Monitoring International Trends

**Posted April 2019**

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 put financial or other pressures on the Australian sector.

Some recent matters of interest appear on pages 5 to 18. Highlights are listed below:

**Safety and Patient Blood Management (begins page 5)**

## Appropriate Transfusion

* + The American Academy of Orthopaedic Surgeons Annual Meeting was told that, compared with tranexamic acid for patients who underwent total knee arthroplasty, epsilon-aminocaproic acid was linked with increased perioperative blood loss.
  + A study has found that rotational thromboelastometry (ROTEM) may be helpful in monitoring therapy for trauma-induced coagulopathy during ongoing traumatic haemorrhage.
  + A retrospective cohort study has examined whether increasing volumes of crystalloids and colloids administered before transfusion of packed red blood cells in women with persistent postpartum haemorrhage is associated with adverse maternal outcomes.
  + An international consensus on red cell transfusion in adults, arrived at during a 2018 conference in Frankfurt, has now been published.
  + Highlights of the 2012-17 AABB Donor Hemovigilance report for the US are now available.

## Preventing and treating anaemia

* + A study has concluded that iron reserves in the body increase better with intravenous iron sucrose compared with oral Iron therapy, in treating iron deficiency in women during pregnancy and the postpartum period.
  + San Antonio company Fe3 Medical is developing a transdermal patch to treat iron deficiency anaemia.
  + Drug firm Zydus Cadila announced phase III clinical trials of Desidustat, an investigational new drug targeted at treating anaemia in non-dialysis dependent chronic kidney disease patients.
  + A panel representing the American Society of Clinical Oncology (ASCO) and the American Society of Hematology (ASH) has updated guidelines for use of erythropoiesis-stimulating agents (ESAs) in patients with cancer.

## Other

* + A US study reviewed 6,539 patients and found that 37 per cent of patients who took warfarin also took aspirin.
  + An observational study comparing direct oral anti-coagulants (DOACS) in older patients with atrial fibrillation found that they all have significant benefits over warfarin in terms of reducing thromboembolic stroke, intracranial haemorrhage and all-cause mortality.
  + Researchers say an experimental stroke drug prevented blood clots without the increased bleeding risk which is the typical side effect of blood thinners.
  + The US National Heart, Lung, and Blood Institute’s [**Recipient Epidemiology and Donor Evaluation Study (REDS)**](https://reds-iii.rti.org/)is entering its fourth phase. This is to focus on the safety and effectiveness of blood transfusion therapies in adults and children.

#### **Products and Treatments (begins page 8)**

## Treating haemophilia

* + A US study found that treatment of haemophilia A with bypassing agents carries significantly higher costs than treatment with factor replacement therapy.
  + In gene therapy for haemophilia, researchers have found that from the standpoint of safety and efficacy, the most promising gene therapy platform is the adeno-associated viral (AAV) vector.

## Treating beta thalassemia and sickle cell disease

* + Researchers in Boston have developed a way to treat sickle cell disease and beta thalassemia, applying CRISPR-Cas9 gene editing to patients' own blood stem cells.
  + The US Food and Drug Administration (FDA) has granted a fast track designation for CTX001 (CRISPR Therapeutics and Vertex Pharmaceuticals Incorporated) for the treatment of transfusion-dependent beta thalassemia (TDT).
  + Researchers in Italy have suggested that using more-precise gene-editing technology that induces fewer breaks in DNA may keep stem cells' natural damage-response pathways under control.

## Other products and treatments

* + Humacyte announced publication of work showing its human acellular vessels repopulate with the patient’s own cells to form a living vascular tissue.
  + A report in the American Journal of Hematology suggests that fostamatinib therapy may provide durable long-term responses for adult patients with immune thrombocytopenia (ITP).
  + A long-term extension study has found that romiplostim is effective in boosting platelet counts in most children with chronic immune thrombocytopenia (ITP) and can lead to a treatment-free response in almost a quarter of children.
  + St. Jude Children’s Research Hospital has published results of a study of lentiviral gene therapy for treatment of infants with X-linked severe combined immunodeficiency.

