Monitoring International Trends

**posted February-March 2017**

The NBA monitors international developments that may influence the management of blood and blood products in Australia. Our focus is on:

* Potential new product developments and applications;
* Global regulatory and blood practice trends;
* Events that may have an impact on global supply, demand and pricing, such as changes in company structure, capacity, organisation and ownership; and
* Other emerging risks that could potentially put financial or other pressures on the Australian sector.

A selection of recent matters of interest appears below. Highlights include:

## Products

* + uniQure’s investigational gene therapy in severe haemophilia B, AMT-060, received breakthrough therapy designation from the US Food and Drug Administration (FDA).
  + A Phase III trial for Shire’s Vonvendi (to treat bleeds in elective surgical settings for adults with severe von Willebrand’s disease), found the drug to be effective.
  + Catalyst Biosciences announced positive preclinical results in haemophilia A and B with its next-generation Factor VIIa, and its next-generation Factor IX.
  + Swedish Orphan Biovitrum (Sobi) and Bioverativ presented new data on the long-term safety and efficacy of their extended half-life therapies in haemophilia A and B.
  + Dimension Therapeutics announced preliminary topline safety and early efficacy results of the company’s Phase I/II study of DTX101 for the treatment of adults with moderate/severe to severe haemophilia B.
  + Shire announced results from the Phase Ib study of lanadelumab which is being investigated for the prevention of attacks in hereditary angioedema.
  + Scientists have developed a hydrogel-based sealant that can be sprayed on wounds to stem severe bleeding, and can later be dissolved to allow surgery.
  + Merck announced results of the Phase III clinical trial of letermovir, for the prevention of clinically-significant cytomegalovirus (CMV) infection in adult CMV-seropositive recipients of an allogeneic hematopoietic stem cell transplant.
  + Biotest announced that the first patient had been treated in a Phase III study investigating IgG Next Generation as immunomodulatory therapy in selected patients with chronic primary immune thrombocytopenia.
  + Protalex provided an update on studies of PRTX-100 in adults with persistent, chronic Immune thrombocytopenia.
  + Prometic Life Sciences announced that PBI-4050 demonstrated early evidence of efficacy following completion of its idiopathic pulmonary fibrosis Phase II clinical trial.
  + bluebird bio announced treatment of the first patient under the amended study protocol in HGB-206, the company’s Phase I study of its LentiGlobin product in patients with severe sickle cell disease.

## Regulatory

* + Armetheon has reached agreement with the FDA for a single 1000 patient final pivotal trial for its oral anticoagulant, tecarfarin.
  + CSL Behring announced that the FDA had accepted for review the clinical efficacy supplement to its Biologics License Application for Privigen. This supplement seeks approval to treat chronic inflammatory demyelinating polyneuropathy
  + The European Medicines Agency (EMA) [granted access](http://seekingalpha.com/pr/16730538-biomarin-receives-access-priority-medicines-prime-regulatory-support-ema-bmn-270-gene-therapy) to its priority medicines (PRIME) regulatory initiative for BioMarin Pharmaceutical's gene therapy candidate for hemophilia A, [BMN-270](http://www.biomarin.com/products/pipeline/bmn-270/).
  + Imara announced that the FDA had granted orphan drug designation to IMR-687 for the treatment of sickle cell disease.
  + Ablynx submitted a marketing authorization application to the EMA seeking approval of caplacizumab, for acquired thrombotic thrombocytopenic purpura.
  + CSL Behring’s Zemaira for the treatment of severe Alpha-1 Antitrypsin deficiency received approval from Australia’s Therapeutic Goods Administration.

## Market structure and company news

* + ADMA Biologics agreed to acquire certain assets from Biotest.
  + Generex Biotechnology is buying 51 per cent of Emmaus Life Sciences, which has submitted a new drug application to the FDA for L-glutamine to treat sickle cell disease.
  + CSL made a net profit of $US 805.5 million in the six months to 31 December, an increase of 12 per cent from a year earlier, attributable in part to strong sales of immunoglobulins and specialty products. The company affirmed its full year guidance for underlying profit growth of 18 to 20 per cent, on a constant currency basis. It says albumin sales in China will generate around $US 600 million this financial year.
  + Kamada and Massachusetts General Hospital are evaluating the potential benefit of Kamada’s liquid Alpha-1 Antitrypsin (AAT) on liver preservation.
  + Russian drugmaker Pharmimex, and the Swedish unit of Swiss firm Octapharma, will invest up to $US102 million in building a new manufacturing plant for human cell-line derived recombinant factor VIII products in Russia.
  + [Swedish Orphan Biovitrum](http://media.ne.cision.com/l/odzxcxrv/www.sobi.com) has elected to add a novel product candidate (rFIXFc-XTEN) for the potential treatment of haemophilia B to the company’s collaboration agreement with Bioverativ.

## Safety and patient blood management

* + Researchers in Martinique screened blood donations during the Zika outbreak in 2016 using nucleic acid testing. They found some donations were positive for ZIKV, but only some of these donors were symptomatic 1 to 6 days after donating blood. They concluded that nucleic acid screening or pathogen reduction technology may be necessary to prevent transfusion-transmission of ZIKV.
  + The *1000 Genomes* project has led to the discovery of 1,000 previously unknown mutations which could have a negative effect in the case of blood transfusions.
  + Researchers compared postoperative outcomes of patients undergoing major gastrointestinal surgery in patients who had received only blood stored fewer than 35 days with outcomes for patients who received at least one unit of blood stored for 35 days or more. They found that after multivariate adjustment, transfusion of one or more of these older blood units increased the risk for postoperative complications. Older blood also led to increased number of days in the intensive care unit and to a longer hospital stay.
  + FibroGen reported positive topline results from two Phase III clinical studies of roxadustat, an orally administered small molecule for treatment of anaemia in dialysis-dependent and non-dialysis-dependent chronic kidney disease patients.
  + The FDA has approved a haemorrhagic shock detection device.
  + Johnson and Johnson and Bayer stopped a trial early after their anti-coagulant Xarelto proved it could beat aspirin at preventing major adverse cardiac events.
  + Eastman Chemical Co. says the results of a clinical trial to evaluate a non-phthalate plasticizer for medical applications suggest the product could be a “lead alternative” to using di-2-ethyyllhexyl phthalate (DEHP) to soften PVC blood bags.

## Research (not elsewhere included)

* + Researchers at the University of North Carolina at Chapel Hill have used light to activate a drug stored in circulating red blood cells so that it is released when and where required.
  + Researchers at the University of Illinois reported they can alter blood cell development through the use of biomaterials designed to mimic characteristics of the bone marrow.

## Infectious diseases

* + The US National Institute of Allergy and Infectious Diseases has begun a Phase 1 trial of a vaccine designed to provide broad protection against a range of mosquito-transmitted diseases, such as Zika, malaria, West Nile fever and dengue fever, and to hinder the ability of mosquitoes to transmit such infections.
  + Scientists have explored at the molecular level whether they can tamper with mosquito reproduction.
  + Researchers are optimistic about developing RNA vaccines for Zika.
  + Scientists have isolated Zika-specific monoclonal antibodies from the blood of a recuperating patient. Two of these bound and neutralised Zika virus in vitro, but did not show any activity against the four known strains of dengue
  + Researchers have found that the Zika virus crosses the placenta by latching on to foetal blood vessels
  + Researchers have identified an enzyme in the immune system that promotes the arthritis which follows infection with chikungunya. Others have identified a mechanism by which the chikungunya virus infects healthy cells and controls how severe the infection will be.
  + Emergent BioSolutions initiated a Phase Ib multiple ascending dose study to evaluate the safety and tolerability of UV-4B, a potential oral treatment for dengue.
  + Victoria has been experiencing its worst outbreak of Ross River virus in a decade.
  + Avian flu outbreaks in birds are occurring round the world, including H5N8, H5N6, H5N2, H5N1 and H7N9.
  + China has had a steady stream of human H7N9 cases. Several Chinese cities closed live poultry markets temporarily to slow the spread of H7N9 to humans, although experts criticised officials for failing to take preventative steps before the peak flu season started. China’s drug regulator announced that four kinds of vaccine for the H7N9 strain of bird flu virus have been approved for clinical trials.
  + As at 11 March 2017, Saudi Arabia had recorded 1573 laboratory-confirmed cases of MERS-CoV infection, including 650 deaths.
  + Positive clinical data has been presented on Inovio’s DNA-based vaccines against MERS and Zika.
  + A team led by two Queensland researchers has developed for Ebola an effective and economical post-exposure treatment, made with antibodies from horses.
  + Emergent BioSolutions will develop monoclonal antibody therapeutics for viral haemorrhagic fever under a task order from the US Biomedical Advanced Research and Development Authority (BARDA).

