Monitoring International Trends

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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:

- ACE 910, was created by Chugai Pharmaceutical and being co-developed by Roche. is an experimental humanised bispecific monoclonal antibody engineered to simultaneously bind factors IXa and X. A study has found that once- weekly subcutaneous administration markedly decreased the bleeding rate in patients who had haemophilia A with or without factor VIII inhibitors. (Section 1)
- Treatment of severe haemophilia A with recombinant factor VIII in previously untreated children was found to have a higher risk of inhibitors than treatment with plasma-derived factor VIII containing von Willebrand factor. (Section 1)
- At the International Congress of the World Federation of Hemophilia (WFH) in Orlando, Florida, Shire showcased the company's strengthened haematology portfolio and pipeline, following its takeover of Baxalta. (Section 1)
- At the WFH Congress CSL Behring presented new data from its recombinant coagulation factor development programs.
- The 21st Congress of the European Hematology Association (EHA) was held in Copenhagen 9-12 June 2016. At this:
  i) Dimension Therapeutics, of Cambridge Massachusetts, reported on the progress of two of its development candidates designed to deliver factor VIII and Factor IX gene expression in haemophilia A and B respectively. (Section 1)
  ii) Spark Therapeutics and Pfizer presented new data showing encouraging initial observations for the first haemophilia B patients dosed in the Phase I/II clinical trial of *SPK-9001.* (Section 1)
  iii) Global Blood Therapeutics announced data from a Phase I/II clinical trial of GBT440 in patients with sickle cell disease. (Section 1)
- At the end of May, just before it merged with Shire. Baxalta reported positive results from a Phase I open-label, dose escalation study assessing the safety and pharmacokinetic profile of BAX 930, for the treatment of patients with severe hereditary thrombotic thrombocytopenic purpura.
- The Alberta Children's Hospital has used a stem cell transplant procedure to cure children of sickle cell anaemia.
- CSL Behring received US Food and Drug Administration (FDA) approval for Afstyla, its long-lasting recombinant factor VIII therapy for adults and children with haemophilia A. (Section 2)
- Shire announced the successful completion of a decentralized procedure to support approval by 17 authorities in Europe for Cuvitru (immunoglobulin 20mg/ml solution for subcutaneous injection. (Section 2)

- The European Commission has granted Alexion Pharmaceuticals orphan drug designation to ALXN1210, a longer-acting C5 antibody being evaluated in patients with paroxysmal nocturnal hemoglobinuria. (Section 2)
- Health Canada approved Cerus' Intercept Blood System for plasma.
- Shire and Kamada announced that the FDA had approved an expanded label for Glassia. (Section 2)
- Shire's $US 32 billion acquisition of Baxalta was completed. (Section 4)
- .Grífols purchased twenty per cent of Singulex and will hold the global licence for the use and commercialisation of Singulex technology for screening blood and plasma donations. (Section 4)
- Grifols is targeting investments of 1.2 billion euros until 2020 (Section 4)
- In a new agreement between CSL and the QIMR Berghofer Medical Research Institute, CSL will advise and support QIMR Berghofer on the key steps that need to be taken to commercialise its research, and the commercial opportunities that exist in promising research. (Section 4)
- LFB USA is spending $US 37 million on new construction. ATryn will be produced at the facility. (Section 4)
- Swedish Orphan Biovitrum announced the first sales in Germany of Alprolix, its extended half-life treatment for haemophilia B. (Section 4)
- Northern Ireland has announced that it is to lift its lifetime ban on blood donation by men who have sex with men. (Section 4)
- In the US, the FDA has raised the minimum level of haemoglobin required in male blood donors. (Section 4)
- A study found that obese men who underwent radical prostatectomy were less likely to require blood transfusions if their surgery was robotic-assisted. (Section 5)
- Researchers found evidence that anaemia can negatively influence the outcomes of patients with traumatic brain injuries. (Section 5)
- A meta-analysis has found that a substantial percentage of patients undergoing percutaneous coronary intervention have some form of anaemia that increases their risks. (Section 5)
- Researchers say heparin administration should cease as soon as heparin-induced thrombocytopenia is suspected and fast-acting, alternate anticoagulation introduced to reduce the risk for thromboembolism. (Section 5)
- A US study concluded that red blood cells transfused in the last seven days of their 42-day storage limit may be associated with adverse clinical outcomes in high-risk patients. (Section 5)
- Scientists from the University of Bath and the Bristol Heart Institute believe that their method of growing blood vessels in a 3-D scaffold using cells from the patient reduces the risk of transplant rejection. (Section 6)
- AlloSource shipped its first bioengineered blood vessels to be used in a clinical trial to see whether the vessels can be approved for implant. (Section 6)
- Researchers have identified the four genetic keys that unlock the genetic code of skin cells and reprogram them to start producing red blood cells instead. (Section 6)
- Scientists have found that the mechanical force required to break the bond between fibrinogen and erythrocytes is higher in patients with chronic heart failure than in healthy subjects. (Section 6)
- Researchers say that inhibition of platelets in Alzheimer's disease patients may become important in therapy in the future. (Section 6)
- Researchers found that pregnant women infected with the Zika virus during the first trimester have a risk of up to 13 per cent that their infant will be born with the microcephaly birth defect. They found "a negligible association in the second and third trimesters." (Section 7)
- China continues to report new human cases of the H7N9 avian flu strain.

- In Hong Kong the Agriculture, Fisheries and Conservation Department declared the live poultry stalls at the Yan Oi Market in Tuen Mun an infected place and it was closed for disinfection. (Section 7)
- A case of human infection in China with avian influenza A(H5N6) virus led the World Health Organization (WHO) to say it considered the risk of international disease spread low at that point in time but would continue to assess the epidemiological situation. (Section 7)
- Scientists have described a way to forecast the antigenic evolution of circulating influenza viruses and facilitate more reliable selection of the viruses used to manufacture global vaccine supplies. (Section 7)
- Mayo Clinic researchers found that certain immune cell subsets appear to be associated with a stronger immune response to the flu vaccine. (Section 7)
- At 22 July 2016 Saudi Arabia had had 1440 laboratory confirmed cases of MERS-CoV infection, including 606 deaths (Section 7)
- A study of household transmission of MERS-CoV identified risk factors as including sleeping in an index patient's room and touching respiratory secretions from an index patient. (Section 7)
- Staff from the US Centers for Disease Control (CDC), the FDA, and the US National Institutes of Health, say that global research on medical countermeasures against MERS Co-V is so far preliminary. They identified the need to prioritize animal models, standardize virus strains for study, develop diagnostics, improve access to nonhuman primates for preclinical testing, further research control measures such as human and camel vaccines, and develop a standardized clinical trial protocol. (Section 7)
- Researchers report that MERS is associated with higher mortality and more severe illness than non MERS severe acute respiratory infection (SARI). (Section 7)
- In Texas, the Southwest Research Institute announced a contract from the Defense Threat Reduction Agency to combine two available medications and test the combination against the Ebola virus. (Section 7)
- Lassa fever is being monitored in Liberia and Nigeria.
- The yellow fever outbreak in Africa continues. Millions have been vaccinated, but there is a global shortage of vaccine. (Section 7)
- Researchers have developed a combination therapy that clears babesosis infection in mice and also prevents recurrence. (Section 7)
- Queensland has had its worst outbreak of congenital syphilis in thirty years. It has also had a consistent increase in new syphilis diagnoses among men who have sex with men over the past few years. (Section 7)
- Health authorities in the Northern Territory at the end of May issued an alert for the potentially fatal mosquito-borne virus Murray Valley Encephalitis. (Section 7)

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1. 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.