**Regulatory matters (begins page 11)**

* + **J**apan's Ministry of Health, Labour and Welfare approved CSL Behring’s Hizentra and Privigen immunoglobulin therapies for the treatment of patients with chronic inflammatory demyelinating polyradiculoneuropathy (CIDP).
  + The FDA approved Asceniv, ADMA’s intravenous immunoglobulin, for the treatment of primary humoral immunodeficiency disease in adults and adolescents (12 to 17 years of age).
  + The European Medicines Agency’s (EMA) Committee for Medicinal Products for Human Use (CHMP) recommended marketing authorisation for Alexion Pharmaceutical’s Ultomiris (ravulizumab) for the treatment of some adult patients with paroxysmal nocturnal haemoglobinuria (PNH).

**Company news (begins page 12)**

* + Bluebird Bio has opened a manufacturing facility in Durham, North Carolina where it will make its cell and gene therapy treatments*.*

**Country news (begins page 13)**

* + A US study found that the chances of finding an unrelated bone marrow donor are higher for US patients of European descent than for those of non-European descent.
  + In the US, Bayer and its partner Johnson & Johnson have agreed to pay $US 775 million to settle thousands of lawsuits related to their blood thinner, Xarelto. There are around 25,000 claimants. The companies are not admitting liability in their settlement.
  + The Australian Government has granted $A 80 million funding to Peter MacCallum Cancer Centre in Melbourne to kick-start it as a potential CAR T-cell manufacturing hub.
  + Research has found that for Queensland patients with secondary immunodeficiency, home‐based subcutaneous immunoglobulin treatment offers better health outcomes and cost savings compared with hospital‐based intravenous immunoglobulin treatment.
  + A study has found that haemophilia care providers in the UK have insufficient knowledge on how to assess the risk of prolonged bleeding associated with dental procedures.
  + Doctors in Canada proposed a set of measures to judge the degree of the success of programs helping teen-age haemophilia patients transition to adult care, especially for those with more severe disease.
  + In Nigeria, the Anambra State House of Assembly, keen to reduce the number of new sickle cell patients in the state, passed a bill that makes genotype testing compulsory before marriage.

**Research not included elsewhere (begins page 14)**

* + Biomedical engineers in the University of Minnesota found that the building blocks of sickle cell disease are much less efficient at organizing than previously thought. They suggest that developing new medicines that are effective at lower doses and cause fewer side effects might be easier than had been thought.

**Infectious diseases (begins page 16)**

## Mosquito-borne diseases

* + Scientists at [QUT](https://www.qut.edu.au/) and the [QIMR Berghofer Medical Research Institute](https://www.qimrberghofer.edu.au/) have found that it is the dengue fever mosquito common to north and central Queensland which poses the greatest danger of spreading the Zika virus in Australia.
  + Emergent BioSolutions announced promising initial results for a Phase II clinical study of its experimental chikungunya vaccine.

## Influenza

* + The European Commission announced 15 member states had signed framework contracts with Seqirus to produce and supply pandemic influenza vaccine. Similar negotiations were under way with a second pharmaceutical company.
  + UK company Enesi Pharma has partnered with the US Department of Health and Human Services Biomedical Advanced Research and Development Authority (BARDA) on needle- free flu vaccines using its ImplaVax technology.
  + Seqirus will manufacture its cell-based influenza vaccine (Flucelvax Quadrivalent) for the 2019/2020 flu season.

## Ebola virus disease

* + By 25 March 2019 the number of Ebola cases in the Democratic Republic of Congo had passed 1000 in the eighth month of the outbreak, with 58 recorded in the previous week. By then 634 deaths had been recorded. Over 91,000 people had been vaccinated with Merck's VSV-EBOV vaccine. A preliminary estimate published by WHO suggests that the vaccine has been more than 97 per cent effective in a ring trial where contacts — and contacts of contacts — of confirmed cases have been offered vaccination.