Table of Contents

[Products 1](#_Toc477852474)

[Regulatory 1](#_Toc477852475)

[Market structure and company news 2](#_Toc477852476)

[Safety and patient blood management 2](#_Toc477852477)

[Research (not elsewhere included) 3](#_Toc477852478)

[Infectious diseases 3](#_Toc477852479)

[1. Products 5](#_Toc477852480)

[Products for treating bleeding disorders 5](#_Toc477852481)

[Other products 7](#_Toc477852482)

[2. Regulatory 9](#_Toc477852483)

[3. Market structure and company news 10](#_Toc477852484)

[4. Country-specific events 12](#_Toc477852485)

[5. Safety and patient blood management 12](#_Toc477852486)

[Appropriate Transfusion 12](#_Toc477852487)

[Treating anaemia 13](#_Toc477852488)

[Other 13](#_Toc477852489)

[6. Research (not elsewhere included) 14](#_Toc477852490)

[7. Infectious diseases 16](#_Toc477852491)

[Mosquito-borne diseases 16](#_Toc477852492)

[Zika 16](#_Toc477852493)

[Chikungunya 18](#_Toc477852494)

[Dengue 18](#_Toc477852495)

[Ross River virus 18](#_Toc477852496)

[Yellow fever 18](#_Toc477852497)

[Malaria 18](#_Toc477852498)

[Avian influenza 19](#_Toc477852499)

[Avian Influenza in birds, wild and/or domestic 19](#_Toc477852500)

[Avian Influenza in humans 19](#_Toc477852501)

[MERS-CoV (Middle East Respiratory Syndrome-Coronavirus) 19](#_Toc477852502)

[Ebola virus disease 20](#_Toc477852503)

[Other diseases: occurrence, diagnosis, prevention and treatment 21](#_Toc477852504)

# Products

*Here the NBA follows the progress in research and clinical trials that may within a reasonable timeframe make new products available, or may lead to new uses or changes in use for existing products.*

## Products for treating bleeding disorders

* + uniQure announced that AMT-060, its proprietary, investigational gene therapy in patients with severe haemophilia B, had received breakthrough therapy designation[[1]](#footnote-1) from the US Food and Drug Administration (FDA). The designation was based on results from the ongoing, dose-ranging Phase I/II study that showed sustained increases in Factor IX , reductions in FIX replacement usage and a near cessation of spontaneous bleeding in patients with severe disease at up to 12 months’ follow-up.
  + In a Phase III trial for Shire’s orphan drug Vonvendi[[2]](#footnote-2) [von Willebrand factor (Recombinant)] to treat bleeds in major, minor and oral elective surgical settings for adults with severe von Willebrand disease (VWD), the drug was found to be effective in controlling bleeding and blood loss. The trial was an uncontrolled, open-label, nonrandomized, international, multi-centre study which enrolled 15 patients 18 years and older diagnosed with severe congenital VWD undergoing major and minor elective surgeries. The trial assessed Vonvendi’s haemostatic efficacy and safety when used before, during or after a surgical procedure, with or without, a recombinant Factor VIII (rFVIII) treatment[[3]](#footnote-3). Overall haemostatic efficacy was rated as “excellent” or “good” for all 15 treated patients in surgical procedures. Shire will submit a supplemental new drug application to the FDA to expand the indication for Vonvendi to preventing blood loss during surgery on VWD patients.
  + Catalyst Biosciences announced positive preclinical results in haemophilia A and B with marzeptacog alfa (activated), a next-generation Factor VIIa, and CB 2679d/ISU304, a next-generation Factor IX. The company said the results highlighted the attractive pharmacodynamics and pharmacokinetic profiles of both coagulation factors based on bioavailability, potency, time to maximal concentration, and half-life that should allow for subcutaneous dosing in individuals with haemophilia. The results were presented in poster sessions at the European Association of Haemophilia and Allied Disorders (EAHAD) 10th Annual Congress in Paris, from 1 to 3 February, 2017[[4]](#footnote-4). Catalyst plans to initiate a subcutaneous efficacy trial of marzeptacog alfa (activated) in people with haemophilia B in 2017. Also, Catalyst and its collaborating partner, ISU Abxis, plan to initiate a Phase I/II proof-of-concept intravenous/ subcutaneous clinical trial of CB 2679d/ISU304 in patients with haemophilia B in the second quarter of 2017.
  + Also at the EAHAD Congress, Swedish Orphan Biovitrum (Sobi) and Bioverativ presented new haemophilia data in nine posters[[5]](#footnote-5), including data on the long-term safety and efficacy of the companies’ extended half-life therapies, Elocta (efmoroctocog alfa), marketed as Eloctate [Antihemophilic Factor (Recombinant), Fc Fusion Protein] in the US, Japan and Canada, and Alprolix (eftrenonacog alfa), in people of all ages with haemophilia A and B, respectively, providing an updated analysis of long-term data from the registration studies ASPIRE and B-YOND.
  + Dimension Therapeutics announced preliminary topline safety and early efficacy results of the company’s multi-centre Phase I/II study of DTX101 for the treatment of adult patients with moderate/severe to severe haemophilia B. DTX101 is designed to deliver stable expression of blood clotting Factor IX (FIX) in patients with haemophilia B. Dimension reported results from the first two cohorts whose patients have been in post-treatment follow-up ranging from 6 to 52 weeks. All patients in both cohorts were said to have improved from moderate/severe-to-severe to either moderate or mild range in terms of factor levels based on World Federation of Hemophilia (WFH) criteria[[6]](#footnote-6). DTX101 has received orphan drug designation from the FDA and the European Commission.
  + Not all news from the Dimension study was good. Yes, DTX101 boosted the levels of the blood-clotting protein Factor IX in six patients. Yes, those on the higher of two tested doses hadn’t needed other drugs since being treated. But five of the six patients—and all three on the higher of the two tested doses—also saw a rise in liver enzyme levels, indicating an immune reaction to the gene therapy. This caused a delay for Dimension which had to await FDA feedback before testing an even higher dose of DTX101. The release of the early data from the Phase I/II trial of DTX101 led to a 49 per cent drop in Dimension’s share price. There are a number of experimental gene therapies being tested for haemophilia, and elevated liver enzymes are not unusual[[7]](#footnote-7).

## Other products

* + Shire announced the publication[[8]](#footnote-8) of results from the Phase Ib study of lanadelumab (SHP643; formerly DX-2930). Lanadelumab is a subcutaneously administered, human monoclonal antibody that specifically binds and inhibits plasma kallikrein, and it is being investigated for the prevention of angioedema attacks in patients with hereditary angioedema (HAE)[[9]](#footnote-9). Dr Paula Busse, of Mount Sinai Hospital, New York, said: "The overall results of this study are encouraging[[10]](#footnote-10); it should be noted that while the duration of treatment was relatively short and only a small number of patients were investigated, the results supported further Phase III investigations, which are currently ongoing."
  + Ionis Pharmaceuticals earned a $US 75M payment from licensee Bayer triggered by the advancement of two drug candidates, IONIS-FXIrx and IONIS-FXI-Lrx, designed to reduce the risk of thrombosis by reducing the production of Factor XI. Their main advantage claimed is the ability to separate antithrombotic activity from bleeding risk. IONIS-FXIrx is set to enter Phase IIb testing in around 200 patients with end-stage renal disease on haemodialysis with the aim of finalizing the optimal dose. IONIS-FXI-Lrx is in Phase I. The trials will be conducted by Ionis. If Bayer chooses to advance the development of the drugs, it will be responsible for all subsequent clinical development, along with regulatory and commercial activities. Ionis will earn milestones and tiered royalties.
  + Scientists in the US led by Boston University’s Mark Grinstaff have developed a hydrogel-based wound sealant that can be sprayed on to stem severe bleeding and later dissolved to allow surgery. So far, the efficacy of the material has been demonstrated in small animals with easily accessible wounds.
  + Merck announced results of the pivotal Phase III clinical trial of letermovir, an investigational antiviral medicine for the prevention of clinically-significant cytomegalovirus (CMV) infection in adult[[11]](#footnote-11) CMV-seropositive recipients of an allogeneic hematopoietic stem cell transplant[[12]](#footnote-12) (HSCT). The study met its primary efficacy endpoint, showing that significantly fewer patients with undetectable CMV DNA at the start of study treatment developed clinically significant CMV infection up to and including Week 24 post-HSCT[[13]](#footnote-13). Letermovir prophylaxis was associated with lower all-cause mortality up to and including Week 24 post-HSCT. Merck will submit regulatory applications for the approval of letermovir in the US and European Union in 2017.
  + Biotest announced that the first patient had been treated in study no. 992 - a Phase III study investigating IgG Next Generation as immunomodulatory therapy in patients with chronic primary immune thrombocytopenia[[14]](#footnote-14), who are either at high risk of bleeding or need their platelet count corrected before surgery. The trial will include around 40 patients and be conducted at sites in Germany, Hungary, Spain, Bulgaria, Czech Republic and Serbia. Study no. 992 is the second pivotal Phase III study in the clinical program for IgG Next Generation, a novel development of Biotest’s polyvalent immunoglobulin G. IgG Next Generation will be manufactured using a new production process and will be the master product for the new Biotest Next Level manufacturing facility[[15]](#footnote-15) currently under construction in Dreieich, Germany.
  + Protalex provided an update on its US Phase I/II and European Phase Ib studies of PRTX-100 in adults with persistent, chronic Immune Thrombocytopenia (ITP). PRTX-100 is a highly-purified form of Staphylococcal protein A. The drug has been granted orphan drug designation in the US and in Europe for the treatment of ITP. Data from initial cohorts in the two dose escalation trials of ITP patients treated with PRTX-100 have demonstrated an acceptable safety profile to support continued enrolment into higher-dose cohorts in both trials.
  + Prometic Life Sciences announced that PBI-4050 continues to demonstrate early evidence of efficacy following completion of its idiopathic pulmonary fibrosis phase II clinical trial. The company says there is early evidence of efficacy as a monotherapy and in combination with a commercially available drug, and that it continues to be very well tolerated, whether used alone or in combination with nintedanib or pirfenidone. Prometic intends in the second quarter of 2017 to initiate a pivotal Phase II/III clinical trial.
  + On 4 February 2017 bluebird bio announced treatment of the first patient under the amended study protocol in HGB-206, the company’s Phase I study of its LentiGlobin product in patients with severe sickle cell disease (SCD). The study now incorporates several changes with the goal of increasing production of therapeutic anti-sickling hemoglobin (HbAT87Q). To accommodate changes to the protocol, the study enrolment has been expanded for up to 29 patients[[16]](#footnote-16).
  + Global Blood Therapeutics on 14 February announced the publication of a paper[[17]](#footnote-17) describing the discovery of GBT440 and its ability to bind to haemoglobin and prevent red blood cells from sickling. GBT440 is in Phase III development as a potentially disease-modifying therapy for sickle cell disease.

