to oligonucleotide delivery that have challenged the application of these modalities against some therapeutic targets, with the ability to reach targets in muscle, heart, liver, tumors and immune cells [22].

Other business news

AveXis

AveXis (Basle, Switzerland), a Novartis company, is expanding its gene therapy commercial manufacturing capacity through the purchase of an advanced biologics therapy campus in Longmont, CO, USA. It will be the largest of four AveXis manufacturing sites, adding to a fully operational site in Illinois, an expanded product development capability in San Diego and an underconstruction building in North Carolina expected to be operational in 2020. The new facility will help production capacity as AveXis prepares to launch its investigational gene therapy product onasemnogene abeparvovec-xioi (Zolgensma®) for spinal muscular atrophy, which is currently under regulatory review, and as the company plans for future gene therapy products in development [23].

Kite Pharma

Another company expanding its manufacturing capabilities for novel therapeutic delivery approaches is Gilead's Santa Monica, USA-based Kite Pharma (CA, USA), which has just announced plans for a new facility in Frederick County, Maryland. The new site will manufacture cell therapies such as axicabtagene ciloleucel (Yescarta®), Kite's first commercially available CAR-T cancer therapy, and they have other, investigational T-cell receptor cell therapies being evaluated in clinical trials. The new site will add to existing capability in California and The Netherlands [24].

Nimble Therapeutics

Nimble Therapeutics (WI, USA) is now a standalone entity, having spun out from Roche and offering its proprietary chemical synthesis technology to other pharmaceutical companies for drug discovery and development. The synthesis platform, which originated within Roche, offers speed and flexibility in the discovery of novel scaffolded natural and modified macrocyclic peptidomimetics. It employs massively parallel chemical synthesis along with a variety of biological assays to aid the optimization of molecules with favorable, drug-like properties [25].

Iveric/Ophthotech

Ophthotech (NY, USA) has announced that as part of its transition strategy to focus on discovering and developing novel gene therapies for the treatment of orphan inherited retinal diseases, it is changing its name to Iveric Bio [26]. Iveric has a number of gene therapy products in the preclinical and research phase. The company's most advanced product is avacincaptad pegol (Zimura[®]), a pegylated RNA aptamer that inhibits cleavage of complement protein C5 and the formation of the terminal fragments, C5a and C5b. C5 plays multiple roles in innate immunity and inflammatory diseases. Decreasing the inflammatory cascade within the retina associated with the presence of the C5 fragments can potentially slow the degeneration of retinal pigment epithelial cells [27].

Product approvals & other regulatory news*CD19/CD22-targeted next-generation programmed T-cell therapy (AUTO3, Autolus Therapeutics)*

The FDA has granted orphan drug status to a CAR-T therapeutic, AUTO3, underdevelopment by Autolus Therapeutics (London, UK). AUTO3 is based on autologous T cells that are genetically modified with a retroviral vector to express two chimeric antigen receptors, CD19 and CD22. By the novel simultaneous targeting of two B-cell antigens, AUTO3 is designed to minimize single antigen loss in patients with B-cell malignancies. Autolus is pursuing an indication of acute lymphoblastic leukemia, predominantly a childhood cancer (~60% of cases are in subjects below 20 years of age). Relapsed or refractory acute lymphoblastic leukemia in children is a significant unmet need, with up to 20% of patients having chemotherapy-resistant disease [28].

Luspatercept (Celgene/Acceleron Pharma)

Collaborators Celgene and Acceleron Pharma (MA, USA) announced they had submitted a BLA and a marketing authorization application (the FDA and EMA, respectively) for fusion protein luspatercept [29,30]. Luspatercept regulates late-stage red blood cell maturation. They are seeking approval for its use for low-/intermediate-risk myelodysplastic syndromes-associated anemia and who have ring sideroblasts and require red blood cell transfusions. They are also seeking approval for use of luspatercept in the treatment of patients with β -thalassemia-associated anemia who require red blood cell transfusions.

Emtricitabine/tenofovir alafenamide-fixed dose combination tablet (Descovy[®], Gilead Sciences)

A supplemental new drug application (NDA) has been submitted by Gilead Sciences for a fixed dose combination of two anti-HIV-1 agents in a single tablet, to be administered once-daily for pre-exposure prophylaxis against sexually acquired HIV-1 infection [31]. The combination of emtricitabine and tenofovir alafenamide (Descovy) is already approved for use with other anti-HIV-1 therapeutics in the treatment of HIV-1 infections, but if approved for prophylaxis, it will be the second product approved for pre-exposure prophylaxis, after Gilead's Truvada[®] (emtricitabine with tenofovir disoproxil fumarate). Through a cascade of enzymatic activation, prodrug tenofovir alafenamide in the new combination delivers the active tenofovir diphosphate into the T cells more efficiently than tenofovir disoproxil fumarate. It results in a better ratio of drug levels in the infected cells to blood, kidneys and bone relative to that achieved with the older prodrug and may therefore have a more favorable side effect profile on long-term dosing [32].

