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Industry Update

Ebola continued to dominate the news in October to mid-November. The initiation of Phase I vaccine trials by GlaxoSmithKline (GSK) brought some hope that a method of preventing the spread of this deadly disease might soon be in sight. Elsewhere cancer immunotherapies remained a hot topic with Prima Biomed's planned acquisition of the French company Immutep being the latest in a series of deals featuring compounds designed to optimize the immune response to cancer. In the clinic positive Phase III data for Acacia Pharma's intravenous formulation of amisulpride brought better therapy for postoperative nausea and vomiting one step closer.

Acquisitions & divestments

Prima BioMed & Immutep

The planned purchase of Immutep SA (Orsay, France) by Prima Biomed Ltd (Sydney, Australia) was made public in early October [1]. The deal is worth up to \$28 million (in the form of cash, shares and warrants) subject to the achievement of certain milestones. Immutep is developing immunotherapies based on its patented lymphocyte activation gene 3 (LAG-3) technology [2]. The LAG-3 is involved in a number of immune pathways and can either act as an immune-stimulant or inhibitor. Immutep's lead product, IMP321, is a LAG-3Ig fusion protein that binds to MHC class II molecules on dendritic cells and triggers their maturation and migration to the lymph nodes. Once in the lymph nodes they enhance the cross-presentation of antigens to T-cells. Repeated injections of IMP321 have been shown to result in sustained antitumor cytotoxic T-cell responses and an improved clinical response when administered together with standard chemotherapy.

IMP321 is being developed at a low dose as an adjuvant for cancer vaccines and at high dose in combination with anti-cancer medication for first-line chemotherapy. The product is being clinically tested in metastatic renal cell cancer, metastatic breast

cancer (EU), advanced pancreatic cancer (US) and as a vaccine adjuvant in post-surgery disease-free melanoma, metastatic melanoma and prostate cancer with biochemical failure. Immutep has global commercialization rights for this product excluding China and Taiwan where the product is licensed to Eddingpharm, Shanghai, China.

Immutep's other products include IMP701, an antagonist antibody which results in T-cell proliferation in cancer patients. It is licensed to CoStim (Novartis). The company has licensed another compound, IMP731, to GSK which is being developed for autoimmune diseases.

The deal enables Prima Biomed, which to date has focused on the development and manufacturing of its autologous dendritic cell-based product, CVac™ for ovarian cancer in remission or resected pancreatic cancer [3], to expand and diversify its portfolio. It also provides the Australian firm with potential revenues through Immutep's existing licensing agreements and commercial sales of LAG-3 research reagents.

Novartis & CSL

The sale of Novartis (Basel, Switzerland) influenza vaccine business including its development pipeline, which was first announced in April 2014, was finally agreed at the end

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of October [4]. The purchaser was CSL Ltd (Victoria, Australia) which acquired the business for US\$ 275 million. The Novartis vaccines will be incorporated into CSL's existing vaccines and pharmaceutical subsidiary, bioCSL, to create the second largest influenza vaccine company in the world with manufacturing sites in the US, UK, Germany and Australia [5]. The deal depends on receiving regulatory approvals and is expected to close in the second half of 2015.

The divestment is the last part of a restructuring and refocusing of Novartis business. This process started in April 2014 with a three-way inter-conditional asset swap with GSK, part of which was the sale of the Novartis vaccine business (with the exception of flu) to GSK. The details of the deal with GSK and the sale of Novartis Animal Health division to Lilly were reported in an earlier edition of *Therapeutic Delivery* [6].

Omega & Perrigo

On 6 November 2014 the Perrigo Company plc (Dublin, Ireland) and Omega Pharma NV (Nazareth, Belgium) announced that Omega had agreed to be acquired by Perrigo for €6.6 billion [7]. Both of these companies are focused on over the counter (OTC) medicines with Omega being the fifth largest OTC firm in Europe with a portfolio of around 2000 products in the areas of skincare, coughs and colds and natural products. Perrigo's portfolio is broader and includes prescription generics, nutritional products and active pharmaceutical ingredients. It also receives royalties from the Multiple Sclerosis drug Tysabri®. The acquisition will expand Perrigo's OTC product offering and enable it to take advantage of Omega's established platform and European distribution networks. The transaction is expected to close in Q1 2015.