Haemophilia treatment

a) In 2015, ACE910, which was created by Chugai Pharmaceutical and is being co-developed by Roche, is an experimental humanised bispecific monoclonal antibody engineered to simultaneously bind factors IXa and X. In 2015 it received from the US Food and Drug Administration (FDA) breakthrough therapy designation for the prophylactic treatment of people who are 12 years or older with haemophilia A with factor VIII inhibitors[1]. Now a study reported in *The New England Journal of Medicine* found that once- weekly subcutaneous administration of emicizumab (ACE 910) markedly decreased the bleeding rate in patients who had hemophilia A with or without factor VIII inhibitors[2].

[1] Roche noted at the time that the designation was based primarily on findings from a Phase I study of ACE910 in patients with severe haemophilia A, as well as a Phase I/II extension study of the same patients. The findings had been reported at the 2015 International Society of Thrombosis and Haemostasis annual meeting. The company indicated that in early research, ACE910 exhibited "promising efficacy" as a prophylactic treatment in patients with severe haemophilia A with and without inhibitors to factor VIII. Roche announced at that time that it was planning to initiate a late-stage study of ACE910 in patients with haemophilia A with factor VIII inhibitors by the end of 2015, a second Phase III trial in patients without inhibitors in 2016, and a clinical trial in paediatric patients with haemophilia A in 2016.

[2] Midori Shima et al., "Factor VIII–Mimetic Function of Humanized Bispecific Antibody in Hemophilia A", *N Engl J Med* 2016; 374:2044-2053 May 26, 2016DOI: 10.1056/NEJMoa1511769. The study was funded by Chugai Pharmaceuticals. The researchers enrolled 18 patients in Japan with severe hemophilia A (with or without factor VIII inhibitors) in an open-label, nonrandomized, interindividual dose-escalation study of emicizumab. They were given subcutaneous emicizumab weekly for 12

b) The SIPPET study[3] (Survey of Inhibitors in Plasma-Products Exposed Toddlers) involved 42 centres in fourteen countries in Europe, North and South America, Africa and Asia. It examined whether factor VIII concentrates from different sources (plasma-derived containing von Willebrand factor or recombinant technology) differ in their risk of inhibitor development in previously untreated children with severe haemophilia A. Results showed treatment of severe haemophilia A with recombinant factor VIII is associated with an 87 per cent higher incidence of inhibitors than treatment with plasma-derived factor VIII containing von Willebrand factor in previously untreated patients[4]. The principal investigators[5] believe this result may have implications in the choice of products for treatment of patients with severe haemophilia A, although recombinant products may have a preferred safety profile in terms of potentially transmitting pathogens.

c) The 21st Congress of the European Hematology Association (EHA) was held in Copenhagen 9-12 June 2016. Dimension Therapeutics, of Cambridge Massachusetts, reported on the progress of two of its development candidates. DTX201 is designed to deliver Factor VIII, or FVIII, gene expression in adult patients with haemophilia A[6]. DTX101 is designed to deliver Factor IX, or FIX, gene expression, in adult patients with moderate/severe to severe haemophilia B[7]. An ongoing Phase I/II clinical trial of DTX101 is expected to report initial data in the second half of 2016.

d) Spark Therapeutics and Pfizer presented new data at the EHA Congress, showing encouraging initial observations for the first haemophilia B patients dosed in the Phase I/II clinical trial of *SPK-9001.* The companies said the data demonstrate that the first three subjects enrolled in the study experienced adeno-associated virus (AAV)-mediated factor IX activity levels following one administration of *SPK-900.* Factor IX activity levels in the first two subjects, without prior history of liver disease, rose consistently through the first four weeks post-administration. Factor IX activity level in the third subject, with a history of liver disease, also rose consistently and

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weeks at a dose of 0.3, 1.0, or 3.0 mg per kilogram of body weight. The end points were safety and pharmacokinetic and pharmacodynamic profiles, and also the annualized bleeding rate (365.25 times the number of bleeding episodes, divided by the number of days in the study period) compared with the six months before the study. The brief study did not find that emicizumab was associated with either serious adverse events or clinically relevant coagulation abnormalities. It found plasma concentrations of emicizumab increased in a dose-dependent manner. The median annualized bleeding rates in the three cohorts decreased from 32.5 to 4.4, 18.3 to 0.0, and 15.2 to 0.0, respectively. There was no bleeding in 8 of 11 patients with factor VIII inhibitors and in 5 of 7 patients without factor VIII inhibitors. For those participants who did ewxpeience bleeds, use of clotting factors to control bleeding was reduced. Antibodies to emicizumab did not develop during the short study.

[3] The study was sponsored by the Angelo Bianchi Bonomi Foundation, with financial support from the Italian Ministry of Health and grants from Grifols, Kedrion and LFB.

[4] Results were published in the 26 May issue of the *New England Journal of Medicine.*

[5] Flora Peyvandi and Pier Mannuccio Mannucci, from the Angelo Bianchi Bonomi Haemophilia and Thrombosis Centre.

[6] Lili Wang et al., *A Dose-Escalating Preclinical Study to Determine the Safety, Efficacy, and Minimum Effective Dose of a Clinical Candidate Vector in a Mouse Model of Hemophilia B* (Abstract No. EHA 2910). The poster reported that preclinical research conducted with Dimension's collaborators at the Perelman School of Medicine at the University of Pennsylvania demonstrated dose-dependent expression of FIX levels and stability of FIX expression after single dose administration across the majority of doses during the 90-day study period. The study also found there were no apparent safety concerns related to the anticipated clinical dosing.