Cabotegravir-/rilpivirine-fixed dose combination injection (ViiV Healthcare)

ViiV Healthcare (Brentford, UK) has submitted an NDA seeking approval for the combination of two anti-HIV-1 drugs as a once-monthly injection for the treatment of adults whose viral load is already suppressed and not resistant to either of the two agents in the product. The long-acting intramuscular injection combines the integrase inhibitor cabotegravir from ViiV with the NNRTI rilpivirine from Janssen Pharmaceutica (Beerse, Belgium) and dosed monthly was found to be as effective as the standard-of-care daily three drug regimen in maintaining suppression

of viral load. The injection offers an additional treatment option for people living with HIV, and the once monthly dosing may be more convenient for some compared with a daily tablet regimen [33,34].

Dolutegravir/lamivudine fixed dose combination tablet (Dovato[®], ViiV Healthcare)

The first, once daily, fixed combination single tablet containing two anti-HIV-1 agents and indicated for the treatment of patients with no prior antiretroviral therapy has been approved by the FDA [35] and has received a positive opinion from the Committee for Medicinal Products for Human Use of the EMA, recommending approval [36]. The combination of integrase inhibitor dolutegravir with nucleoside reverse transcriptase inhibitor lamivudine from ViiV Healthcare (Dovato) was noninferior to a standard-of-care three drug regimen. For treatment-naïve subjects, an effective two drug regimen may offer advantages by exposing them to fewer drugs at the start of treatment then managing prolonged therapy (e.g., resistance development) may be less concerning.

Oral semaglutide (Novo Nordisk)

Novo Nordisk has announced the submission of a marketing authorization application to the EMA seeking approval of the oral tablet formulation of its GLP-1 analog, semaglutide, for the treatment of Type-2 diabetes [37]. We have covered announcements of positive clinical trials of this SNAC-enabled oral delivery formulation of the 4000 Daltons molecular weight peptide in a previous Industry Update article [38]. In head-to-head trials against orally dosed small molecules sitagliptin and empagliflozin, and injectable GLP-1 analogs liraglutide and dulaglutide oral semaglutide produced greater improvements in HbA1c, a marker for the disease, and in weight loss. Oral semaglutide is also under regulatory review in the USA and Canada [37].

Brolucizumab, Novartis

The BLA for brolucizumab (Novartis) has been accepted by the FDA and Novartis used a Priority Review voucher with the submission to expedite regulatory review. Brolucizumab inhibits activation of VEGF, increased signaling that is associated with pathologic ocular angiogenesis and retinal edema. An indication for treatment of wet age-related macular degeneration is being sought and if approved, the product could be available by the end of 2019. Brolucizumab is the most clinically advanced, humanized single-chain antibody fragment to progress to this stage of development. Single-chain antibody fragments are attractive protein drug candidates as they are the smallest piece of an antibody still retaining full binding capacity to its target. They have a smaller molecular size compared with clinically studied Fab fragments (at approximately half the molecular mass) or complete antibodies (at about a fifth the molecular mass) and have good tissue penetration and rapid clearance from the systemic circulation, so if introduced locally exert a predominantly local action. However, single-chain fragments require some effort to adapt them into materials with biophysical properties appropriate to commercial drug development, which Novartis has achieved in the case of brolucizumab [39].

Pembrolizumab, Keytruda[®], Merck plus axitinib, Inlyta[®], Pfizer

Immuno-oncology figures frequently in Industry Update articles and news on immuno-oncology this month include the approval of anti-PD-1 therapy pembrolizumab (Keytruda, Merck, NJ, USA) in combination with tyrosine kinase inhibitor axitinib (Inlyta, Pfizer, NY, USA) as first-line treatment for patients with advanced renal cell carcinoma. The combination therapy was superior to existing standard treatment with tyrosine kinase inhibitor sunitinib (Sutent[®], Pfizer) given as sole therapy. This is the first indication for pembrolizumab in advanced renal cell cancer and the first anti-PD-1 therapy approved by the FDA as a combination treatment that shows significant improvement over sunitinib as measured by overall survival, progression-free survival and overall response rate [40].