# Regulatory

*The NBA monitors overseas regulatory decisions on products, processes or procedures which are or may be of relevance to its responsibilities.*

* + Armetheon has reached agreement with the FDA for a single 1000 patient final pivotal trial for its oral anticoagulant, tecarfarin, prior to filing a new drug application in 2019. The trial will include patients with prosthetic heart valves, repeat deep vein thrombosis and chronic kidney disease.
  + CSL Behring announced that the FDA had accepted for review the clinical efficacy supplement to its Biologics License Application (BLA) for Privigen (Immune Globulin Intravenous (Human), 10% Liquid). Privigen has previously been approved by the FDA to treat chronic immune thrombocytopenic purpura (ITP). This supplement seeks approval to treat chronic inflammatory demyelinating polyneuropathy (CIDP), a disease that may cause permanent nerve damage, to reduce neuromuscular impairment and to prevent relapse. Privigen received approval to treat CIDP in Europe in 2013. Two studies (PRIMA and PATH) have examined the efficacy of immunoglobulin therapy in treating CIDP. Data from the Phase III PRIMA study suggests that Privigen may help decrease weakness and loss of motor function.
  + The European Medicines Agency (EMA) [granted access](http://seekingalpha.com/pr/16730538-biomarin-receives-access-priority-medicines-prime-regulatory-support-ema-bmn-270-gene-therapy) to its priority medicines (PRIME) regulatory initiative for BioMarin Pharmaceutical's gene therapy candidate for hemophilia A, [BMN-270](http://www.biomarin.com/products/pipeline/bmn-270/). PRIME allows more intensive guidance from regulators and an accelerated review of the marketing application.
  + Imara announced that the FDA had granted orphan drug designation[[18]](#footnote-18) to the company’s lead product candidate IMR-687 for the treatment of sickle cell disease. Imara is conducting a Phase I a clinical study to evaluate the safety and pharmacokinetics of IMR-687 in healthy volunteers. It will also assess pharmacodynamic markers. The company says IMR-687 is a potentially disease-modifying therapeutic for sickle cell disease as well as other haemoglobinopathies. It reports that pre-clinical data demonstrate IMR-687 reduces both the sickling of red blood cells and blood vessel occlusion that cause severe pain, organ damage, and early death.
  + Belgian company Ablynx submitted a marketing authorization application (MAA) to the European Medicines Agency (EMA) seeking approval of its anti-von Willebrand factor (vWF) nanobody caplacizumab, for acquired thrombotic thrombocytopenic purpura (aTTP). The application relied on data from the Phase II Titan trial in patients with aTTP. The trial showed a statistically-significant and clinically-meaningful reduction in the time to platelet count normalization and reduced recurrences during treatment. Post-hoc analyses of the trial data showed that caplacizumab significantly reduced the number of patients experiencing major thromboembolic events, compared with placebo.
  + In Australia, CSL Behring’s Zemaira for the treatment of severe Alpha-1 Antitrypsin deficient (AATD) patients has received Therapeutic Goods Administration (TGA) approval and is now listed on the Australian Register of Therapeutic Goods (ARTG).

# Market structure and company news

*The NBA’s business intelligence follows company profitability, business forecasts, capital raisings or returns, mergers and takeovers, arrangements for joint research and/or development, contracts for supply of manufacturing inputs, and marketing agreements. Companies considered include suppliers, potential suppliers and developers of products which may be of interest.*

* + ADMA Biologics signed an agreement to acquire certain assets[[19]](#footnote-19) from Biotest Pharmaceuticals Corporation (BPC), a wholly-owned subsidiary of Biotest AG. ADMA’s lead product candidate, RI-002, is manufactured at BPC’s facility in Boca Raton, Florida. ADMA has been working closely with BPC on resolving certain issues at this facility in connection with deficiencies identified by the FDA in ADMA’s Complete Response Letter for RI-002 (July 2016). RI-002 is a specialty plasma-derived, polyclonal, intravenous immune globulin (IVIg). ADMA is pursuing an indication for the use of this specialty product for treatment of patients diagnosed with Primary Immune Deficiency Disease (PIDD). Adam Grossman, President and Chief Executive Officer, Director and Founder of ADMA Biologics, said: “We believe that combining these acquired assets with our innovative immune globulin intellectual property will afford ADMA an expedited and less costly pathway for exploring additional hyperimmune globulin product candidates, as well as other potential plasma derived products. We believe the plasma industry and market are poised for growth in the coming years…. ADMA believes that it has secured a prime place for it and its stockholders to reap the rewards associated with marketing novel plasma derived therapies.”
  + Canadian company Generex Biotechnology has moved to buy 51 per cent of Emmaus Life Sciences, the California based company that has submitted a new drug application to the FDA for L-glutamine to treat sickle cell disease.
  + The University of Pittsburgh and Bayer will collaborate to advance research for heart, lung and blood disease indications. The agreement covers early research studies, drug development and data analysis including real-world evidence studies.
  + CSL says albumin sales in China will generate around $US 600 million this financial year. CSL made a net profit of $US 805.5 million in the six months to 31 December, an increase of 12 per cent from a year earlier, attributable to in part to strong sales of immunoglobulins and specialty products. The company affirmed its full year guidance for underlying profit growth of 18 to 20 per cent, on a constant currency basis.
  + Kamada announced a collaboration with Massachusetts General Hospital to conduct a proof of concept study evaluating the potential benefit of Kamada’s liquid Alpha-1 Antitrypsin (AAT) on liver preservation[[20]](#footnote-20).
  + On 6 February, Kamada announced financial results for the twelve months ended December 31, 2016. Net loss was $US 6.7 million in 2016, compared with a net loss of $US 11.3 million in the same period of 2015. CEO Amir London said: “We met our revenue guidance for full year 2016, with over 30 per cent growth in our Proprietary Products revenues compared with the previous year…… Moreover, the extension of our supply agreement with Shire for GLASSIA® through 2020 underscores Shire’s solid outlook for higher long-term demand for GLASSIA® in the US. Our US Phase II study of inhaled Alpha-1 Antitrypsin (AAT) for the treatment of AAT Deficiency met its primary endpoint of a significant increase in endothelial lining fluid inhibitory capacity. We recently submitted this data to the European Medicines Agency (EMA) in support of our filed Inhaled AAT Marketing Authorization Application (MAA) and will also use it in our discussions with the FDA.” The company had already announced plans for a Phase II/III clinical trial in the US of Alpha-1 Antitrypsin IV (G1-AAT IV) for the treatment of Graft-Versus-Host Disease (GvHD) in collaboration with Shire[[21]](#footnote-21). It had also received advice from the Committee for Medicinal Products for Human Use (CHMP) of the EMA around the development program in Europe for G1-AAT IV for the treatment of acute GvHD with lower gastrointestinal involvement, including guidance related to the design of a planned Phase II/III European study.
  + Portola Pharmaceuticals sold the royalty rights to andexanet alfa (AndaxXa) to HealthCare Royalty Partners (HCR) for up to $US 150 million, to finance further development and commercialization of this Factor Xa inhibitor antidote. The recombinant protein has FDA’s Breakthrough Therapy designation. AndaxXa is a modified human Factor Xa molecule which reverses the anticoagulant effect of an oral or injectable Factor Xa inhibitor. Portola’s Biologics License Application to the FDA for AndexXa had been on an accelerated approval track in August 2016 when the FDA issued a Complete Response Letter requesting “additional information primarily related to manufacturing”. AndexXa’s marketing authorization application is under review by the EMA.
  + Russian drug maker Pharmimex, and the Swedish unit of Swiss biotech firm Octapharma, have announced plans to invest up to $US102 million in building of a new manufacturing plant for human cell-line derived recombinant factor VIII products in the Russian region of Ryazan. Construction will commence in 2017 and the plant will reach its full design capacity in 2022. Alexander Apazov, president of Pharmimex, says that the plant will undertake full-cycle production of von Willebrand factor, factor VIII, factor IX, immunoglobulin concentrate of 5 per cent and 10 per cent. The project also involves the establishment of eight plasma collection centers and modernization of the existing stations of blood banks with the capacity of 600 tonnes of plasma per year.
  + [Swedish Orphan Biovitrum](http://media.ne.cision.com/l/odzxcxrv/www.sobi.com) (Sobi) announced that it has elected to add a novel product candidate (rFIXFc-XTEN) for the potential treatment of haemophilia B to the company’s collaboration agreement with Bioverativ. By making a one-time payment to Bioverativ Sobi gains an opt-in right to participate in the final development and commercialisation of this product candidate. The opt-in right may be exercised by Sobi in connection with the submission of the marketing authorisation application for rFIXFc-XTEN with the EMA. Milan Zdravkovic, Senior Vice President, Chief Medical Officer, and Head of Research & Development at Sobi, said: “Sobi is committed to help address the unmet needs for people affected by haemophilia and we are pleased to engage with this innovative product candidate which has been designed for the subcutaneous treatment of haemophilia B.”