[7] Jenny A. Greig et al., *Optimized AAV-Mediated Human Factor VIII Gene Therapy in Hemophilia A Mice and Cynomolgus Macaques (Abstract No. EHA-2892).* The poster reported that preclinical research conducted with collaborators at the University of Pennsylvania demonstrated which combination of specific product components might optimize long-term expression of FVIII. The FVIII expression levels, achieved during the 30-week study supported advancement of DTX201 into Investigational New Drug (IND)-enabling studies.

was at 16 per cent of normal at three weeks post-administration. The companies said that circulating factor activity levels sustained at a threshold of greater than or equal to 12 per cent of normal generally are considered to be sufficient to reduce the risk of joint bleeds and the need for prophylactic clotting factor infusions. Katherine A. High, co-founder, president and chief scientific officer of Spark, said: "We are highly encouraged by these initial data, which are supportive of the target profile of a potential gene therapy product capable of eliminating the need for regular infusions to control and preventing bleeding episodes through a one-time, intravenous administration. Our hypothesis had been that delivery of a highly optimized gene therapy at low doses could allow expression of therapeutic levels of FIX while avoiding the need for immunosuppression. The data summarized in the abstract of *SPK-9001* appear to support this hypothesis, although we will continue to monitor and investigate the validity of the hypothesis as well as assess long-term efficacy and safety of the product candidate." Spark and Pfizer began collaboration in 2014. Spark is responsible for conducting all Phase I/II studies for any product candidates that may be developed under the SPK-FIX program, while Pfizer will assume responsibility for pivotal studies, any regulatory activities and potential global commercialization of any products that may result from the collaboration.

e) At the International Congress of the World Federation of Hemophilia (WFH) in Orlando, Florida, July 24-28, 2016, Shire showcased the company's strengthened haematology portfolio and pipeline, following the Baxalta takeover. During WFH 2016, Shire researchers addressed the PROPEL study, which compares the safety and efficacy of Adynovate [Antihaemophilic Factor [Recombinant], PEGylated] following pharmacokinetic-guided prophylaxis targeting two different Factor VIII trough levels. The novel design of the study is built upon preliminary data indicating that maintaining higher trough levels may be able to help enhance bleed protection and help more patients reach zero bleeds. Shire presented more than a dozen scientific updates on the company's broad portfolio of treatments for bleeding disorders, including Adynovate, its latest treatment for haemophilia A patients. Adynovate is an extended half-life factor VIII replacement treatment built on Advate [Antihaemophilic Factor (Recombinant)] that offers demonstrated results with twice-weekly dosing. The company also featured Vonvendi [von Willebrand factor (Recombinant)], which launches commercially in the US in the third quarter of 2016. Vonvendi is the first recombinant treatment for von Willebrand disease. The company has also nitiated research on an innovative patient-reported outcome (PRO) measure. The measure is intended to support broader bleeding disorder management by supplementing standard clinical outcome measures with those that are patient-centered, customizable and sensitive to change across patients and patient populations.

f) At the WFH Congress CSL Behring presented new data from its recombinant coagulation factor development programs. Six posters[8] highlighted new Idelvion [Coagulation Factor IX (Recombinant), Albumin Fusion Protein] data, including

[8] **"**Half-life extended recombinant fusion protein linking factor IX with albumin is recycled via the intracellular FcRn-mediated pathway". Poster #2.
"Performance of a recombinant fusion protein linking coagulation factor IX with albumin (rIX-FP) in the one-stage assay". Poster #74.
"Efficacy and safety of long-acting recombinant fusion protein linking factor IX with albumin (rIX-FP) in hemophilia B patients undergoing surgery". Poster #84.
"Interim results of a Phase IIIb safety and efficacy extension study of a recombinant fusion protein linking coagulation factor IX with albumin (rIX-FP) in patients with hemophilia B". Poster #113.
"Long-term safety and efficacy of recombinant fusion protein linking coagulation factor IX with albumin (rIX-FP) in previously treated patients with hemophilia B". Poster #122.
"Effect of once-weekly prophylaxis treatment with a recombinant fusion protein linking coagulation factor IX with albumin (rIX-FP) on target joints in patients with hemophilia B during the PROLONG-9FP clinical trial program". Poster #138.

interim results on CSL's Phase IIIb safety and efficacy study in haemophilia B. One oral[9] and six poster[10] presentations showcased Afstyla [Antihaemophilic Factor (Recombinant), Single Chain] data, including paediatric results highlighting a Phase III pharmacokinetic, efficacy and safety study in haemophilia A. A satellite symposium was offered on Idelvion[11], with another on Afstyla[12]. Poster presentations were also offered on rVIIa-FP (CSL Behring's long-acting fusion protein linking recombinant coagulation factor VIIa with recombinant albumin)[13] and on plasma-derived von Willebrand factor /FVIII concentrate[14].

Other

g) At the end of May, Baxalta reported positive results from a Phase I open-label, dose escalation study assessing the safety and pharmacokinetic profile of BAX 930, for the treatment of patients with severe hereditary thrombotic thrombocytopenic purpura. The results were presented as a poster at the 62nd annual Scientific and Standardization Committee meeting of the International Society on Thrombosis and Haemostatis (ISTH) in Montpellier, France[15]. BAX 930 has orphan drug status in the US and EU.

h) At the EHA meeting in Copenhagen in June, Global Blood Therapeutics announced what it regarded as encouraging data from a Phase I/II clinical trial of GBT440 in patients with sickle cell disease (SCD). Patients who received GBT440 had a sustained median reduction of around 70 per cent in irreversibly sickled cells compared with an increase of 15 per cent for placebo. GBT440 is an oral, once-daily SCD treatment that increases haemoglobin's affinity for oxygen via its binding to 20 per cent of the total haemoglobin in the patient's blood. Oxygenated haemoglobin does not polymerize which prevents the sickling of red blood cells.

i) Also at the EHA meeting Amgen announced results from a post-hoc analysis of the pivotal Phase III ASPIRE study which highlighted the benefit of continued treatment with Kyprolis (carfilzomib) in combination with lenalidomide and dexamethasone (KRd) in patients with relapsed multiple myeloma. Separate sub-analyses of the Phase III ENDEAVOR study further confirmed efficacy and depth of response benefits of Kyprolis plus dexamethasone (Kd). Six additional abstracts presented at EHA further demonstrate the benefit of Kyprolis-based regimens across a range of patient populations[16]:

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[9] "The effect of non-neutralizing anti-drug antibodies on PK and bleeding rates in children less than 12 years of age with severe hemophilia A treated with rVIII-SingleChain". Topic #3.