## MERS-CoV

* + By 28 March, Saudi Arabia had recorded 111 confirmed MRS-CoV cases so far this year.

## Other diseases

* + Emergent Biosolutions has initiated a Phase III trial to evaluate the lot consistency, immunogenicity, and safety of AV7909 (anthrax vaccine adsorbed with CPG 7909 adjuvant) following a two-dose schedule administered intramuscularly in healthy adults.
  + Measles cases in the US have already exceeded the highest number on record in a single year since the disease was declared eliminated in 2000. Officials say most people who have fallen ill were unvaccinated.
  + Less than a year after WHO verified elimination of rubella in Australia (meaning there was no ongoing local transmission) cases have returned. To 23 April, 13 had been reported, over half in NSW. The disease was recorded 10 times each in 2018 and 2017.

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# Safety and patient blood management

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

## Appropriate Transfusion

* + The American Academy of Orthopaedic Surgeons Annual Meeting was told[[1]](#footnote-1) that, compared with tranexamic acid for patients who underwent total knee arthroplasty, epsilon-aminocaproic acid was linked with increased perioperative blood loss. However, there was no significant difference between the medications regarding the transfusion rate, according to Kendall E. Bradley. She said: “Looking at the difference in the change in hemoglobin, 1.9 vs. 2.1, we felt it wasn’t clinically significant and certainly did not contribute to the need for a transfusion. Orthopedic surgeons should be able to select their antifibrinolytic acid based on cost and regional availability, as in our institution we sometimes have some shortages and the cost for epsilon-aminocaproic acid is about six-times less than what it is for tranexamic acid.”
  + A study[[2]](#footnote-2) has found that rotational thromboelastometry (ROTEM) may be helpful in monitoring therapy for trauma-induced coagulopathy during ongoing traumatic haemorrhage.
  + In a retrospective cohort study[[3]](#footnote-3) of nearly 900 women, researchers studied whether increasing volumes of crystalloids and colloids administered before transfusion of packed red blood cells in women with persistent postpartum haemorrhage is associated with adverse maternal outcomes. They found outcomes suggested an independent association of clear fluids volume >4 L with adverse maternal outcome in women with persistent postpartum haemorrhage.
  + An international consensus on red cell transfusion in adults, arrived at during a 2018 conference in Frankfurt, has now been published.[[4]](#footnote-4)
    1. [Patient Blood Management Recommendations From the 2018 Frankfurt Consensus Conference](https://jamanetwork.com/journals/jama/fullarticle/2727453) supported the use of a restrictive transfusion haemoglobin threshold of 7-8 g/dL (70-80g/L) for most hospitalised patients. There were two strong exceptions for specific patient groups – a threshold of < 7g/dL (<70g/L) for critically ill but stable ICU patients and <7.5g/dL (<75g/L) for patients undergoing cardiac surgery. There were conditional recommendations for a threshold of <8g/dL (<80g/L) for patients with hip fracture and cardiovascular disease or other risk factors, and 7-8 g/dL(70-80g/L) for haemodynamically stable patients with acute gastrointestinal bleeding.
    2. One of the many co-authors of the published paper, Erica Wood[[5]](#footnote-5), commented[[6]](#footnote-6): “I think there are still some patient groups where we have relatively little solid evidence – patients in haematology and oncology who receive a lot of red cells for bone marrow failure and other conditions, but also elderly patients. We need to know more about the impact of anaemia and transfusion on older people who are of course receiving a lot of transfusions.”
    3. Recommendations on treating anaemia before elective surgery (to reduce transfusion rates) included the use of iron supplementation, but not routine use of erythropoiesis-stimulating agents. There was some support for adding short-acting erythropoietins to iron supplementation in patients with preoperative haemoglobin levels <13 g/dL (>130g/L) about to undergo major orthopaedic surgery.
  + Highlights of the 2012-17 AABB Donor Hemovigilance report for the US are [now available.](http://r.smartbrief.com/resp/ltrGBXhNnkDhljiqCicezfBVSndQ) They provide a snapshot of donations and donor adverse reactions reported by facilities that participated in the Donor Hemovigilance Analysis and Reporting Tool (DonorHART) platform. Analytical methods were described in earlier [reports](http://r.smartbrief.com/resp/ltrGBXhNnkDhljirCicezfBVSXpj). Female, first-time and younger donors were more likely to experience an adverse reaction. The overall donor reaction rates ranged from 20.8 to 24.3 per 1,000 donations. Vasovagal reactions without loss of consciousness were the most commonly reported adverse events. Current AABB donor hemovigilance activities may be found on the AABB Donor Hemovigilance [web page.](http://r.smartbrief.com/resp/ltrGBXhNnkDhljisCicezfBVVbXk)