Licensing & collaborations

Bristol-Myers & F-Star

On 28 October 2014 it was announced that the Bristol-Myers Squibb (BMS) Company (NY, USA) had acquired an exclusive option to purchase F-star Alpha Ltd (Cambridge, UK) and obtain global rights to its FS102 investigational product [8]. FS102 is a human epidermal growth factor receptor 2 (HER2)-targeted therapy intended for the treatment of breast and gastric cancer among a well-defined population of HER2-positive patients who do not respond or become resistant to current therapies. FS102 binds to a unique site on HER2 and then induces programmed cell death in HER2-positive tumor cells. Preclinical data show that treatment with FS102 results in major tumor regression in certain HER2-positive cancers that are refractory to treatment with trastuzumab plus pertuzumab.

FS102 is a bispecific antibody produced using F-star's Modular Antibody Technology which is about to enter Phase I [9]. The Modular Antibody Technology results in constant (Fc) regions with the ability to bind to a target of interest. This redesigned Fc antibody is called an Fcab. An Fcab against a target of interest can be combined with the variable region (Fab) of an existing antibody to generate a full-length bispecific antibody or mAb2. These bispecific monoclonal antibodies have the full functionality, structural integrity and stability associated with antibodies. The Fcabs can also be used as mono-specific antibody fragments and combined with drugs or toxins to form antibody-drug conjugates.

BMS will make payments aggregating to \$50 million that consist of an option fee for the right to acquire F-star Alpha Ltd, payment for certain rights and licenses from F-star Alpha Ltd and a clinical milestone payment upon initiation of a Phase I trial. The US giant will be responsible for development and its funding during the option period. BMS can exercise the option once it has decided to proceed with a Phase 2b trial. The total amount paid to F-star may total \$475 million. This includes the aforementioned \$50 million, the option exercise fee and key milestone payments.

Intarcia & Servier

In mid-November Intarcia Therapeutics LLC (MA, USA) made public that it had signed a partnership with Servier (Suresnes, France) for the exclusive rights to develop and commercialize its ITCA 650 treatment for Type 2 diabetes outside of the US and Japan [10]. ITCA 650 contains the well-established GLP-1 agonist, exenatide. The product is unique in that the exenatide is delivered continuously via a small, match-stick-sized osmotic mini-pump placed subdermally. Placement of the pump by a doctor, nurse or doctor's assistant is required only once or twice a year. This has advantages for patients as it frees them from the need to have regular injections as is the case with currently marketed GLP-1 agonists. Both the pump technology and the formulation technology, which enables the stabilization of the peptide for up to 12 months at body temperature, are proprietary to Intarcia [11].

The product is currently being evaluated in four separate Phase III trials. Top-line results from two of these studies have shown that the primary endpoints have been met and global regulatory filings are planned for the first half of 2016.

Under the terms of the agreement Intarcia will receive an upfront payment of around \$171 million and total potential development, regulatory and sales milestone payments of more than \$1 billion. In addition, the company will also be eligible for ex-US/Japan tiered sales-related payments ranging from the low double

digits to the mid-30s as a percentage of sales of product supplied through a manufacturing and supply agreement. It is also foreseen that both parties will co-invest in an additional manufacturing site outside of the US and share in global development costs on new mutually planned and agreed superiority studies and combination regimens. Servier will be responsible for funding any territory-specific trials required for marketing approvals.

The deal does not impact on Intarcia's ability to develop and commercialize the product in the US or find another partner for it in Japan.

Geron & Janssen

The Geron Corporation (CA, USA) issued a press statement on 13 November 2014 regarding its recently signed exclusive worldwide license and collaboration agreement with Janssen Biotech, Inc. (PA, USA). The collaboration is focused on the development and commercialization of imetelstat, Geron's telomerase inhibitor product candidate [12,13]. This product, which is a modified oligonucleotide, has potential to treat cancer and in particular hematologic malignancies such as myelofibrosis (MF), myelodysplastic syndrome (MDS) and acute myelogenous leukemia. It acts to inhibit the action of the enzyme, telomerase, whose physiological role in cells, such as stem cells, is to maintain the stability and length of the telomeres (repeated sequences of DNA which cap the ends of the chromosomes) and prevent them from shortening during cell division. Telomerase is known to be upregulated in many tumor cells. Although this upregulation is not directly responsible for the development of malignancy, it plays a critical role in tumor progression as the telomeres never shorten during cell division to the critical length after which apoptosis or a cessation of cell division would naturally occur in normal cells. The tumor cells can therefore continue to divide indefinitely.

Under the terms of the agreement, Geron will receive an upfront payment of \$35 million and is eligible to receive up to a potential total of \$900 million if development, regulatory and commercial milestones are achieved. It also has rights to royalties on worldwide net sales. The clinical development plan, which will be agreed between both companies, is likely to include Phase II studies in MF and MDS as initial studies, additional registration studies in MF and MDS, and exploratory Phase II and potential follow-on Phase III studies in acute myelogenous leukemia. The initial Phase II study in MF is expected to start in mid-2015.