[10] "Potency determination of single-chain rFVIII concentrate". Poster #10.
"Characteristics of rVIII-SingleChain in the one-stage and the chromogenic substrate assay: results of an international field study". Poster #70.
"rVIII-SingleChain, results of the pivotal efficacy data from a phase III PK, efficacy and safety clinical study in children less than 12 years of age with severe hemophilia A". Poster #87.
"rVIII-SingleChain in surgical prophylaxis: efficacy and safety in 21 major surgeries". Poster #108.
"Tolerance induction in a pediatric patient with severe hemophilia A and a low titer inhibitor using an intensified prophylaxis regimen with rVIII-SingleChain". Poster #89.
"Population pharmacokinetic model of recombinant single-chain factor VIII (rVIII-SingleChain) in patients with hemophilia A". Poster #142.

[11] "Revolutionizing the Treatment of Hemophilia B".

[12] "rVIII-SingleChain: Novel Technology in the Treatment of Hemophilia A".

[13] "Intracellular trafficking and FcRn-dependent recycling of recombinant factor VIIa-albumin fusion protein (rVIIa-FP) provides a mechanism for half-life extension *in vivo*". Poster #88.

[14] "Comparison of the pharmacokinetic parameters of a plasma-derived VWF/FVIII concentrate (Voncento®) in adult/adolescent and pediatric subjects with von Willebrand disease (SWIFT-VWD and SWIFTLY-VWD study)". Poster #185.
"Pharmacokinetics of a plasma-derived VWF/FVIII concentrate (Voncento®) in adult/adolescent and pediatric subjects with severe hemophilia A (SWIFT-HA and SWIFTLY-HA studies)". Poster #141.

[15] Poster #FIBO4 – abstract available in the *Journal of Thrombosis and Haemostasis*.

[16] The seven abstracts are currently available on the EHA website.

j) At EHA, Alnylam Pharmaceuticals reported initial results of its ALN-CC5 Phase1/II clinical trial. The clinical study showed that it can reduce the dose and frequency of eculizumab, a treatment for paroxysmal nocturnal hemoglubinuria PNH with a known side-effect of breakthrough haemolysis[17]. The study supported the theory that ALN-CC5 as adjunct therapy can help improve the disease control of inadequate responders to eculizumab. ALN-CC5 is administered subcutaneously; it is an investigational RNAi therapeutic.

k) Janssen-Cilag International announced results at the EHA Congress[18]. from the international Phase III, randomised, double-blind, placebo-controlled, multicentre study, EPOANE 3021. The company said the study demonstrated the efficacy and safety of Eprex (epoetin alfa) as a treatment for anaemia, in adult patients with low or intermediate-1 risk myelodysplastic syndromes, as classified by an International Prognostic Scoring System. These data, along with three registry studies from across Europe, were submitted to the French health authority Agence Nationale de Sécurité du Médicament et des Produits de Santé (ANSM), as the reference health authority for Eprex within the mutual recognition procedure, to extend the existing marketing authorisation in Europe.

l) The Alberta Children's Hospital has used a stem cell transplant procedure to cure children of sickle cell anaemia. Dr Greg Guilcher, a paediatric oncologist who leads the sickle cell blood and marrow transplant program in Calgary, said that the "protocol uses the lightest doses of medication—no chemotherapy but immune suppressing drugs only, with a low dose of radiation." While the protocol was developed and is used in the US, Dr Guilcher said he's not aware of any other hospital using it on children. He said there have been no incidents of stem cell rejection.

m) At the EHA meeting on 10 June Incyte Corporation announced new 28-week data from the Phase III RESPONSE-2 study of Jakafi (ruxolitinib). The company said the data showed that Jakafi was superior to the best available therapy in maintaining hematocrit control without the need for phlebotomy in patients with inadequately

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EHA Abstract #P275: Carfilzomib, Lenalidomide, and Dexamethasone Versus Lenalidomide and Dexamethasone in Patients with Relapsed Multiple Myeloma: Analysis of Response and Progression-Free Survival Hazard Ratio Over Time

EHA Abstract #E1266: Carfilzomib and Dexamethasone Versus Bortezomib and Dexamethasone: Subgroup Analysis of the Phase 3 ENDEAVOR Study to Evaluate the Impact of Prior Treatment on Patients with Relapsed Multiple Myeloma

EHA Abstract #E1267: Carfilzomib and Dexamethasone Versus Bortezomib and Dexamethasone: Subgroup Analysis of Patients with Relapsed Multiple Myeloma by Baseline Cytogenetic Risk Status (Phase 3 ENDEAVOR Study)

EHA Abstract #E1274: Carfilzomib and Dexamethasone Versus Bortezomib and Dexamethasone in Patients with Relapsed Multiple Myeloma: Analysis of the Phase 3 ENDEAVOR Study by Age Subgroup

EHA Abstract #E1328: Outcomes for Asian Patients With Relapsed Multiple Myeloma Treated With Carfilzomib and Dexamethasone Versus Bortezomib and Dexamethasone: A Subgroup Analysis of the Phase 3 ENDEAVOR Study

EHA Abstract #P659: Carfilzomib and Dexamethasone Versus Subcutaneous Bortezomib and Dexamethasone in Patients with Relapsed or Refractory Multiple Myeloma: Secondary Analysis from the Phase 3 Study ENDEAVOR

EHA Abstract #P663: Efficacy and Safety by Cytogenetic Risk Status: Phase 3 Study (ASPIRE) of Carfilzomib, Lenalidomide and Dexamethasone Versus Lenalidomide and Dexamethasone in Patients with Relapsed Multiple Myeloma

[17] Haemolysis is the rupturing of red blood cells and the release of their contents into surrounding plasma.

[18] Abstract#P248

controlled polycythemia vera, resistant to or intolerant of hydroxyurea, who did not have an enlarged spleen[19].

2. Regulatory

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

a) CSL Behring announced on 26 May that the U.S. Food and Drug Administration (FDA) had approved Afstyla [Antihaemophilic Factor (Recombinant), Single Chain], its long-lasting recombinant factor VIII single-chain therapy for adults and children with haemophilia A. It is designed for long-lasting protection from bleeds with two to three times weekly dosing. The company said that in clinical trials, patients treated prophylactically with Afstyla demonstrated a median annualized spontaneous bleeding rate of 0.00. It said that once activated, Afstyla is identical to natural factor VIII. Afstyla is indicated for routine prophylaxis to reduce the frequency of bleeding episodes; for on-demand treatment and control of bleeding episodes; and for the perioperative management of bleeding. The approval of Afstyla was based on results from the AFFINITY clinical development program. AFFINITY included two pivotal studies and one extension open-label multi-centre study evaluating the safety and efficacy of Afstyla in children, adolescents and adults with haemophilia A. Afstyla is for intravenous use only. It can be self-administered. Higher dose per kilogram body weight and/or more frequent dosing may be needed for paediatric patients.