Erdaftinib, Balversa[™], Janssen

The approval of the first FGF receptor (FGFR) kinase inhibitor along with its combination diagnostic for the treatment of locally advanced or metastatic urothelial carcinoma in specific patients identified as having susceptible *FGFR3* or *FGFR2* genetic alterations was announced by Janssen. Erdaftinib (Balversa[®]), along with *therascreen*[®] FGFR test kit, represents a targeted approach to treatment of a subset of patients with metastatic urothelial cancer who otherwise had limited treatment options. It gained accelerated approval on the basis of a Phase II clinical trial, which included subjects that had failed to respond to anti-PD-1 immuno-oncology therapy [41]. Janssen has progressed erdaftinib as a consequence of a 2008 collaboration agreement with Astex Pharmaceuticals (Cambridge, UK) to develop and commercialize the compound.

Clinical trials

Gene therapy onasemnogene abeparvovec-xioi (Zolgensma[®], AveXis) successfully transduced intended CNS targets in Phase III trial

The expansion of manufacturing capacity by AveXis for its developing gene therapy pipeline was noted earlier in this article and the company has also announced Phase III trial results of its late-stage asset onasemnogene abeparvovec-xioi (Zolgensma), which is currently in regulatory review. The interim Phase III data shared in the announcement showed prolonged event-free survival in the treatment of children with spinal muscular atrophy, along with increase in scores assessing motor skills. Biodistribution studies in tissues from a deceased patient showed that treatment successfully transduced tissues in brain and spinal cord motor neurons and that there was widespread expression of the SMN protein missing in subjects affected by the genetic defect, comparable to tissues from an unaffected individual. Normal, abundant motor neurons were observed in the treated subject, whereas analysis of tissue from an untreated subject showed few motor neurons. As the replacement copy of the gene is delivered using the adeno-associated viral vector 9, there is concern that patients may have been previously exposed to the virus (which does not cause human disease) and carry antibodies to the vector. This would risk an immune response to the vector and reduce effectiveness of the gene delivery system. Pretreatment screening showed only 5% of subjects had elevated adeno-associated viral vector 9 antibody titers, which excluded them from treatment. Hence, there appears to be a low prevalence of anti-AAV antibodies in young children [42].

Marinosolv[®] technology platform (Marinomed Biotech) successfully delivers budesonide in nasal spray to achieve effectiveness at lower dose compared with established formulation

Marinomed Biotech (Vienna, Austria) announced that its novel nasal spray formulation of budesonide, Budesolv[®], is as effective as currently available budesonide products, but at a significantly lower dose. The product uses Marinomed's Marinosolv technology that employs natural products glycyrrhizin and escin as solubilizers to provide a micellar solution of the otherwise water-insoluble budesonide, as opposed to the suspension formulation of the already-marketed product. The solubilized form has better bioavailability in the nasal tissues and so can be provided at an optimized lower dose relative to traditionally formulated products. Results of the Phase III study will be published later this year [43].

Positive data from trial of a cryopreserved stem cell formulation (ReNeuron) in retinitis pigmentosa

Further improvements in the vision of subjects with retinitis pigmentosa treated with its stem cell therapy were announced by ReNeuron (Bridgend, UK). ReNeuron is evaluating its human retinal progenitor cell product in subjects with advanced retinitis pigmentosa who have some remaining retinal function. Preliminary findings in three subjects were provided in February 2019, but now the follow-up data on those subjects are available and it is suggested that the cell therapy not only provides an initial improvement in visual acuity but that ongoing improvements in vision may continue for several months. ReNeuron notes that additional subjects will need to be treated and monitoring of progress for longer periods will be required to move the investigational therapy toward a registration pathway [44].

Proof-of-concept study data for combination therapy in NASH favourable but Phase III selonsertib trial fails (Gilead Sciences)

Mention has already been made of Gilead's engagement in efforts to identify effective treatments for NASH and news of two of their clinical programs highlighted the challenges and possibilities in this endeavor. The combination of cilofexor and firsocostat has been evaluated in a proof-of-concept study and data shared at The International Liver Congress (10–14 April 2019, Vienna, Austria) indicated that, in a study in 20 patients over 12 weeks, treatment resulted in improvements in hepatic steatosis (at least 30% reduction in hepatic fat as measured by MRI), liver stiffness, liver biochemistry and serum markers of fibrosis. Phase II trials of cilofexor with firsocostat in NASH are ongoing. Triple therapy with cilofexor with firsocostat plus selonsertib, an apoptosis signal-regulating kinase 1 inhibitor is also being studied in advanced fibrosis of the liver due to NASH [45]. In a separate announcement, however, Gilead advised that selonsertib as monotherapy in the treatment of bridging fibrosis due to NASH did not meet its end point of a prespecified histologic improvement in fibrosis without worsening of NASH [46]. Gilead further asserted that effective therapy of NASH will likely require targeting of multiple distinct disease pathways, which aligns with the approach they are pursuing in a number of their other NASH clinical programs.