# Country-specific events

*The NBA is interested in relevant safety issues which arise in particular countries, and also instances of good practice. We monitor health issues in countries from which Australia’*s *visitors and immigrants come.*

* + Switzerland decided to lift its 40-year ban on gay and bisexual men giving blood, but will still prohibit donations from those who have had sex in the previous year, in line with other European countries like Britain and France. Swissmedic said the new rules will come into effect on July 1.
  + In the US, Emory University’s grant to establish the National Ebola Training and Education Center (NETEC) has been doubled from $US 12 million to $US 24 million.
  + In the US, the Centers for Disease Control (CDC) have awarded the University of Rochester (N.Y.) Medical Center $US 9 million over the next five years to continue its infectious disease surveillance efforts and conduct research to understand and prepare for emergent pathogens.

# Safety and patient blood management

*We follow current issues in patient safety and achieving favourable patient outcomes.*

## Appropriate Transfusion

* + Researchers in Martinique screened 4129 blood donations during the Zika outbreak in 2016 using nucleic acid testing. Over six months, 1.8 per cent of the blood donations were positive for ZIKV, with a peak of 3 per cent near the end of the study. The researchers followed a subset of ZIKV positive donors for symptoms, estimating that 80-85 per cent of infected donors never required medical care, although approximately 55 per cent of them were symptomatic 1 to 6 days after donating blood. The researchers concluded that nucleic acid screening or pathogen reduction technology may be necessary to prevent transfusion-transmission of ZIKV[[22]](#footnote-22).
  + The international project *1000 Genomes[[23]](#footnote-23)* has led to the discovery of 1,000 previously unknown mutations which could have a negative effect in the case of blood transfusions[[24]](#footnote-24). The project mapped blood group genes in healthy people, whereas hitherto most blood group variants were discovered when a blood transfusion failed. Not all variants lead to new antigens. Currently, there are over 350 known antigens, mainly identified in Europe and North America. As research expands into Africa and elsewhere, the discovery of new antigens can be expected.
  + The Peter Munk Cardiac Centre at Toronto General Hospital announced the launch of the FIBrinogen[[25]](#footnote-25) REplenishment in Surgery (FIBRES) study in acquired fibrinogen deficiency. FIBRES is a prospective, multi-centre, randomized, active-control, Phase III clinical trial comparing fibrinogen concentrate with cryoprecipitate[[26]](#footnote-26) for the treatment of acquired hypofibrinogenemia in bleeding adult cardiac surgical patients. The primary objective of this study is to demonstrate that a specific fibrinogen concentrate is non-inferior to cryoprecipitate with respect to efficacy in bleeding cardiac surgical patients in whom fibrinogen supplementation is ordered according to accepted clinical standards. Efficacy will be measured by the total number of allogeneic blood products administered during the first 24 hours after termination of cardiopulmonary bypass. Up to 12 Canadian hospitals and around 1,200 adult cardiac surgical patients (who require fibrinogen supplementation as a result of excessive bleeding due to acquired hypofibrinogenemia) will participate in the study. The human fibrinogen concentrate in the study is Octafibrin, under development by Octapharma for the treatment of congenital fibrinogen deficiencies. Octapharma is supporting the study.
  + In a single-centre nonrandomized trial, researchers compared postoperative outcomes of patients undergoing major gastrointestinal surgery (pancreatic, hepatic, or colonic) in 936 patients who had received only blood stored fewer than 35 days with outcomes for 429 patients who received at least one unit of blood stored for 35 days or more. They found that after multivariate adjustment, transfusion of one or more of these older blood units increased the risk for postoperative complications by 20 per cent (P=.03). Older blood also led to increased number of days in the intensive care unit and to a longer hospital stay[[27]](#footnote-27).

## Treating anaemia

* + FibroGen and its subsidiary FibroGen China Medical Technology Development Co., reported positive topline results from the two Phase III clinical studies of roxadustat (FG-4592) designed to support a new drug application submission in China. Roxadustat is a first-in-class, orally administered small molecule for treatment of anaemia in dialysis-dependent and non-dialysis-dependent chronic kidney disease patients. Both of the Phase III studies met their primary efficacy endpoints, which were evaluated in the comparator-controlled portions of the studies.

## Other

* + The FDA has approved a haemorrhagic shock detection device developed by US Army researchers, scientists and engineers from the University of Colorado, and **Flashback Technologies**. Victor Convertino, a senior scientist with the Army Institute of Surgical Research, said the device will help medics attend to wounded warriors in battlefield conditions where there are “lots of noise, lots of adrenaline and not much equipment.” USAISR noted traditional methods to take vital signs cannot detect when a patient is in danger of crashing or going into haemorrhagic shock which could lead to death due to blood loss.
  + Johnson and Johnson and Bayer announced that they had stopped a trial early after their next-generation anti-coagulant Xarelto proved it could beat aspirin at preventing major adverse cardiac events—including heart attack, stroke and CV death—in patients with coronary artery disease or peripheral artery disease. The study had been set to run through March of next year.
  + A Danish study has examined the clinical effectiveness and safety of (reduced doses) apixaban 2.5 mg, dabigatran 110 mg, and rivaroxaban 15 mg compared with warfarin among patients with atrial fibrillation who had not previously taken an oral anticoagulant[[28]](#footnote-28). Researchers concluded in this propensity weighted nationwide study of reduced dose non-vitamin K antagonist oral anticoagulant regimens that apixaban 2.5 mg twice a day was associated with a trend towards higher rates of ischaemic stroke/systemic embolism compared with warfarin, while rivaroxaban 15 mg once a day and dabigatran 110 mg twice a day showed a trend towards lower thromboembolic rates. Rates of bleeding (the principal safety outcome) were significantly lower for dabigatran, but not significantly different for apixaban and rivaroxaban compared with warfarin.
  + Eastman Chemical Co. says the results of a clinical trial to evaluate a non-phthalate plasticizer for medical applications suggest the product[[29]](#footnote-29) could be e a “lead alternative” to using di-2-ethyyllhexyl phthalate (DEHP) to soften PVC blood bags. DEHP migrates at low levels into the blood product. The European Commission has classified DEHP and three other phthalates as substances of very high concern and is expected to ban their use in medical devices by mid-2021.

# Research (not elsewhere included)

*A wide range of scientific research has some potential to affect the use of blood and blood products. However, research projects have time horizons which vary from “useful tomorrow” to “at least ten years away”. Likelihood of success of particular projects varies, and even research which achieves its desired scientific outcomes may not lead to scaled-up production, clinical trials, regulatory approval and market development.*

* + In a presentation to the Society for Maternal-Fetal Medicine's annual meeting[[30]](#footnote-30), researchers reported findings of a study titled *Randomized double-blind placebo controlled evaluation of the safety and efficacy of recombinant Antithrombin versus placebo in preterm preeclampsia*. The study was sponsored by rEVO Biologics. Preeclampsia can cause maternal and perinatal mortality and morbidity. This trial examined the effects of recombinant antithrombin (specifically ATryn), and its potential to prolong gestation and improve maternal and neonatal outcomes. The study was completed in patients who developed preeclampsia very early in pregnancy, 23-30 weeks' gestational age. Baha Sibai, from the University of Texas Health Science Center at Houston, reported that the study found no improvement in outcomes from the therapy but there were no reported safety events relating to it.
  + Researchers at Emory University report that the red berries of the Brazilian peppertree contain an extract with the power to disarm dangerous antibiotic-resistant staph bacteria[[31]](#footnote-31).
  + Kawasaki disease is the leading cause of acquired heart disease in infants and children in the US. Researchers at the University of California San Diego School of Medicine, Rady Children's Hospital-San Diego and Betty Irene Moore School of Nursing at University of California Davis have received a $US 2 million grant from the Patient-Centered Outcomes Research Institute (PCORI) for a three-year study to look at the effectiveness of two treatment options for children with Kawasaki disease who are resistant to initial therapy. Standard treatment is intravenous immunoglobulin, but up to 20 per cent of patients are resistant to this therapy, putting them at a higher risk coronary artery damage and aneurysms. Most patients receive either a second infusion of IVIG or an engineered antibody called infliximab that inactivates a molecule that promotes inflammation. The recent PCORI grant will support a study to compare the effectiveness of these two approaches for IVIG-resistant KD patients.
  + Researchers at the University of North Carolina at Chapel Hill have used light to activate a drug stored in circulating red blood cells so that it is released when and where required[[32]](#footnote-32). Research leader David Lawrence[[33]](#footnote-33) says the technique could reduce the amount of a drug needed and hence its side effects.
  + Scientists have shown[[34]](#footnote-34) neutrophil extracellular traps (NETs) contribute to organ dysfunction in sepsis by inducing widespread intravascular thrombosis, resulting in impaired tissue perfusion and end-organ damage.
  + T2 Biosystems of Lexington, Massachusetts, announced that a new study[[35]](#footnote-35), supporting the use of T2 Magnetic Resonance technology as a platform with the potential to provide a more sensitive and biologically relevant read-out of platelet dysfunction than traditional diagnostic methodologies, including Light Transmission Aggregometry (LTA). T2 Magnetic Resonance uses miniaturized magnetic resonance technology that measures how water molecules react in the presence of magnetic fields. The method is highly sensitive to changes in the microenvironment of a blood sample, such as clot formation, contraction and lysis. This facilitates quick identification of clinically relevant haemostasis changes.
  + A research team at the University of North Carolina[[36]](#footnote-36) has engineered a new method to attach specific cancer-fighting antibodies to the surface of platelets, which then travel to the wound site after cancer surgery to kill cancerous micro-tumors or circulating tumor cells. It was tested in mice with melanoma and breast cancer tumours. Treated mice **had prolonged survival and reduced risk of cancer regrowth and metastatic spread.**
  + Researchers at the University of Illinois reported they can alter blood cell development through the use of biomaterials designed to mimic characteristics of the bone marrow. Their findings[[37]](#footnote-37) are a first step toward developing more effective bone marrow treatments for diseases like leukemia and lymphoma.