## Preventing and treating anaemia

* + A study[[7]](#footnote-7) has concluded that iron reserves in the body increase better with intravenous iron sucrose compared with oral Iron therapy, in treating iron deficiency in women during pregnancy and the postpartum period.
  + San Antonio company Fe3 Medical is developing a transdermal patch to treat iron deficiency anaemia. Its first human study of the device concentrated on the safety and tolerability of the company’s iontophoretic transdermal technology designed to bypass ionic resistance build up in the skin. This human study followed a series of successful preclinical studies demonstrating the safe delivery of iron through the skin.
  + Drug firm Zydus Cadila announced phase III clinical trials of Desidustat, an investigational new drug targeted at treating anaemia in non-dialysis dependent chronic kidney disease patients. The company’s regulatory filing said: "This phase III study will be a multicenter (50-60 sites), randomised, active-controlled clinical trial to evaluate the efficacy and safety of Desidustat versus Darbepoetin for the treatment of anaemia in patients with chronic kidney disease (CKD) who are not on dialysis."
  + A panel representing the American Society of Clinical Oncology (ASCO) and the American Society of Hematology (ASH) has updated guidelines[[8]](#footnote-8) for use of erythropoiesis-stimulating agents (ESAs) in patients with cancer.

## Other

* + A US study**[[9]](#footnote-9)** reviewed 6,539 patients and found that 37 per cent of patients who took warfarin also took aspirin. Of those using aspirin and warfarin 5.7 per cent experienced major bleeding events after one year, compared with 3.3 per cent of those on warfarin only. The mortality rates at one year were similar between both groups, and 2.3 per cent of those on both medications had a thrombotic event at one year compared with 2.7 per cent of those on warfarin alone.
  + An observational study[[10]](#footnote-10) comparing direct oral anti-coagulants (DOACS) in older patients with atrial fibrillation found that they all have significant benefits over warfarin in terms of reducing thromboembolic stroke, intracranial haemorrhage and all-cause mortality.
  + Researchers say[[11]](#footnote-11) an experimental stroke drug prevented blood clots without the increased bleeding risk which is the typical side effect of blood thinners.
  + [**Versiti Blood Research Institute**](https://www.versiti.org/research/blood-research-institute)**,** based at the Milwaukee Regional Medical Center in Wauwatosa, has been awarded a seven-year, $US 7.4 million federal contract to participate in a national program aimed at protecting the nation’s blood supply and improving the collection and use of blood products. The National Heart, Lung, and Blood Institute’s [**Recipient Epidemiology and Donor Evaluation Study (REDS)**](https://reds-iii.rti.org/) is entering its fourth phase. This is to focus on the safety and effectiveness of blood transfusion therapies in adults and children. The study will link demographic, clinical and laboratory data on blood donors and their recipients, which will allow investigators to address key research questions in blood banking and transfusion medicine and inform blood policy decisions.