b) Shire announced the successful completion of a decentralized procedure to support approval by 17 authorities in Europe for Cuvitru (immunoglobulin 20mg/ml solution for subcutaneous injection), a treatment for paediatric and adult patients with primary and certain secondary immunodeficiency disorders. With the addition of Cuvitru, following the completion of the acquisition of Baxalta, Shire has a broad immunoglobulin portfolio. Shire expects a regulatory decision for Cuvitru in the US later this year in response to Baxalta's submission for licensing late in 2015 based on a separate Phase II/III study. The company expects to initiate additional global regulatory submissions in 2016.

c) The European Commission has granted Alexion Pharmaceuticals orphan drug designation[20] to ALXN1210, a longer-acting C5 antibody being evaluated in patients with paroxysmal nocturnal hemoglobinuria (PNH). PNH is a rare blood disorder in which uncontrolled activation of complement, a component of the immune system, leads to haemolysis (destruction of red blood cells). Martin Mackay, Executive Vice President and Global Head of R&D at Alexion said: “Soliris has been approved for the treatment of patients with PNH since 2007 and has dramatically changed the outlook for patients with this disease. Preliminary results from our ongoing clinical studies of ALXN1210[21], which has a half-life nearly three times that of Soliris, have

[19] Polycythemia vera is typically characterized by elevated hematocrit, the volume percentage of red blood cells in whole blood, which can lead to a thickening of the blood and an increased risk of blood clots, as well as an elevated white blood cell and platelet count. Patients who fail to consistently maintain appropriate blood count levels, including appropriate hematocrit levels, have an approximately four times higher risk of major thrombosis (blood clots) or cardiovascular death. Patients with polycythemia vera can also suffer from an enlarged spleen and symptoms attributed to thickening of the blood and lack of oxygen to parts of the body.

[20] The European Commission grants orphan medicinal product status to provide incentives to develop medicinal products to treat, prevent or diagnose diseases or conditions that affect no more than five in 10,000 persons in the EU. Incentives include a period of market exclusivity

[21] information on clinical trials is available at www.clinicaltrials.gov under the identifiers NCT02598583 and NCT02605993. Interim data from a Phase I/II study of ALXN1210 were presented at the 21st

shown rapid, complete, and sustained complement inhibition in treated patients with PNH."

d) Health Canada approved Cerus' Intercept Blood System for plasma, to be used for the *ex vivo* preparation of pathogen-reduced, whole blood derived or apheresis plasma as a means of decreasing the risk of transfusion-transmitted infection.
e) Shire and Kamada announced that the US Food and Drug Administration (FDA) had approved an expanded label for GLASSIA [Alpha-1 Proteinase Inhibitor (Human)], marking the first treatment for adult patients with emphysema due to severe Alpha-1 Antitrypsin (AAT) Deficiency that can be self-infused at home after appropriate training.

3. 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.

Mergers. takeovers and spinoffs

- Shire's $US 32 billion acquisition of Baxalta was completed. Baxalta shareholders approved the definitive agreement with Shire, with approximately 76.9 per cent of the shares outstanding voting in favour of the proposal.
- Grífols purchased twenty per cent of Singulex by signing a capital increase worth $US 50 million. Singulex is a life science product provider based in Alameda, California. Grífols will be part of the board at Singulex and hold the global licence for the use and commercialisation of Singulex technology such as diagnostic technology for screening blood and plasma donations in order to ensure the safety of transfusions and plasma products.
- PBM Capital, a private investment firm based in Charlottesvlle, Virginia, announced that one of its affiliates had acquired all of the shares of AkaRx from Eisai. Eisai transferred to PBM ownership of AkaRx and the worldwide rights to develop, market and manufacture avatrombopag. This is an investigational small molecule thrombopoietin agonist being evaluated in two global Phase III studies under a Special Protocol Assessment with the US Food and Drug Administration (FDA) as a potential treatment for thrombocytopenia in patients with chronic liver disease who are undergoing an elective procedure. The company says that treatment of thrombocytopenia[22] to enable elective surgery for patients with chronic liver disease remains a significant unmet medical need, as no drug is currently approved for this indication in the US or EU. Platelet transfusions are the current standard of care.

Congress of the European Hematology Association (EHA) in Copenhagen. (*ALXN1210, a Long-Acting C5 Inhibitor, Results in Rapid and Sustained Reduction of LDH with a Monthly Dosing Interval in Patients with PNH: Preliminary Data from a Dose-Escalation Study*-Abstract LB2247**).** In a separate poster at EHA, additional interim results were presented from a Phase II trial evaluating ALXN1007, a novel anti-inflammatory antibody targeting complement protein C5a, in patients with acute graft-versus-host disease of the lower gastro-intestinal tract, which can occur as a complication of stem cell or bone marrow transplantation. (*Phase 2A Study of ALXN1007, A Novel C5a Inhibitor, in Subjects with Newly Diagnosed Acute Graft-Versus-Host Disease (GVHD) Involving the Lower Gastrointestinal Tract* -Abstract LB2269)·

[22] a deficiency of platelets in the blood

Agreements

- A1M Pharma is collaborating with CSL Behring to investigate the potential of combining Alpha 1 Microglobulin (A1M) with proteins extracted from the fractionation of human plasma (such as haemopexin and haptoglobin[23]) to develop new therapies.
- In a new agreement between CSL and the QIMR[24] Berghofer Medical Research Institute, CSL will advise and support QIMR Berghofer on the key steps that need to be taken to commercialise its research, and the commercial opportunities that exist in promising research. QIMR Berghofer's Director and CEO, Professor Frank Gannon, said the Institute will maintain the rights to any subsequent intellectual property. He said: "At QIMR Berghofer, our priority is to take our research from the laboratory bench, to the biotech lab, to the hospital bedside so it can benefit the community. We call that our B2B2B plan. This financial assistance and commercial input from CSL will help us to do that. CSL's Chief Scientific Officer, Dr Andrew Cuthbertson, said CSL's collaboration with academia was important in improving the rates of early stage research translated into the clinic and ultimately to patients. He said:"In our Centenary year, CSL is especially committed to furthering excellence in Australian research. Our partnership with QIMR Berghofer is one of a number of new initiatives– such as the launch of our $25 million CSL Centenary Fellowship program– designed to support the brightest minds in biomedical research and continue our support of Australian medical discovery". QIMR Berghofer will give researchers the opportunity to take a leave of absence for up to two years to work in the biotechnology sector. The researchers will retain entitlements at the Institute.