# Infectious diseases

*The NBA takes an interest in infectious diseases because: the presence of disease in individual donors (e.g. influenza), or potential disease resulting from travel (e.g. malaria) means a donor must be deferred; temporary disease burden within a community (e.g. dengue in North Queensland) may limit blood collection in the community for a time; and some people may not be permitted to donate at all (e.g. people who lived in the UK for a period critical in the history of vCJD). Blood donations are tested for a number of diseases (e.g. HIV and Hepatitis B), but there are also emerging infectious diseases for which it may become necessary to test in the future (e.g. Chagas disease, Zika virus and the tick-borne babesiosis and Lyme disease).*

## Mosquito-borne diseases

* + Microsoft and partners are engaging in [Project Premonition](https://www.microsoft.com/en-us/research/project/project-premonition/) to predict the outbreaks of emerging infectious diseases such as Zika, Ebola, Chikungunya and MERS. Drones identify hotspots of mosquitoes, which are then captured by robots that extract the blood sucked by mosquitoes. These samples are analysed by cloud scale gene sequencers that use machine learning to identify diseases.
  + In the US, the National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health, has begun a Phase 1 trial[[38]](#footnote-38) of a vaccine designed to provide broad protection against a range of mosquito-transmitted diseases, such as Zika, malaria, West Nile fever and dengue fever, and to hinder the ability of mosquitoes to transmit such infections. The vaccine, AGS-v, was developed by the London-based company SEEK, now in a joint venture with hVIVO. AGS-v is designed to trigger an immune response to mosquito saliva rather than to a specific pathogen carried by mosquitoes[[39]](#footnote-39).
  + Scientists at the University of California, Riverside have explored at the molecular level whether they can tamper with mosquito reproduction. They focussed on small regulatory RNA molecules, called microRNAs, which are critical to mosquito egg maturation[[40]](#footnote-40).

### Zika

* + Disease ecologist Barbara Han**[[41]](#footnote-41)** told the American Society for Microbiology Biothreats meeting in Washington DC on 6 February that “spillback” of the Zika virus into primates raises risk of future human outbreaks. In areas where Zika is raging among humans and mosquitoes are abundant, the virus may be transmitted to monkeys or other wild primates which will serve as reservoirs for future human outbreaks and make it nearly impossible to get rid of the virus**[[42]](#footnote-42)**.
  + Two publications provide optimistic results concerning the promise of developing RNA vaccines for Zika.
    1. Researchers have protected mice against Zika by injecting them with synthetic messenger RNA that encodes for virus proteins. The cells of the mice then build parts of the virus, training the immune system to recognize a future infection[[43]](#footnote-43). A human clinical trial for Zika RNA vaccine is currently recruiting[[44]](#footnote-44). Mouse studies are needed to test whether the vaccine can prevent mother-to-foetus transmission.
    2. Researchers report that a single dose of an experimental Zika vaccine protected mice and monkeys from the virus. They say this is the first vaccine to show strong and long-lasting protection against Zika without the use of a live virus. This vaccine uses tiny strands of RNA that contain the genetic codes for making viral proteins[[45]](#footnote-45).
  + Scientists have isolated Zika-specific monoclonal antibodies from the blood of a recuperating patient[[46]](#footnote-46). Two of these bound and neutralised Zika virus in vitro, but did not show any activity against the four known strains of dengue. Mice infected with Zika virus were protected when either monoclonal antibody was administered one day after infection. The researchers say the results show the promise of antibody-based immunotherapy against Zika virus, and provide a basis for the design of future Zika-specific antivirals[[47]](#footnote-47).
  + Researchers have found that the Zika virus crosses the placenta by latching on to foetal blood vessels[[48]](#footnote-48).
  + The Florida Department of Health has awarded The University of Miami a $US 13 million grant from to fund Zika-related research, including rapid testing and assessments of infants with mothers who have the virus.

### Chikungunya

* + Researchers at QIMR Berghofer Medical Research Institute have identified in a mouse study an enzyme in the immune system that promotes the arthritis which follows infection with chikungunya[[49]](#footnote-49). The international study was led by Professor Andreas Suhrbier from the Inflammation Biology Laboratory at QIMR Berghofer. He said: "We've got a brand new drugable target that will hopefully lead to better treatment for this kind of disease and hopefully also related diseases like Ross River disease."
  + Researchers led by the Johns Hopkins Bloomberg School of Public Health have identified a mechanism by which the chikungunya virus infects healthy cells and controls how severe the infection will be. They believe the mechanism can be found in a number of other related viruses, and that their findings[[50]](#footnote-50) could be a first step toward developing drugs to treat or prevent diseases caused by alphaviruses (such as chikungunya) and coronaviruses (such as SARS).

### Dengue

* + Emergent BioSolutions announced the initiation of a Phase Ib multiple ascending dose study to evaluate the safety and tolerability of UV-4B, an antiviral candidate being developed as a potential oral treatment for dengue. This study, to enrol 40 healthy adults at US sites, follows a successful Phase Ia single ascending dose study completed in 2016. Preclinical studies have shown that UV-4B is active in vitro against all four dengue virus subtypes and in vivo studies have shown improved survival even when dosing was delayed by up to 48 hours after infection.

### Ross River virus

* + Nearly 150 cases of Ross River Virus were reported to Murrumbidgee Local Health District in January 2017, up from 116 in the previous month. "This is a significantly higher number of notifications than we usually see in January," district public health director Tracey Oakman said. Over the summer, she had received notification of a number of different arboviruses detected in mosquitoes, including Ross River Virus, Barmah Forest Virus, Kunjin and Sindbis Virus. Victoria has been experiencing its worst outbreak of Ross River virus in a decade, with 654 cases diagnosed in January alone.

### Yellow fever

* + The Brazilian government announced on 3 February 2017 that the number of confirmed deaths caused by so far by a yellow fever outbreak had reached 60, while 87 more suspicious deaths were being investigated. The country had moved to expand its yellow fever vaccine profile by 11.5 million doses.

### Malaria

* + Scientists say multidrug-resistant malaria superbugs are threatening to undermine progress against the disease. The superbugs - malaria parasites that can beat off the best current treatments, artemisinin and piperaquine - have spread throughout Cambodia, with even fitter multidrug resistant parasites spreading in southern Laos and north eastern Thailand.

## Avian influenza

*Because of the capacity of influenza viruses for reassortment, the spread of influenza strains in animals and birds is of interest as one or more strain may eventually develop the potential to cause a pandemic in humans. There are also strains which, while primarily infecting and being transmitted by animals or birds, nevertheless can infect humans, and the concern there is that human-to-human transmission might develop.*

### Avian Influenza in birds, wild and/or domestic

* + On 23 January Italy announced a new outbreak of H5N8 in poultry. Further reports of H5N8 avian flu outbreaks have been sent to the World Organisation for Animal Health (OIE) from a number of European countries including France, Germany, Poland, Croatia, Spain, Greece, Russia and Slovakia. H5N8 was detected in breeding pheasants in the UK and in poultry in the Middle East. New outbreaks are occurring. South Korea has culled over 33 million hens during an outbreak of H5N6, leaving the country short of about 15million dozen eggs per week. Taiwan reported its first H5N6 avian flu outbreak in birds. H5N6 had earlier been reported in Chinese poultry flocks, and since 2014 the virus has been linked to 17 infections in humans, all of them in China. In other Taiwan developments, officials reported seven more highly pathogenic H5N2 outbreaks to the OIE, Taiwan has reported scores of H5N2 outbreaks since early 2015. Vietnam reported H5N6 and H5N1 outbreaks. Egypt reported H5N1.

### Avian Influenza in humans

* + China’s drug regulator announced that four kinds of vaccine for the H7N9 strain of bird flu virus have been approved for clinical trials. They have been developed by Beijing Tiantan Biological Products Co, a State-owned enterprise.
  + China has had a steady stream of H7N9 avian flu cases. Several Chinese cities closed live poultry markets temporarily in an attempt to slow the spread of H7N9, although experts criticised officials for failing to take preventative steps before the peak flu season started.
    1. “Work should be done even before the first human case is found each year,” said Professor Malik Peiris, a public health virologist at the University of Hong Kong. “Local governments should step up regulating farm and market inspection, instead of only reacting by closing down markets once cases are detected.” Prof Peiris said all provincial governments must carry out regular checks of local live poultry markets, which he said was the most effective way to prevent human infection.
    2. Professor George Fu Gao, from the Institute of Microbiology affiliated with the Chinese Academy of Sciences, said authorities had lowered their guard after the past two years, when outbreaks were less severe. “The measures needed are quite clear: Shut down live poultry markets,” said Prof Gao. “We have advocated permanent closure of live poultry markets and for only quarantined chicken to be traded, but the enforcement is lagging.” India has been experiencing a severe outbreak of swine flu in humans.