# Products and treatments

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

## Treating haemophilia

* + A real-world study[[12]](#footnote-12) in the US found that treatment of [haemophilia A](https://hemophilianewstoday.com/hemophilia-type-a/) with bypassing agents carries significantly higher costs than treatment with factor replacement therapy.
  + In gene therapy for haemophilia, researchers have found that from the standpoint of safety and efficacy, the most promising gene therapy platform is the adeno-associated viral (AAV) vector[[13]](#footnote-13).
    1. AMT-061 is uniQure’s investigational AAV-based gene therapy incorporating the factor IX-Padua variant for the treatment of patients with severe and moderately severe haemophilia B[[14]](#footnote-14). An ongoing phase I/ II trial of uniQure’s first-generation AAV-based gene therapy, AMT-160, consists of an AAV5 vector carrying gene cassette with the standard wild-type factor IX gene. While that earlier trial has been promising, by replacing the wild-type factor IX gene with the bioengineered Padua variant[[15]](#footnote-15), researchers have accomplished factor IX levels of 25 per cent to 50 per cent of normal (with AMT-061), compared with levels of 5 per cent to 10 per cent with AMT-060.
    2. Another gene therapy for haemophilia B, SPK-9001, being developed by Spark Therapeutics and Pfizer, is also based on the Padua variant. The therapy has been shown to be effective in reducing bleeding and factor IX infusions in phase I/ II and is [now in phase III testing](https://clinicaltrials.gov/ct2/show/NCT03587116?term=NCT03587116&rank=1). Principle investigator Lindsey George[[16]](#footnote-16) said: "We had sustained expression of factor IX -an average of 35 per cent for 15 haemophilia B patients. From a safety standpoint there were no major safety concerns, and no adverse events." She said there was almost a complete resolution of bleeding, with one patient having a bleeding event that was remarkably reduced from his baseline; that “there has been virtual elimination of the requirement of factor use; and that "this partnership between these bioengineered molecules and the AAV platform is proving to be very successful and we are seeing the same thing happen with factor VIII."[[17]](#footnote-17) It is still too soon for researchers to be certain how long expression in patients treated with gene therapies will last.
  + Researchers in Italy say[[18]](#footnote-18) that a combination of [Cyklokapron](https://www.pfizermedicalinformation.com/en-us/cyklokapron/dosage-admin) and [Feiba](https://www.feiba.com/) —often avoided due to a perceived risk of blood clots — appears to be safe and effective for treating patients with acquired [haemophilia A](https://hemophilianewstoday.com/hemophilia-type-a/) (AHA), though these early study results need to be confirmed in clinical trials.
  + A case study report[[19]](#footnote-19) says that recognizing risk factors of [thrombosis](https://www.hopkinsmedicine.org/health/conditions-and-diseases/thrombosis) and carefully monitoring medication doses are crucial for minimizing thrombotic complications in older patients with [acquired haemophilia](https://hemophilianewstoday.com/types-of-hemophilia/acquired-hemophilia/) and serious illnesses like cardiovascular disease.

## Treating beta thalassemia and sickle cell disease

* + Researchers in Boston[[20]](#footnote-20) have developed a way to treat sickle cell disease and beta thalassemia, applying CRISPR-Cas9 gene editing to patients' own blood stem cells[[21]](#footnote-21). Their approach overcomes earlier technical challenges, editing blood stem cells more efficiently than has previously been possible. Their studies show that the gene-edited cells generate genetically corrected red blood cells producing functional haemoglobin.
  + Researchers in Italy have suggested[[22]](#footnote-22) that using more-precise gene-editing technology that induces fewer breaks in DNA may keep stem cells' natural damage-response pathways under control.
  + The US Food and Drug Administration (FDA) has granted a fast track designation for CTX001 (CRISPR Therapeutics and Vertex Pharmaceuticals Incorporated) for the treatment of transfusion-dependent beta thalassemia (TDT)[[23]](#footnote-23). CTX001 is an investigational, autologous, gene-edited hematopoietic stem cell therapy for patients with severe haemoglobinopathies. The new therapy is also being evaluated for the treatment of sickle cell disease (SCD) and received fast track designation status for the purpose in January 2019. The experimental ex vivo therapy modifies the hematopoietic stem cells to produce high levels of foetal haemoglobin (HbF) in red blood cells. HbF is a form of the oxygen-carrying haemoglobin that is present at birth and is then replaced by the adult form of haemoglobin. Elevating HbF through CTX001 could relieve the transfusion requirements for TDT patients as well as the painful, debilitating crises in patients with SCD.