Other

- Grifols announced it is targeting investments of 1.2 billion euros until 2020
- ExThera Medical Corporation announced the closure of a Series B financing round with an equity investment led by new investor Fresenius Medical Care Ventures GmbH. Proceeds will support European and US clinical trials and regulatory approvals, and scale up manufacturing of the company's therapeutic blood filter, designed to decrease mortality and complications from bloodstream infections and blood-borne diseases[25].
- Framingham-based LFB USA is spending $US 37 million on new construction in Marlborough. The drug ATryn will be produced at the facility.
- Shares in Global Blood Therapeutics rose significantly after the company released encouraging results from the ongoing Phase I/II trial for GBT440, a drug to treat sickle cell disease. The company said the trials showed that sickled haemoglobin would not lump together in patients taking the drug. CEO Ted Love said in a statement: "Overall, the data collected to date in study GBT440-001 indicate that we have a drug candidate that we can move into a pivotal trial later this year. We look forward to discussing the design of that trial with the U.S. Food and Drug Administration."

[23] Haemopexin binds haem, scavenging the haem released by the turnover of haem proteins such as haemoglobin, protecting the body. Haptoglobin binds free haemoglobin released from erythrocytes and therefore also inhibits oxidative activity.
[24] Queensland Institute of Medical Research
[25] ExThera says its Seraph Microbind Affinity Blood Filter is the only device of its kind capable of capturing and removing a broad range of sepsis-causing bacteria, viruses, toxins and pro-inflammatory cytokines from whole blood; that is has been validated in preclinical studies; that it is under evaluation in a first-in-human clinical trial in Europe; and that it addresses significant unmet needs for the immediate treatment of suspected or known bloodstream infections. While the immediate focus is on high-risk populations such as patients undergoing dialysis, the company says Seraph could eventually offer treatment for drug-resistant 'superbugs', and the purification of blood for use by blood banks.

- ❖ Following the approval of the extended half-life therapy Alprolix by the European Commission for the treatment of haemophilia B, Swedish Orphan Biovitrum announced the first sales of Alprolix in Germany. Alprolix is currently approved for the treatment of haemophilia B in the US, European Union, Canada, Japan, Australia, New Zealand, and other countries, to provide prolonged protection from bleeds.

4. 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.

a) Northern Ireland has announced that it is to lift its lifetime ban on blood donation by men who have sex with men. The ban was lifted in England, Scotland and Wales in November 2011. Northern Ireland Health Minister, Michelle O'Neill, said that she would lift the ban in favour of a "one-year deferral system" to be introduced in September to bring Northern Ireland in line with the rest of the UK.

b) In the US, the FDA issued new regulations concerning male blood and platelet donors. Previously, the haemoglobin test required that men be at a minimum of 12.5 grams per decilitre. From 23 May the minimum level accepted was raised to 13.0.

5. Safety and patient blood management

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

Appropriate Transfusion

a) A US study[26] examined records of 9,108 obese men who underwent radical prostatectomy[27]. Around sixty per cent underwent robotic-assisted radical prostatectomy and the rest underwent open prostatectomy. The patients undergoing robotic-assisted surgery were 83 percent less likely to require blood transfusions and 72 per cent less likely to require prolonged hospital stays. However robotic-assisted surgery did not reduce the risk of infections and other complications.

b) A French study[28] has concluded that the strength of association between massive transfusion and coagulation status on admission was strongly influenced by surgical bleeding; so that coagulopathy monitoring in trauma patients without considering the surgical bleeding does not allow a reliable determination of massive transfusion probability.

c) A US study[29] concluded that red blood cells transfused in the last seven days of their 42-day storage limit may be associated with adverse clinical outcomes in high-risk patients.

Anaemia

d) Researchers from the University of Missouri School of Medicine have found evidence that anaemia can negatively influence the outcomes of patients with traumatic brain

[26] by senior author Gopal Gupta, Department of Urology of Loyola University Chicago Stritch School of Medicine, and colleagues. The study was published in the journal *Current Urology.*

[27] removal of the prostate gland and some surrounding tissue

[28] Charbit, J, et al., "Influence of surgical bleeding on the relationship between admission coagulopathy and risk of massive transfusion: lesson from 704 severe trauma patients", *Vox Sanguinis*. doi:10.1111/vox.12401

[29] Goel, R, et al., "Red blood cells stored 35 days or more are associated with adverse outcomes in high-risk patients", Transfusion, volume 56:pp1690–1698, July 2016. doi: 10.1111/trf.13559

injuries. "More research is needed to develop treatment protocols for anemic patients with traumatic brain injuries," said N. Scott Litofsky, lead author of the study[30].

e) A meta-analysis[31] of 44 studies published between 2003 and 2014 and encompassing 230,795 patients has found that a substantial percentage of patients undergoing percutaneous coronary intervention have some form of anaemia that increases their risk for mortality, bleeding, and myocardial infarction.

Other

e) US researchers have reviewed the diagnosis and management of heparin-induced thrombocytopenia[32] (HIT). Benjamin S. Salter, from the Mount Sinai Medical Center in New York City, and his colleagues noted that the prevalence of HIT ranges can be as high as five per cent in patients given heparin. Mortality from HIT is reported can be as high as thirty per cent in these patients. Factors strongly linked to risk are duration of therapy, type and dose of heparin, indication for treatment, and patient gender. Thrombosis is seen in up to ninety per cent of untreated patients. The authors say heparin administration should cease as soon as HIT is suspected and fast-acting, alternate anticoagulation introduced to reduce the risk for thromboembolism. The anticoagulant should be selected according to the type of patient, organ function, likelihood of additional procedures, and bleeding risk.

6. Research

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.

a) Scientists from the University of Bath and the Bristol Heart Institute believe that their method of growing blood vessels in a 3-D scaffold using cells from the patient reduces the risk of transplant rejection[33]. They see heart failure as a possible application of tissue engineering, where the heart muscle has become weak or stiff. Theoretically, new heart muscle engineered in the lab could replace the worn out tissue. Dr Giordano Pula, research team leader and lecturer in pharmacology at the University of Bath, said: "A major challenge in tissue engineering and regenerative medicine is providing the new tissue with a network of blood vessels, and linking this to the patient's existing blood supply; this is vital for the tissue's survival and integration with adjacent tissues."

b) AlloSource shipped its first bioengineered blood vessels to be used in a clinical trial to see whether the vessels can be approved for implant. The company manufactured the blood vessels from human cells for Humacyte, a North Carolina-based research biotech. The blood-vessel grafts are being tested in 350 kidney dialysis patients with end-stage renal disease to improving vascular access needed for treatment. They are being compared with the synthetic replacement blood vessels commonly used for such implants. The grafts created for Humacyte used