## MERS-CoV (Middle East Respiratory Syndrome-Coronavirus)

* + As at 11 March 2017, Saudi Arabia had recorded 1573 laboratory-confirmed cases of MERS-CoV infection, including 650 deaths.
  + Researchers[[51]](#footnote-51) have analysed the antiviral activities of resveratrol, a compound found in grape seeds and skin and in red wine, against MERS-CoV infection. They reported that resveratrol inhibited MERS-CoV infection and prolonged cellular survival after infection.
  + Inovio Pharmaceuticals announced on 23 February that Dr. David B. Weiner, Inovio’s co-founder, presented positive clinical data on Inovio’s DNA-based vaccines against MERS (GLS-5300) and Zika (GLS-5700) at the Coalition for Epidemic Preparedness Innovation (CEPI)’s First Scientific Meeting on *Vaccines Against Emerging Infections - A Global Insurance* in Paris[[52]](#footnote-52). Dr J. Joseph Kim, Inovio’s CEO, said: “Advancing DNA vaccine technology for broadly applicable, rapid response against infectious diseases of epidemic potential is one of Inovio’s priorities. We quickly designed and manufactured vaccines for two recent emerging infectious pathogens, MERS CoV and Zika, and these products join our Ebola program in generating significant immune responses with a favorable safety profile in phase I studies[[53]](#footnote-53). We are pleased to see CEPI moving forward on its vision for proactive and accelerated vaccine development for epidemic threats and to contribute to their first scientific meeting.”

## Ebola virus disease

* + Researchers who treated patients in Sierra Leone during the 2013-2015 Ebola outbreak published a study[[54]](#footnote-54) to assist healthcare providers to judge which Ebola patients need the most attention in the critical first days after diagnosis.
  + Researchers[[55]](#footnote-55) reported 6 February at the American Society for Microbiology Biothreats meeting[[56]](#footnote-56) that they are developing a quicker and more effective test for the presence of the Ebola virus.
  + An international team led by two Queensland researchers[[57]](#footnote-57) reported it had developed for Ebola an effective and economical post-exposure treatment, made with antibodies from horses[[58]](#footnote-58).

## Other diseases: occurrence, diagnosis, prevention and treatment

* + Emergent BioSolutions will develop monoclonal antibody therapeutics for viral haemorrhagic fever under a task order from the US Biomedical Advanced Research and Development Authority (BARDA) that is valued at up to $US 30.5 million.
  + Researchers at the UK’s National Institute for Biological Standards and Control have found a way to produce a stable fragment of poliovirus, which could enable safer production of vaccines[[59]](#footnote-59).
  + A Canadian man contracted HIV even though he had been taking daily prophylactic medication. Genetic analysis of the virus showed he was infected with a strain of HIV that had become resistant to the anti-HIV drug Truvada.

1. In the US, the 2012 Food and Drug Administration Safety and Innovation Act (FDASIA) established the Breakthrough Therapy designation to expedite the development and review of new drugs with preliminary clinical evidence demonstrating that they may offer a substantial improvement over available therapies for patients with serious or life-threatening diseases. The Breakthrough Therapy designation is a distinct status from both accelerated approval and priority review, which can also be granted to the same drug if relevant criteria are met. According to FDA data for its fiscal year 2016, the Center for Biologics Research and Review received a total of 23 requests for Breakthrough Therapy designation with only 4 designations granted. [↑](#footnote-ref-1)
2. Vonvendi is the first FDA-approved recombinant von Willebrand factor. The FDA approved Vonvendi for VWD in December 2015. [↑](#footnote-ref-2)
3. If the patient’s baseline plasma FVIII:C level is below 40 per cent, or is unknown, it is necessary to administer an approved (non–von Willebrand factor–containing) rFVIII with the first infusion of Vonvendi to achieve a haemostatic plasma level of FVIII. [↑](#footnote-ref-3)
4. ***Pharmacokinetics and Pharmacodynamics Of Daily Subcutaneously Administered Marzeptacog Alfa (Activated) In Hemophilia Dogs*** (Poster abstract #P076) Howard Levy, Timothy Nichols, Martin Lee, Elizabeth Merricks, Robin Raymer, and Andrew Hetherington**; *Pharmacokinetics of Subcutaneously Administered CB 2679D/ISU304 In Minipig Compared with Benefix*** (Poster abstract #P074) Seung-Beom Hong, Howard Levy, Jae Yong Jung, Minkyung Park, A Rim Seo, and June Young Park; and ***Pharmacokinetics and Pharmacodynamics of Daily Subcutaneously Administered CB 2679D/ISU304 In Hemophilia B Dogs*** (Poster abstract #P075) Howard Levy, Timothy Nichols, Elizabeth Merricks, Robin Raymer, and Andrew Hetherington. Posters are available for viewing and download from the company’s website. [↑](#footnote-ref-4)
5. * Elocta/Eloctate – Long-term safety and efficacy data across all age groups
   * Poster P023: *Dosing Regimens Before and During Long-Term Treatment With Recombinant Factor VIII Fc Fusion Protein (rFVIIIFc) in Children With Severe Haemophilia A: An Updated Analysis of the ASPIRE Study*
   * Poster P100: *Dosing Regimens Before and During Long-Term Treatment With Recombinant Factor VIII Fc Fusion Protein (rFVIIIFc) in Adults and Adolescents With Severe Haemophilia A: An Updated Analysis of the ASPIRE Study*
   * Alprolix – Long-term safety and efficacy data across all age groups
   * Poster P108: *Individualised Prophylaxis in Children With Haemophilia B Treated Long Term With Recombinant Factor IX Fc Fusion Protein (rFIXFc): Updated Interim Results of the B-YOND Extension Study*
   * Poster P094: *Individualised Prophylaxis with Recombinant Factor IX Fc Fusion Protein (rFIXFc) in Adults/Adolescents with Haemophilia B: Updated Interim Results of the B-YOND Extension Study*
   * Poster P069: *Long-Term Safety and Efficacy of Recombinant Factor IX Fc (rFIXFc) For Treatment of Severe Haemophilia B: European Subgroup Interim Analysis of the B-Yond Study*
   * Poster P088: *Impact of Adherence on Outcomes of Prophylactic Treatment in Severe Haemophilia Patients*
   * Furthering the understanding of the potential with the haemophilia treatments
   * Poster P195: *The Cost-Utility Analysis of ELOCTA® (Efmoroctocog Alfa) in the Swedish Setting*
   * Poster P098: *Utilisations and Costs of Bypass Therapies for the Management of Haemophilia A Patients With Inhibitors*
   * Poster P086: *Burden of Illness in Haemophilia Across the Life Course*