## Other products and treatments

* + [Humacyte](https://cts.businesswire.com/ct/CT?id=smartlink&url=http%3A%2F%2Fwww.humacyte.com%2F&esheet=51960552&newsitemid=20190327005673&lan=en-US&anchor=Humacyte&index=1&md5=2f9ab1e2d94638ff1e4b90f3335182ff) announced publication[[24]](#footnote-24) of work showing its human acellular vessels (HAVs) repopulate with the patient’s own cells to form a living vascular tissue. The company said the study presents a comprehensive microscopic evaluation of HAV samples retrieved 16 weeks to 4 years after implantation in patients enrolled in Phase II clinical trials providing vascular access for haemodialysis; and that the results suggest that the bioengineered HAV may develop characteristics of a living tissue over time. Senior author of the report was Heather Prichard, Humacyte’s Chief Operations Officer. The product received the [FDA’s Fast Track Designation](https://cts.businesswire.com/ct/CT?id=smartlink&url=https%3A%2F%2Fwww.humacyte.com%2Fnews%2Fhumacyte-receives-fast-track-designation-humagraft-vascular-access-hemodialysis-program%2F&esheet=51960552&newsitemid=20190327005673&lan=en-US&anchor=FDA%27s+Fast+Track+Designation&index=3&md5=90e6b76bb2f90da758e7302ca2dde1ac) in 2014 and the [Regenerative Medicine Advanced Therapy (RMAT)](https://cts.businesswire.com/ct/CT?id=smartlink&url=https%3A%2F%2Fwww.humacyte.com%2Fnews%2Fhumacyte-receives-fda-regenerative-medicine-advanced-therapy-rmat-expedited-review-designation-humacyl-vascular-access-hemodialysis%2F&esheet=51960552&newsitemid=20190327005673&lan=en-US&anchor=Regenerative+Medicine+Advanced+Therapy+%28RMAT%29&index=4&md5=5a0097cdff44a65f05ef72f0167922b0) designation in 2017.
  + A report in the American Journal of Hematology*[[25]](#footnote-25)* suggests that fostamatinib therapy may provide durable long-term responses for adult patients with immune thrombocytopenia (ITP). Trials reviewed by researchers included two randomized, double blind trials in adult patients with long-term ITP ([ClinicalTrials.gov](http://ClinicalTrials.gov) Identifiers: [NCT02076399](https://clinicaltrials.gov/ct2/show/NCT02076399) and [NCT02076412](https://clinicaltrials.gov/ct2/show/NCT02076412)) and a follow-up, open label extension study ([ClinicalTrials.gov](http://ClinicalTrials.gov) Identifier: [NCT02077192](https://clinicaltrials.gov/ct2/show/NCT02077192)). The authors considered that fostamatinib demonstrated feasibility and durability of stable and overall platelet responses but recommended further studies to evaluate mechanisms and patterns of treatment response.
  + A long-term extension [study](http://www.haematologica.org/content/early/2019/03/01/haematol.2018.202283.long) has found[[26]](#footnote-26) that romiplostim is effective in boosting platelet counts in most children with chronic immune thrombocytopenia (ITP) and can lead to a treatment-free response in almost a quarter of children. The study enrolled 66 children from previous Phase I/ II and Phase III studies comparing romiplostim with placebo. Participants were recruited from 28 sites in the US, Canada, Spain and Australia.
  + St. Jude Children’s Research Hospital has published results of a study of lentiviral gene therapy for treatment of infants with X-linked severe combined immunodeficiency[[27]](#footnote-27). The multi-center Phase I/ II clinical trial is led by Ewelina Mamcarz, at St. Jude[[28]](#footnote-28). She said: “The results have been very good thus far. We’ve been able to restore a full immune system pretty quickly. All of these patients were able to come off isolation and they’ve returned home with immune systems that were fully functional. We had patients come to us with very severe infections and they cleared them through the emergence of this newly developed immune system.” Martina Sersch, Chief Medical Officer of industry partner Mustang Bio, said: “We are extremely encouraged by the Phase I / II clinical data published in the *New England Journal of Medicine.* They underscore the potential of MB-107 as a novel approach and potentially curative treatment option for newly diagnosed infants with XSCID. We are excited to continue working with St. Jude to evaluate MB-107 in this clinical trial, and we look forward to transferring the IND[[29]](#footnote-29) to Mustang by the end of this year, after which patients’ cells from all three participating clinical trial sites will be processed in our Worcester, Massachusetts, facility.”
  + Orchard Therapeutics announced that the [first patient has been dosed](https://seekingalpha.com/pr/17487710-orchard-therapeutics-announces-first-patient-dosed-cryopreserved-formulation-otlminus-103) in an open-label, six-subject [Phase I/ II clinical trial](https://clinicaltrials.gov/ct2/show/NCT03837483?intr=Wiskott-Aldrich+Syndrome&lead=orchard+therapeutics&rank=2) evaluating a cryopreserved[[30]](#footnote-30) formulation of its lentiviral gene therapy [OTL-103](https://www.orchard-tx.com/disease-areas-and-pipeline/medical-professionals/primary-immune-deficiencies) in patients with [Wiskott-Aldrich syndrome](https://ghr.nlm.nih.gov/condition/wiskott-aldrich-syndrome), which is associated with abnormal immune system function and a compromised ability to form blood clots. The expected primary completion date is February 2022. The primary endpoint is the number of participants with successful engraftment after six months. Orchard said it used a fresh cell formulation of OTL-103 in the registration study, but it will commercialize the cyropreserved formulation, if approved.