IGF-1R-targeted teprotumumab (Horizon Therapeutics) shows promise in active thyroid eye disease

Horizon Therapeutics (Dublin, Ireland) provided an update on the Phase III trial of its IGF-1 receptor (IGF-1R) targeted mAb teprotumumab at the American Association of Clinical Endocrinologists Scientific and Clinical Congress (23–28 April 2019, CA, USA) [47]. Positive primary and secondary end point data were announced in February 2019 [48]. Teprotumumab treatment provided for a dramatic reduction in proptosis (eye bulging) in active thyroid eye disease and may alleviate other inflammatory symptoms of the disease. This is a major symptom of the disease and disease progression can further result in misalignment of the eyes, double vision and potentially blindness. Apart from complex eye surgery, the disease has no treatment. A BLA is expected to be submitted mid-2019.

Novel Type-2 diabetes agent imeglimin (Poxel/Sumitomo Dainippon Pharma) has positive outcome in Phase III trial

Partners Poxel SA (Lyon, France) and Sumitomo Dainippon Pharma (Osaka, Japan) have announced positive top-line results from a Phase III trial in Japanese subjects of Poxel's novel therapy for Type-2 diabetes, imeglimin. Imeglimin is a first-in-class agent targeting mitochondrial bioenergetics and acting in the liver, in muscle and in the pancreas, to enhance insulin secretion in response to glucose, improve insulin sensitivity and suppress gluconeogenesis. In the trial, end points based on Hb1Ac and fasting plasma glucose were met, with additional secondary end points currently being analyzed. The partners are preparing for submission of a Japanese NDA in 2020. Imeglimin has potential for both monotherapy and add-on therapy with other oral treatments for Type-2 diabetes [49].

Benefit seen in pancreatic cancer patients with BRCA1, BRCA2 or PALB2 mutations when treated with PARP inhibitor rucaparib (Rubraca®; Clovis Oncology)

PARP inhibitors have shown efficacy in cancers associated with *BRCA* mutations, including certain ovarian and breast cancers. Now, in an investigator-initiated Phase II trial of PARP inhibitor rucaparib (Rubraca), Clovis Oncology (CO, USA) has shown potential for disease control in pancreatic cancer among patients with mutations in *BRCA1*, *BRCA2* or *PALB2*. These mutations occur in between 5 and 8% of patients diagnosed with pancreatic cancer. Treatment was initiated as first-line maintenance following induction with platinum-based chemotherapy and the study results were presented at the American Association for Cancer Research Annual Meeting in Atlanta (29 March–3 April 2019, Atlanta, Georgia, USA) [50]. These results and those from other trials of rucaparib in pancreatic cancer are under consideration by Clovis as to further the clinical and regulatory pathways for the PARP inhibitor in this disease.

Immuno-oncology disappointments in gastric cancer & head & neck cancer

Merck has announced results from a Phase III trial of its anti-PD-1 therapy pembrolizumab (Keytruda), both as monotherapy and in combination with chemotherapy for first-line treatment of patients with advanced gastric cancer or gastroesophageal junction adenocarcinoma. It showed that immuno-oncology monotherapy was no more effective than chemotherapy alone and that adding pembrolizumab to chemotherapy did not result in a better outcome compared with chemotherapy alone. Gastric cancer is difficult to treat and is associated with high mortality rates, especially once advanced to the metastatic stage, and new more effective treatments are much needed [51]. The second immuno-oncology clinical trial disappointment this month was disclosed in the first-quarter financial results from Bristol-Myers Squibb [52] where it was noted that a Phase II trial of anti-PD-1 nivolumab (Opdivo®) added to anti-CTLA4 ipilimumab (Yervoy®) in patients with recurrent or metastatic squamous cell carcinoma of the head and neck did not meet its primary end points. Nivolumab alone is already approved for the therapy of head and neck cancer in patients previously treated with platinum-based chemotherapy and whose disease has returned or spread after treatment.

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.

No writing assistance was utilized in the production of this manuscript.

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