   Abstracts are available through the EAHAD 2017 web site, <http://eahad2017.com/> [↑](#footnote-ref-5)
6. Additional information about Dimension’s Phase I/IIstudy of DTX101 may be found at [ClinicalTrials.gov](http://clinicaltrials.gov), using Identifier NCT: NCT02618915. [↑](#footnote-ref-6)
7. Eg Spark therapeutics and Uniqure in haemophilia B and Biomarin Pharmaceutical in haemophilia A. This is thought to suggest that patients’ immune systems are attacking their liver cells, which are the ones that take up the therapeutic gene and producing the new clotting protein. Patients have usually received a short course of immunosuppressive steroids and have avoided serious side effects, but this could dampen the response to gene therapy. [↑](#footnote-ref-7)
8. Aleena Banerji, Paula Busse, Mustafa Shennak, William Lumry, Mark Davis-Lorton, Henry J. Wedner, Joshua Jacobs, James Baker, Jonathan A. Bernstein, Richard Lockey, H. Henry Li, Timothy Craig, Marco Cicardi, Marc Riedl, Ahmad Al-Ghazawi, Carolyn Soo, Ryan Iarrobino, Daniel J. Sexton, Christopher TenHoor, Jon A. Kenniston, Ryan Faucette, J. Gordon Still, Harvey Kushner, Robert Mensah, Chris Stevens, Joseph C. Biedenkapp, Yung Chyung, and Burt Adelman, “Inhibiting Plasma Kallikrein for Hereditary Angioedema Prophylaxis”, *N Engl J Med* 2017; 376:717-728, February 23, 2017DOI: 10.1056/NEJMoa1605767 [↑](#footnote-ref-8)
9. HAE results in recurrent, localized oedema (swelling). The areas of the body most commonly affected are the extremities, gastrointestinal tract, and upper airways. [↑](#footnote-ref-9)
10. Dr. Aleena Banerji, of Massachusetts General Hospital, said: "In this Phase Ib study, no serious adverse events or discontinuations due to adverse events were observed at all doses studied. Pre-specified efficacy analyses in patients with at least 2 attacks in the 3 months prior to enrolment demonstrated that from day 8 to day 50, the administration of two doses of lanadelumab (300 or 400 mg) 14 days apart, reduced the rate of attacks by 100% and 88% respectively, when compared with placebo. In addition, all subjects were attack-free in the 300mg group and 82% were attack-free in the 400 mg group, compared to 27% in the placebo group." [↑](#footnote-ref-10)
11. 18 years and older [↑](#footnote-ref-11)
12. known as a bone marrow transplant (BMT). [↑](#footnote-ref-12)
13. using a non-complete equals failure approach, in which patients who discontinued from the study prior to Week 24 post-transplant or had a missing outcome at Week 24 post-transplant were counted as failures [↑](#footnote-ref-13)
14. This is an autoimmune disease in which the immune system attacks and destroys the body's own platelets [↑](#footnote-ref-14)
15. Biotest is more than doubling the production capacity of the Biotest Group with the "Biotest Next Level" investment program. This program includes the construction of a basic plasma fractionation facility with 1.4 million litre capacity, and bulk production plants for albumin, new fibrinogen and IgM concentrate product lines, and next-generation polyvalent immunoglobulins. [↑](#footnote-ref-15)
16. For more information on the HGB-206 Study, go to [http://www.clinicaltrials.gov](http://cts.businesswire.com/ct/CT?id=smartlink&url=http%3A%2F%2Fwww.clinicaltrials.gov&esheet=51504526&newsitemid=20170203005101&lan=en-US&anchor=http%3A%2F%2Fwww.clinicaltrials.gov&index=2&md5=b912e7b8481e6598a0330bbe6f90b4bd) using identifier NCT02140554. [↑](#footnote-ref-16)
17. [Brian Metcalf](http://pubs.acs.org/author/Metcalf%2C+Brian), [Chihyuan Chuang](http://pubs.acs.org/author/Chuang%2C+Chihyuan), [Kobina Dufu](http://pubs.acs.org/author/Dufu%2C+Kobina), [Mira P. Patel](http://pubs.acs.org/author/Patel%2C+Mira+P), [Abel Silva-Garcia](http://pubs.acs.org/author/Silva-Garcia%2C+Abel), [Carl Johnson](http://pubs.acs.org/author/Johnson%2C+Carl), [Qing Lu](http://pubs.acs.org/author/Lu%2C+Qing), [James R. Partridge](http://pubs.acs.org/author/Partridge%2C+James+R), [Larysa Patskovska](http://pubs.acs.org/author/Patskovska%2C+Larysa), [Yury Patskovsky](http://pubs.acs.org/author/Patskovsky%2C+Yury), [Steven C. Almo](http://pubs.acs.org/author/Almo%2C+Steven+C), [Matthew P. Jacobson](http://pubs.acs.org/author/Jacobson%2C+Matthew+P), [Lan Hua](http://pubs.acs.org/author/Hua%2C+Lan), [Qing Xu](http://pubs.acs.org/author/Xu%2C+Qing), [Stephen L. Gwaltney](http://pubs.acs.org/author/Gwaltney%2C+Stephen+L+II)II, [Calvin Yee](http://pubs.acs.org/author/Yee%2C+Calvin), [Jason Harris](http://pubs.acs.org/author/Harris%2C+Jason), [Bradley P. Morgan](http://pubs.acs.org/author/Morgan%2C+Bradley+P), [Joyce James](http://pubs.acs.org/author/James%2C+Joyce), [Donghong Xu](http://pubs.acs.org/author/Xu%2C+Donghong), [Athiwat Hutchaleelaha](http://pubs.acs.org/author/Hutchaleelaha%2C+Athiwat), [Kumar Paulvannan](http://pubs.acs.org/author/Paulvannan%2C+Kumar), [Donna Oksenberg](http://pubs.acs.org/author/Oksenberg%2C+Donna), and [Zhe Li](http://pubs.acs.org/author/Li%2C+Zhe), “Discovery of GBT440, an Orally Bioavailable R-State Stabilizer of Sickle Cell Hemoglobin”, American Chemical Society Medicinal Chemistry Letters, 2017, 8 (3), pp 321–326 Publication Date (Web): January 23, 2017 **DOI:**10.1021/acsmedchemlett.6b00491 [↑](#footnote-ref-17)
18. The FDA Office of Orphan Products Development grants orphan drug designation to novel drugs and biologics that are intended for the safe and effective treatment, diagnosis or prevention of rare diseases or disorders that affect fewer than 200,000 people in the US. [↑](#footnote-ref-18)
19. Including property, facilities, laboratories, equipment and certain employees located at 5800 and 5900 Park of Commerce Blvd, Boca Raton, Florida. This encompasses a fully equipped plasma fractionation and purification plant of FDA licensed biologics, testing laboratories, office space, ambient and cold storage warehouses, and a commercial scale monoclonal antibody production facility. ADMA also acquires FDA licensed products including Nabi-HB (Hepatitis B Immune Globulin, Human) and BIVIGAM (Immune Globulin Intravenous, Human)

    Biotest AG will maintain its existing distribution rights granted for RI-002 in Europe, Near and Middle East and selected other territories and a right of first offer to BPC for the distribution of potential future ADMA developed plasma based products in the territories. [↑](#footnote-ref-19)
20. The study will be led by James F. Markmann., Chief, Division of Transplant Surgery at the hospital and Claude E. Welch Professor of Surgery at Harvard Medical School. [↑](#footnote-ref-20)
21. This US clinical trial will be a two-part, multi-centre, prospective study to evaluate the safety and efficacy of G1-AAT IV as an add-on biopharmacotherapy to conventional steroid treatment in up to 168 patients with acute GvHD with lower gastrointestinal involvement. G1-AAT IV previously received orphan drug designation from the FDA and EMA for the treatment of GvHD, and an Investigational New Drug Application was submitted to the FDA earlier this year. [↑](#footnote-ref-21)
22. Benjamin RJ. “Zika virus in the blood supply”. *Blood* 2017;**129**: 144-5. and Gallian P, Cabie A, Richard P, Paturel L, Charrel RN, Pastorino B, Leparc-Goffart I, Tiberghien P, de Lamballerie X. “Zika virus in asymptomatic blood donors in Martinique”. *Blood* 2017;**129**: 263-6. [↑](#footnote-ref-22)
23. The 1000 Genomes project was completed in 2015. [**www.erythrogene.com**](http://www.erythrogene.com) [↑](#footnote-ref-23)
24. [**https://www.sciencedaily.com/releases/2017/01/170126081721.htm**](https://www.sciencedaily.com/releases/2017/01/170126081721.htm)and M. Moller, M. Joud, J. R. Storry, M. L. Olsson.” **Erythrogene: a database for in-depth analysis of the extensive variation in 36 blood group systems in the 1000 Genomes Project”.** Blood Advances, 2016; 1 (3): 240 DOI: [10.1182/bloodadvances.2016001867](http://dx.doi.org/10.1182/bloodadvances.2016001867) [↑](#footnote-ref-24)
25. Fibrinogen is a protein that helps form blood clots. [↑](#footnote-ref-25)
26. A plasma-based frozen blood product [↑](#footnote-ref-26)
27. ### Kim Y, Amini N, Gani F, et al, “Age of Transfused Blood Impacts Perioperative Outcomes Among Patients Who Undergo Major Gastrointestinal Surgery”, Ann Surg. 2017; 265:103-110. DOI: 10.1097/SLA.0000000000001647

    [↑](#footnote-ref-27)
28. Peter Brønnum Nielsen, Flemming Skjøth, Mette Søgaard, Jette Nordstrøm Kjældgaard, Gregory Y H Lip, and Torben Bjerregaard Larsen, “Effectiveness and safety of reduced dose non-vitamin K antagonist oral anticoagulants and warfarin in patients with atrial fibrillation: propensity weighted nationwide cohort study”, BMJ 2017; 356 doi: <https://doi.org/10.1136/bmj.j510> (Published 10 February 2017) [↑](#footnote-ref-28)
29. di-2-ethylhexyl terephthalate (DEHT). [↑](#footnote-ref-29)
30. On 27 January 2017. Abstract LB02 *Randomized double-blind placebo controlled evaluation of the safety and efficacy of recombinant Antithrombin versus placebo in preterm preeclampsia* Baha Sibai¹, Michael J. Paidas² , The PRESERVE Study Group ¹University of Texas Health Science Center at Houston - McGovern Medical School, Houston, TX, ²Yale School of Medicine, New Haven, CT [↑](#footnote-ref-30)
31. Amelia Muhs, James T. Lyles, Corey P. Parlet, Kate Nelson, Jeffery S. Kavanaugh, Alexander R. Horswill, Cassandra L. Quave. “**Virulence Inhibitors from Brazilian Peppertree Block Quorum Sensing and Abate Dermonecrosis in Skin Infection Models”**. Scientific Reports, 2017; 7: 42275 DOI: [10.1038/srep42275](http://dx.doi.org/10.1038/srep42275) [↑](#footnote-ref-31)
32. ### Prof. Robert M. Hughes, Christina M. Marvin, Dr. Zachary L. Rodgers, Dr. Song Ding, Dr. Nathan P. Oien, Dr. Weston J. Smith, Prof. David S. Lawrence, “Phototriggered Secretion of Membrane Compartmentalized Bioactive Agents”, *Angewandte Chemie*, Volume 55, Issue 52, December 23, 2016 Pages 16080–16083. DOI: 10.1002/anie.201609731

    [↑](#footnote-ref-32)
33. Fred Eshelman Distinguished Professor in the Eshelman School of Pharmacy [↑](#footnote-ref-33)
34. # [Susan J. Allison](http://www.nature.com/nrneph/journal/v13/n3/full/nrneph.2017.7.html#auth-1) , “NET-induced coagulation induces organ damage in sepsis”, *Nature Reviews Nephrology,* Volume:13. DOI: doi:10.1038/nrneph.2017.7