Product approvals

Sulfur hexafluoride lipid-type A microspheres

The US FDA approved Lumason, Bracco's (Milan, Italy) sulfur hexafluoride lipid-type A microspheres

injectable suspension for intravenous injection on October 10 [14]. The product is a microbubble ultrasound contrast agent for use in patients with suboptimal echocardiograms in order to opacify the left ventricular chamber and improve the delineation of the left ventricular endocardial border. Lumason (sulfur hexafluoride lipid-type A microspheres) for injectable suspension is supplied as a kit which includes one Lumason vial containing 25 mg of lipid-type A sterile lyophilized powder with the headspace filled with 60.7 mg of sulfur hexafluoride (SF₆) gas and one prefilled syringe containing the diluent, 5 ml sodium chloride 0.9% injection, USP. Following reconstitution with the provided saline, a milky suspension is formed containing $1.5\text{--}5.6 \times 10^8$ microspheres/ml with 45 mcg/ml of sulfur hexafluoride. The microspheres are composed of SF₆ gas in the core surrounded by an outer shell monolayer of phospholipids. The lipid layer is comprised of 1,2-distearoyl-sn-glycero-3-phosphocholine and 1,2-dipalmitoyl-sn-glycero-3-phospho-rac-glycerol sodium with palmitic acid employed as a stabilizer. They have a mean particle size diameter of 1.5–2.5 microns. Approval was based on the results of three clinical trials involving 191 patients with suspected cardiac disease whose echocardiograms were difficult to read and interpret [15]. Like all microbubble contrast agents the product will carry a black box warning due to the risk of serious cardiopulmonary reactions, including fatal cardiac or respiratory arrest.

Industry & regulatory update on Ebola

The severity and spread of the latest outbreak of Ebola virus disease in Africa, together with a few high-profile cases of infection in the US and Europe, meant that the deadly disease was rarely out of the headlines in October and November [16,17]. The virus is transmitted to people from wild animals and spreads through human-to-human transmission via direct contact with bodily fluids of infected people, and with contaminated surfaces and materials. On average 50% of patients affected by the disease will die from it. The current outbreak began in March 2014. It is the largest Ebola outbreak in terms of scale and number of countries affected since the virus was discovered in 1976.

On August 8 2014 the WHO declared the Ebola outbreak an international emergency. Since then there has been numerous initiatives undertaken by regulatory authorities to support the fight against this disease. For example on 22 October 2014 EMA made public its intention to start assessment of Ebola vaccines and treatments as soon as data are made available through a process of rolling review [18]. This will be conducted by a group of European experts with specialized knowledge in vaccines, infectious diseases and clinical trial

design. The EMA will share the initial review and subsequent updates with healthcare decision-makers in other countries.

The first review of this kind was conducted on an investigational Ebola virus vaccine from GSK [19]. This vaccine is being developed in conjunction with the US NIH's Vaccine Research Center and other partners and has entered clinical trials in USA, UK, Mali and Switzerland [20]. GSK acquired the vaccine when it bought the company, Okairos, in 2013. The vaccine uses chimpanzee adenovirus type 3 (ChAd3) as a carrier to deliver genetic material from two strains of the Ebola virus – the Sudan strain and the Zaire strain, the latter being responsible for the current Ebola outbreak in West Africa. GSK and the NIH are working together on the bivalent version of the candidate vaccine and a monovalent version targeting only the Zaire strain. The other vaccine for Ebola currently in Phase I clinical trials is an attenuated strain of the vesicular stomatitis virus that has been modified to express a specific Ebola protein that is involved in establishing infection [21]. Development of the vaccine was initiated at the Public Health Agency of Canada and then licensed to BioProtection Systems, a subsidiary of NewLink Genetics (IA, USA).

Other Ebola vaccine news in the time-frame of this article was Johnson & Johnson's (J&J) announcement [22] that it planned to invest up to \$200 million to accelerate and expand the development of an experimental Ebola vaccine regimen that was discovered in collaboration with NIH. The vaccine regimen has two components. One is based on AdVac® technology (novel adenovirus vectors) from Crucell Holland B.V., which is part of J&J. The other was developed by Bavarian Nordic A/S (Kvistgaard, Denmark) and is based on its MVA-BN® technology (further attenuated version of the Modified Vaccinia Ankara (MVA) virus, which itself is a highly attenuated strain of the poxvirus Chorioallantois Vaccinia virus Ankara (CVA) [23]). The regimen has achieved positive results in preclinical studies, and a safety and immunogenicity in healthy volunteers is planned in January in Europe, the US and Africa. The J&J's collaboration with Bavarian Nordic includes an equity investment in the Danish company.