[30] The study, "The Negative Impact of Anemia in Outcome from Traumatic Brain Injury," was presented at the 84th American Association of Neurological Surgeons Annual Scientific Meeting and was published in the journal *World Neurosurgery*.
[31] Kwok CS et al. "Meta-analysis of the prognostic impact of anemia in patients undergoing percutaneous coronary intervention". *Am J Cardiol*. 2016;Epub 29 May ahead of print.
[32] Salter BS, Weiner MM, Trinh MA, et al. "Heparin-induced thrombocytopenia. A comprehensive clinical review". *J Am Coll Cardiol*. 2016;67(21):2519-2532. doi: 10.1016/j.jacc.2016.02.073.
[33] They described their new technique in *Scientific Reports*.

donated human vascular cells that were altered to remove much of the material unique to the donor, creating a structure to minimize the risk of rejection.

c) Researchers at Lund University in Sweden, with colleagues at Center of Regenerative Medicine in Barcelona, say they have identified the four genetic keys that unlock the genetic code of skin cells and reprogram them to start producing red blood cells instead[34]. Johan Flygare, who was in charge of the study, said: "We have performed this experiment on mice, and the preliminary results indicate that it is also possible to reprogram skin cells from humans into red blood cells. One possible application for this technique is to make personalised red blood cells for blood transfusions, but this is still far from becoming a clinical reality".

d) Scientists led by Nuno C Santos from the Faculty of Medicine at the University of Lisbon have found that the mechanical force required to break the bond between fibrinogen and erythrocytes is higher in patients with chronic heart failure than in healthy subjects[35]. They also found that erythrocytes in chronic heart failure patients also show changes in their elasticity and behaviour while in the blood stream. Santos says their technique can be used to identify patients at higher risk for this disease, and that the group now needs to extend their study to a larger number of patients (only 45 were followed in this pilot experiment) so they can “translate their findings into clinical applications”.

e) Researchers say that inhibition of platelets in Alzheimer's disease patients may become important in therapy in the future.[36]

7. 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).

Zika Virus

- Researchers from the US Centers for Disease Control and Prevention and Harvard University calculated that pregnant women infected with the Zika virus during the first trimester have a risk of up to 13 per cent that their infant will be born with the microcephaly birth defect. They wrote[37] that they found "a strong association between the risk of microcephaly and infection risk in the first trimester" of pregnancy, but "a negligible association in the second and third trimesters."

Influenza: strains, spread, prevention and treatment

b) China continues to report new human cases of the H7N9 avian flu strain.

c) In Hong Kong the Food and Environmental Hygiene Department (FEHD) is responsible for a routine surveillance programme for avian influenza at markets and fresh provision shops, which it commissions the University of Hong Kong to conduct.

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[34] The research was reported in the journal *Cell Reports*.

[35] The research was reported in *Nature Nanotechnology* doi:10.1038/nnano.2016.52

[36] L. Donner,et al., “Platelets contribute to amyloid-aggregation in cerebral vessels through integrin IIb3-induced outside-in signaling and clusterin release”**.** *Science Signaling*, 2016; 9 (429): ra52 DOI: 10.1126/scisignal.aaf6240

[37] in the *New England Journal of Medicine*

FEHD said on 5 June that a sample of faecal droppings of live poultry taken from a poultry stall in Yan Oi Market in Tuen Mun had tested positive for the H7N9 avian influenza virus. The Agriculture, Fisheries and Conservation Department declared the live poultry stalls at the market as an infected place and it was closed for disinfection. In accordance with the contingency plan for detection of avian influenza virus in Hong Kong, trading of live poultry was suspended pending follow-up investigations to trace the source of the virus.

d) On 30 May 2016, the National Health and Family Planning Commission (NHFPC) of China notified WHO of one laboratory-confirmed case of human infection with avian influenza A(H5N6) virus. WHO's risk assessment was as follows: "This report does not change the overall public health risk associated with avian influenza A(H5N6) viruses. Although influenza A(H5N6) has caused severe infection in humans, until now human infections with the virus seem to be sporadic with no ongoing human to human transmission and close contacts of the case remain healthy. However, the characterization of this virus is ongoing and its implication to the evolution and emergence of a pandemic strain is unknown. The risk of international disease spread is considered to be low at this point in time. WHO continues to assess the epidemiological situation and conduct further risk assessment based on the latest information."
e) A research team led by the Chinese Center for Disease Control and Prevention and the World Health Organization (WHO) has analyzed 907 human cases of H5N1, 483 (53.3per cent) of which were fatal, reported globally from May 1997 to April 2015. Of the 819 (90.3 per cent) patients admitted to the hospital, median time from symptom onset to admission was 4 days. The vast majority of patients (748, or 87.5 per cent) had a history of poultry exposure, and their median age was 19 years. About two thirds of cases (592, or 67.2 per cent) occurred from December to March each year. In Egypt, 363 human H5N1 cases were reported from 2006 to 2015, 116 (32 per cent) of which were fatal. About half of Egypt's total cases (185, or 51 per cent) occurred from Nov 1, 2014, to Apr 30, 2015[38].
f) Scientists led by University of Wisconsin-Madison School of Veterinary Medicine virologist Yoshihiro Kawaoka have described[39] a way to forecast the antigenic evolution of circulating influenza viruses and facilitate more reliable selection of the viruses used to manufacture global vaccine supplies.
g) CSL received FDA approval for a formulation of its Flucelvax quadrivalent influenza vaccine. It is a cell culture-derived vaccine, approved for use in adults and children aged four years and older. Flucelvax will be manufactured in the North Carolina vaccine plant CSL acquired when it purchased Novartis' flu vaccine business in 2015 for $US275 million. CSL plans to market the vaccine during the 2016-2017 US flu season.
h) Mayo Clinic researchers reported[40] found that certain immune cell subsets appear to be associated with a stronger immune response to the flu vaccine. Gregory Poland, from the Mayo Clinic, Rochester, said in a press release: "Ultimately, we hope that increasing our understanding of how the immune system functions at a cellular level will allow us to develop more effective vaccines."

MERS-CoV (Middle East Respiratory Syndrome-Coronavirus)

i) At 22 July 2016 Saudi Arabia had had 1440 laboratory confirmed cases of MERS-CoV infection, including 606 deaths [reported case fatality rate 42.1 percent].