    [↑](#footnote-ref-34)
35. Adam Cuker, Holleh Husseinzadeh, Tatiana Lebedeva, Joseph E. Marturano, Walter Massefski, Thomas J. Lowery, Michele P. Lambert, Charles S. Abrams, John W. Weisel, Douglas B. Cines, “Rapid evaluation of platelet function with T2 magnetic resonance,” American Journal of Clinical Pathology (AJCP)Volume 146, Issue 6. pp 681-693. DOI: <https://doi.org/10.1093/ajcp/aqw189> [↑](#footnote-ref-35)
36. Senior author Zhen Gu from the School of Medicine. Jornal reference: Chao Wang, Wujin Sun, Yanqi Ye, Quanyin Hu, Hunter N. Bomba, Zhen Gu. “**In situ activation of platelets with checkpoint inhibitors for post-surgical cancer immunotherapy”**. Nature Biomedical Engineering, 2017; 1: 0011 DOI: [10.1038/s41551-016-0011](http://dx.doi.org/10.1038/s41551-016-0011) [↑](#footnote-ref-36)
37. # Ji Sun Choi and Brendan A. C. Harley, "Marrow-inspired matrix cues rapidly affect early fate decisions of hematopoietic stem and progenitor cells" , Science Advances, 06 Jan 2017:Vol. 3, no. 1, e1600455 DOI: 10.1126/sciadv.1600455

    [↑](#footnote-ref-37)
38. To examine the vaccine’s safety and capacity to generate an immune response. [↑](#footnote-ref-38)
39. The vaccine contains four synthetic proteins from mosquito salivary glands. These proteins induce antibodies and cause a modified allergic response that can prevent infection. For more information about the trial, see [clinicaltrials.gov](http://clinicaltrials.gov) using the trial identifier [NCT03055000](https://clinicaltrials.gov/ct2/show/NCT03055000). [↑](#footnote-ref-39)
40. [Xiufeng Zhang](http://www.pnas.org/search?author1=Xiufeng+Zhang&sortspec=date&submit=Submit), [Emre Aksoy](http://www.pnas.org/search?author1=Emre+Aksoy&sortspec=date&submit=Submit), [Thomas Girke](http://www.pnas.org/search?author1=Thomas+Girke&sortspec=date&submit=Submit), [Alexander S. Raikhel](http://www.pnas.org/search?author1=Alexander+S.+Raikhel&sortspec=date&submit=Submit), and [Fedor V. Karginov](http://www.pnas.org/search?author1=Fedor+V.+Karginov&sortspec=date&submit=Submit), “Transcriptome-wide microRNA and target dynamics in the fat body during the gonadotrophic cycle of Aedes aegypti”, Proceedings of the National Academy of Sciences, vol. 114 no. 10 doi: 10.1073/pnas.1701474114 [↑](#footnote-ref-40)
41. # of the Cary Institute of Ecosystem Studies in Millbrook, New York.

    [↑](#footnote-ref-41)
42. # Black-striped capuchin monkeys and common marmosets are already known to be infected with a Zika strain matching the human strain in Brazil. Capuchins are of particular concern because they are often kept as pets and used to attract tourists.

    [↑](#footnote-ref-42)
43. Richner and Himansu et al.: "Modified mRNA vaccines protect against Zika virus and minimize antibody enhancement of dengue virus infection", Cell, <http://www.cell.com/cell/fulltext/S0092-8674(17)30195-2>. The 17 February publication in Cell, follows a 2 February 2 Letter in Nature (doi:10.1038/nature21428) that showed similar positive results for a messenger RNA vaccine for Zika in mice and monkeys. (see below) [↑](#footnote-ref-43)
44. The US Biomedical Advanced Research and Development Authority (BARDA), is funding the clinical trials of Moderna's Zika mRNA vaccine. [↑](#footnote-ref-44)
45. Norbert Pardi, Michael J. Hogan, Rebecca S. Pelc, Hiromi Muramatsu, Hanne Andersen,Christina R. DeMaso, Kimberly A. Dowd, , Laura L. Sutherland,, Richard M. Scearce, Robert Parks,Wendeline Wagner, ,Alex Granados, Jack Greenhouse, Michelle Walker, Elinor Willis, , Jae-Sung Yu, ,Charles E. McGee, Gregory D. Sempowski, Barbara L. Mui, Ying K. Tam, Yan-Jang Huang, Dana Vanlandingham, ,Veronica M. Holmes, Harikrishnan Balachandran, , Sujata Sahu, Michelle Lifton, Stephen Higgs, ,Scott E. Hensley, Thomas D. Madden, Michael J. Hope, Katalin Karikó, Sampa Santra, , Barney S. Graham, Mark G. Lewis,, Theodore C. Pierson, Barton F. Haynes,& Drew Weissman, et al. “Zika virus protection by a single low-dose nucleoside-modified mRNA vaccination”, *Nature,* Volume: 543, Pages:248–251, 09 March 2017 doi:10.1038/nature21428 Published online 02 February 2017 [↑](#footnote-ref-45)
46. Previous attempts to isolate human monoclonal antibodies against Zika virus have led to broadly neutralising antibodies that also exhibit activity against dengue. If used as therapy for Zika, such “cross-reactivity” could increase the severity of dengue if patients later became infected with dengue. [↑](#footnote-ref-46)
47. See Science Translational Medicine (online, 14 December 2016), and *Clinical Pharmacist*, Vol 9, No 2, online | DOI: 10.1211/CP.2017.20202257 [↑](#footnote-ref-47)
48. PNAS, 2017. DOI: [10.1073/pnas.1620558114](http://dx.doi.org/10.1073/pnas.1620558114) [↑](#footnote-ref-48)
49. Jane A. C. Wilson, Natalie A. Prow, Wayne A. Schroder, Jonathan J. Ellis, Helen E. Cumming, Linden J. Gearing, Yee Suan Poo, Adam Taylor, Paul J. Hertzog, Francesca Di Giallonardo, Linda Hueston, Roger Le Grand, Bing Tang, Thuy T. Le, Joy Gardner, Suresh Mahalingam, Pierre Roques, Phillip I. Bird, Andreas Suhrbier, “RNA-Seq analysis of chikungunya virus infection and identification of granzyme A as a major promoter of arthritic inflammation”, *PLOS Pathogens*: published February 16, 2017 | <http://dx.doi.org/10.1371/journal.ppat.1006155> [↑](#footnote-ref-49)
50. # Robert Lyle McPherson, Rachy Abraham, Easwaran Sreekumar, Shao-En Ong, Shang-Jung Cheng, Victoria K. Baxter, Hans A. V. Kistemaker, Dmitri V. Filippov, Diane E. Griffin, Anthony K. L. Leung. “**ADP-ribosylhydrolase activity of Chikungunya virus macrodomain is critical for virus replication and virulence”**. Proceedings of the National Academy of Sciences, 2017; 201621485 DOI: [10.1073/pnas.1621485114](http://dx.doi.org/10.1073/pnas.1621485114)

    [↑](#footnote-ref-50)
51. Lin S-C, et al. “Effective inhibition of MERS-CoV infection by resveratrol”. BMC Infectious Diseases. 2017; 17:144. [↑](#footnote-ref-51)
52. Officially launched at the World Economic Forum in Davos in January, 2017, CEPI received an initial $US 460 million from the governments of Germany, Japan and Norway, plus the Bill & Melinda Gates Foundation and Wellcome Trust, as part of a drive to bring together a total of $US 1 billion to fund and support its goal of stimulating, financing and coordinating the advancement of safe, effective and affordable vaccines. [↑](#footnote-ref-52)
53. **Significant immune responses were reported in 100 per cent of Zika-vaccinated subjects and 98 per cent of MERS-vaccinated human subjects in separate phase I studies.**  [↑](#footnote-ref-53)
54. Mary-Anne Hartley, Alyssa Young, Anh-Minh Tran, Harry Henry Okoni-Williams, Mohamed Suma, Brooke Mancuso, Ahmed Al-Dikhari, Mohamed Faouzi, “Predicting Ebola Severity: A Clinical Prioritization Score for Ebola Virus Disease” PLoS Negl Trop Dis**,** Published: February 2, 2017, <http://dx.doi.org/10.1371/journal.pntd.0005265> [↑](#footnote-ref-54)
55. Immunologist Haley DeMers of the University of Nevada, Reno School of Medicine, and colleagues. [↑](#footnote-ref-55)
56. 6 February 2017 [↑](#footnote-ref-56)
57. Professor Alexander Khromykh from the University of Queensland’s School of Chemistry and Molecular Biosciences and Professor Andreas Suhrbier from QIMR Berghofer Medical Research Institute. [↑](#footnote-ref-57)
58. The report was published online 3 February 2017 in *Scientific Reports*. Professor Khromykh said monoclonal antibodies were used in the UK to treat infected health workers returning from Africa. He said: “The down side is that monoclonal antibodies require considerable investment for scale-up and manufacture, and are expensive. Equine antibodies are a considerably cheaper alternative, with manufacturing capacity already in place in Africa. Antibodies from vaccinated horses provide a low-cost alternative, and are already in use for rabies, botulism and diphtheria.” [↑](#footnote-ref-58)
59. Their report was published in the journal [*PLOS Pathogens*](http://journals.plos.org/plospathogens/article?id=10.1371/journal.ppat.1006117). [↑](#footnote-ref-59)