Other treatments for Ebola in the news include ZMapp, a cocktail of three humanized monoclonal antibodies against Ebola. It is being developed by Mapp Biopharmaceuticals, Inc. (CA, USA) in collaboration with LeafBio (CA, USA), Defyrus, Inc. (Toronto, Canada), the US government and the Public Health Agency of Canada [24]. It has been in the headlines several times this year as it was administered to US health workers and a Spanish priest infected with Ebola despite never having been tested in humans as

there were no other treatments available. The health workers survived but sadly the priest did not. More recently in October it was again in the media when the US Biomedical Advanced Research and Development Authority requested three Centers for Innovation in Advanced Development and Manufacturing (run by or in partnership with major pharmaceutical or biotech companies) for plans, budgets and timelines to manufacture the drug after Mapp ran out of supplies [25]. Amgen, Inc. (CA, USA) independently pledged support for the efforts to obtain sufficient supplies of the product by [25] creating mammalian cell production lines for ZMapp; the use of mammalian cells being a more established method of producing monoclonals than the tobacco plants used by Mapp.

Clinical trials

APD421

On October 7 2014 Acacia Pharma Ltd (Cambridge, UK) made public the positive results from its Phase III studies of APD421 in post-operative nausea and vomiting (PONV) [26]. Significant numbers of patients suffer from PONV despite prophylactic treatment with currently available anti-emetics (5HT₃ antagonists, such as ondansetron, and/or corticosteroids). It is estimated that 30% of surgery patients experience vomiting and 50% nausea with the numbers affected by PONV rising to 80% in high-risk patients. The presence of PONV can increase the length of hospital stays and the number of re-admissions and, hence, add to overall healthcare costs. The trial data showed APD421 resulted in a statistically significant reduction in the incidence of PONV in adult surgical patients compared with placebo ($p = 0.005$). The two double-blind placebo-controlled trials involved 689 surgical patients with two or more of the validated 'Apfel' risk factors for PONV of whom 626 could be evaluated per protocol. The 'Apfel' risk factors are being female, a non-smoker, a previous history of PONV or motion sickness and the expected use of post-operative opioid analgesic. Each of these risk factors raise the risk of PONV by 20% so that patients with two of these factors have a moderate risk of experiencing PONV while those with all four have a 80% chance. In the Phase III studies APD421 resulted in a relative risk reduction of 19.4% of patients experiencing PONV, without an increase in side effects compared with placebo.

APD421 is the D2/D3 dopamine antagonist, amisulpride, formulated for intravenous use [27]. The drug is already licensed for the treatment of schizophrenia and is available in oral dosage forms. Acacia are positioning the drug as a rescue treatment for patients who are experiencing PONV despite prophylaxis treatment. In addition, APD421 is believed to have potential in

prophylactic therapy in high-risk patients in combination with 5HT3 antagonist and steroids. At present there is no satisfactory rapid therapy for PONV and therefore the company believes that APD421 meets a significant unmet need.

Patents

Sanovas

Sanovas, Inc. (CA, USA) released the news on 13 October 2014 that the United States Patent and Trademark Office (USPTO) had issued US Patent No. 8834544 [28]. The company as a whole is developing products to enable surgeons to access, visualize, diagnose, measure and treat obstructed passageways that are currently inaccessible [29]. The patent, entitled 'Photodynamic Therapy for Tumors with Localized Delivery' deals with new methods and systems for treatment of hypoxic tumors [30]. These include the positioning of a catheter with an inflatable balloon in a bodily cavity adjacent to the tumor tissue followed by the delivery of a photosensitizing agent to the tumor tissue via the delivery device, and then radiating the tumor tissue with light. The technology will enable clinicians to target therapy locally to diseased structures, for example, within the lung while protecting healthy tissue. It will also allow clinicians to monitor the effects of treatment in real time. The patent gives Sanovas broad IP protection for this technology.

Viacyte

Viacyte, Inc. (CA, USA) are developing a stem cell-derived pancreatic islet replacement therapy for the treatment of diabetes. On 6 November 2014 the firm announced that the USPTO had granted a patent, Patent 8859286 [31,32], which covers manufacturing methods for human pancreatic progenitor and endocrine cells for use in replacement therapy. The pancreatic progenitor cells are intended for implantation into the human body where they are designed to mature into islet cells which produce insulin. The patent concerns alternative methods for producing PEC-01, the company's proprietary pancreatic progenitor-containing cell population used in its VC-01 product candidate which is currently being tested in a Phase I/II trial. The patent also provides protection for methods to produce insulin-expressing cells closer to full differentiated beta cells *in vitro*.