[38] Their study was published online May 17 in *The Lancet Infectious Diseases*, and in print Volume 16, No. 7, e108–e118, July 2016. "DOI: http://dx.doi.org/10.1016/S1473-3099(16)00153-5
[39] 23 May 23, 2016 in *Nature Microbiology*
[40] In *Immunology,* 17 May 2016.

j) A study published in *Emerging Infectious Diseases*[41] examined household transmission of MERS-CoV and identified risk factors as including sleeping in an index patient's room and touching respiratory secretions from an index patient. Casual contact and simple proximity were not found in this study to be associated with transmission[42].

k) Also writing in *Emerging Infectious Diseases*[43], staff from the US Centers for Disease Control (CDC), the FDA, and the US National Institutes of Health, say that although appreciable progress has been made on development of and research on medical countermeasures against MERS Co-V, the work to date is so far preliminary and the measures are for the most part not yet ready for human clinical trials[44]. They identified the urgent need to prioritize animal models, standardize virus strains for study, develop diagnostics, improve access to nonhuman primates for preclinical testing, further research control measures such as human and camel vaccines, and develop a standardized clinical trial protocol. They concluded that "partnering with clinical trial networks in affected countries to evaluate safety and efficacy of investigational therapeutics will strengthen efforts to identify successful medical countermeasures".

l) Researchers report[45] that MERS is associated with higher mortality and more severe illness than non MERS severe acute respiratory infection (SARI). They examined data on 299 patients with laboratory-confirmed MERS and 218 patients with SARI alone treated at 14 hospitals in four Saudi Arabian cities. They found that patients with MERS had a higher mortality rate and were more likely to be hypoxemic and require invasive mechanical ventilation, vasopressor therapy and renal replacement therapy compared with non-MERS patients. Results also showed that patients with MERS were more likely to be febrile compared with those with non-MERS SARI; however, cough, shortness of breath, sputum production, and chronic comorbidities including diabetes and liver disease, were similar between groups.

Ebola virus disease

m) In San Antonio, Texas, the Southwest Research Institute (SwRI) announced a one-year[46], $US 3.4 million contract award from the Defense Threat Reduction Agency (DTRA) to combine two available medications and test the combination against the Ebola virus. SwRI is collaborating with Texas Biomedical Research Institute (Texas Biomed) on the program. SwRI will create a more easily absorbed formulation of cepharanthine (CEPN)[47]. In screening for chemical compounds that could potentially

[41] Arwady MA, et al., "Middle East respiratory syndrome coronavirus transmission in extended family, Saudi Arabia, 2014", *Emerg Infect Dis*. 2016 August, volume 22 no.8. http://dx.doi.org/10.3201/eid2208.152015 DOI: 10.3201/eid2208.152015

[42] The study group was an extended family in Saudi Arabia where MERS-CoV spread in in 2014. Family members were tested by using real-time reverse transcription PCR (rRT-PCR) and serologic methods. Of 79 relatives, nineteen were MERS-CoV positive; eleven were hospitalized, and two died. Eleven tested positive by rRT-PCR; while eight tested negative by rRT-PCR but positive by serology. Compared with MERS-CoV–negative adult family members, MERS-CoV–positive adult family members were older, and more likely to be male and to have chronic medical conditions. The researchers noted that serology was more sensitive than standard rRT-PCR for identifying infected relatives, pointing to the need to include serology in future investigations.

[43] Uyeki TM et al., "Development of medical countermeasures to Middle East respiratory syndrome coronavirus", *Emerg Infect Dis*. 2016 July, volume 22 no.7 . http://dx.doi.org/10.3201/eid2207.160022 DOI: 10.3201/eid2207.160022

[44] Although there has been a phase 1 study of a candidate vaccine

[45] Arabi YM, et al. Abstract 9954. Presented at: American Thoracic Society International Conference. May 13-18, 2016; San Francisco.

[46] With two additional option years

[47] CEPN is a Japanese drug that has been safely used by humans for more than 40 years to treat a range of illnesses.

fight Ebola virus infection, Texas Biomed scientists discovered CEPN was effective at combatting the Ebola virus but required very high doses. Dr. Robert Davey, scientist and chair of the department of Virology and Immunology at Texas Biomed said: "We had earlier found that chloroquine, a drug traditionally used to treat malaria, also stopped the Ebola virus, but again, at very high doses. After reading that chloroquine combined with cepharanthine had a synergistic effect in treating malaria we put two and two together and wanted to test the idea that this combination could create a powerful Ebola virus inhibitor cocktail". Texas Biomed will conduct efficacy testing of formulations of the new readily bioavailable CEPN combined with chloroquine in its Biosafety Level 4 Laboratory.

Other diseases: occurrence, prevention and treatment

o) The World Health Organization (WHO) posted notices on rises in Lassa fever cases in Liberia, and a haemorrhagic fever syndrome outbreak in South Sudan. Lassa fever is also being monitored in Nigeria.

p) The yellow fever outbreak in Africa continues. Millions have been vaccinated, but there is a global shortage of vaccine.

q) The tick-borne parasitic disease of the red blood cells, Babesiosis, can be especially serious in those with weakened immune systems or those without a spleen. It can be transmitted through blood transfusions. Now researchers at the Yale School of Medicine and colleagues have developed a combination therapy that clears the infection in mice and also prevents recurrence[48].

r) Queensland has had its worst outbreak of congenital syphilis in thirty years. Since 2015, 167 new cases have been diagnosed in North Queensland, and at least three children have died. State Health Minister Cameron Dick announced a five-year $15.7 million plan to tackle the sexually transmitted disease. Congenital syphilis infects babies when a pregnant woman contracts the disease and passes it along to her child. It can be treated with penicillin if diagnosed early. North Queensland's Aboriginal and Torres Strait Islander Sexually Transmissible Infections Action Plan will disperse eight new specialists to north Queensland to increase the number of regular sexual health screenings. Sexual health education will also be administered in remote areas such as Doomadgee and Kowanyama.

s) Queensland has had a consistent increase in new syphilis diagnoses among men who have sex with men MSM over the past few years, but the recent sharp increase in 2015 has continued. Queensland Health says if the current trajectory continues, there will be 952 new infections this year compared with 855 in 2015.

t) Health authorities in the Northern Territory at the end of May issued an alert for the potentially fatal mosquito-borne virus Murray Valley Encephalitis.

[48] The study was published online 6June in *The Journal of Experimental Medicine.* The team first tested in mice with weakened immune systems four drugs currently used in the form of two combinations to treat human babesiosis. Only one, atovaquone, was effective in attacking a target enzyme that, when mutated, allows the parasite to develop resistance. In the mouse model, the researchers observed efficacy with a fifth drug (ELQ) that has a similar mechanism to atovaquone but at a different enzyme target site. They found the combination of atovaquone and ELQ-334, at low doses, cleared the infection and prevented recurrence up to 122 days after treatment. "This is the first radical cure against this parasite," said Choukri Ben Mamoun, associate professor of infectious diseases. "We are developing a better analog for ELQ that will be used in clinical trials. We could test the safety of the compound in humans". In the US the incidence of babesiosis is increasing and nearly 20 per cent of the ticks and up to 42 per cent of the mammalian hosts (mice and other rodents) that carry the bacteria that cause Lyme disease are co-infected with *B. microti*.