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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References

- 1 Prima BioMed announces strategic acquisition of Immutep SA.
www.primabiomed.com.au/media/pm/2014/1173.php
- 2 Immutep website.
www.immutep.org
- 3 Prima BioMed website.
www.primabiomed.com.au/about_us
- 4 Novartis announces divestiture of influenza vaccines business to CSL for USD 275 million.
www.novartis.com/newsroom/media-releases/en/2014/1865897.shtml
- 5 CSL to acquire Novartis' influenza vaccine business.
www.csl.com.au/s1/cs/auhq/1187378853299/news/1252899900233/prdetail.htm
- 6 Rosenmayr-Templeton L. Industry update. *Ther. Deliv.* 5(7), 749–755 (2014)
- 7 Perrigo Company plc to acquire Omega Pharma NV for EUR 3.6 billion creating a top five global OTC company.
www.prnewswire.com/news-releases/perrigo-company-plc-to-acquire-omega-pharma-nv-for-eur-36-billion-creating-a-top-five-global-otc-company-281745261.html
- 8 Bristol-Myers Squibb enters into agreement that provides an exclusive option to acquire F-star Alpha Ltd. and its novel HER2-targeted therapy. 10.28.
www.f-star.com/documents/2014.10.28BristolMyersSquibb_000.pdf
- 9 F-star website.
www.f-star.com/about.php
- 10 Intarcia and Servier sign Ex-US partnership for ITCA 650 in diabetes; Intarcia retains independence & full control of the US & Japan.
<http://intarcia.com/media/press-releases/2014-nov-12-ex-us-partnership.html>
- 11 Intarcia therapeutics website.
<http://intarcia.com>
- 12 Geron announces global strategic collaboration with Janssen to develop and commercialize Imetelstat.
www.geron.com/Announcement-Janssen
- 13 The Geron company website.
www.geron.com/management
- 14 Entry for Lumason on drugs @FDA.
www.accessdata.fda.gov/drugsatfda_docs/nda/2014/203684Orig1s000Lbl.pdf
- 15 FDA approves a new ultrasound imaging agent. FDA news release.
www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm418509.htm
- 16 Ebola virus disease Fact sheet N°103 Updated September 2014.
www.who.int/mediacentre/factsheets/fs103/en/

- 17 Cases of Ebola diagnosed in the United States.
www.cdc.gov/vhf/ebola/outbreaks/2014-west-africa/united-states-imported-case.html
- 18 EMA ready to start assessment of Ebola vaccines and treatments as soon as data are made available.
www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2014/10/news_detail_002192.jsp&mid=WC0b01ac058004d5c1
- 19 EMA advises on development plan for GSK Ebola vaccine.
www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2014/10/news_detail_002202.jsp&mid=WC0b01ac058004d5c1
- 20 Our contribution to the fight against Ebola. GSK website.
www.gsk.com/en-gb/our-stories/health-for-all/our-contribution-to-the-fight-against-ebola/
- 21 NewLink Genetics Corporation.
<http://newlinkgenetics.com/>
- 22 Johnson & Johnson announces major commitment to speed Ebola vaccine development and significantly expand production.
www.jnj.com/news/all/Johnson-Johnson-Announces-Major-Commitment-to-Speed-Ebola-Vaccine-Development-and-Significantly-Expand-Production
- 23 Section on MVA-BN on Bavarian Nordic website.
www.bavarian-nordic.com/what-we-do/technologies/mva-bn.aspx
- 24 Mapp Biopharmaceutical Inc.,
www.mappbio.com
- 25 Begley S. US requests production plans for Ebola drug ZMapp.
www.reuters.com/article/2014/10/17/us-health-ebola-usa-zmapp-exclusive-idUSKCN0I624P20141017
- 26 Acacia Pharma announces positive Phase III results for APD421 in PONV.
http://acaciapharma.com/index.php/news/acacia_pharma_announces_positive_phase_3_results_for_apd421_in_ponv
- 27 Acacia Pharma website.
<http://acaciapharma.com/index.php>
- 28 Sanovas awarded seminal patent for novel radiation oncology drug/device platform.
www.sanovas.com/index.php/company/press-releases
- 29 Sanovas website
www.sanovas.com/
- 30 Gerrans LJ and Gunday EH. US8834544 (2014)
- 31 ViaCyte receives US patent claiming alternative methods to manufacture pancreatic progenitor cells *In Vitro*.
<http://viacyte.com/news-events-2/news/>
- 32 Agulnick AD. US8859286 (2014).