# Regulatory

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

* + Japan's Ministry of Health, Labour and Welfare has approved two CSL Behring immunoglobulin therapies for the treatment of patients with chronic inflammatory demyelinating polyradiculoneuropathy (CIDP).  Hizentra, previously approved to treat primary immunodeficiency, is now the first and only subcutaneous immunoglobulin (SCIG) approved for maintenance therapy to treat CIDP in Japan.  Privigen, an intravenous immunoglobulin (IVIG), is now approved for both acute and maintenance therapy of CIDP in Japan.
  + ADMA Biologics announced that the FDA had approved Asceniv, its intravenous immunoglobulin, for the treatment of primary humoral immunodeficiency disease in adults and adolescents (12 to 17 years of age). ADMA expects to have the product available for commercial launch during the second half of 2019.
  + Silence Therapeutics has applied to the UK Medicines and Healthcare Products Regulatory Agency to begin a clinical trial for its lead SLN124 treatment, to ameliorate anaemia in rare conditions. SLN124 has been shown to lower serum iron levels in preclinical trials. Silence hopes to begin a Phase Ib first-in-human study for beta-thalassemia and myelodysplastic syndrome. First patients are expected to be enrolled in the study in the third quarter of 2019.
  + The European Medicines Agency’s (EMA) Committee for Medicinal Products for Human Use (CHMP) recommended marketing authorisation for Alexion Pharmaceutical’s Ultomiris (ravulizumab) for the treatment of adult patients with paroxysmal nocturnal haemoglobinuria (PNH) with haemolysis with clinical symptoms indicative of high disease activity, and also for adult patients who are clinically stableafter having been treated with Soliris (eculizumab) for at least the past six months.
  + CHMP also recommended approval for Novo Nordisk's Esperoct (turoctocog alfa pegol) for the treatment and prophylaxis of haemophilia A in patients at least 12 years old. Final decisions from the European Commission usually take around 60 days.
  + **Kamada** announced that the FDA has acknowledged the path forward for commencing a Phase III study on its inhaled Alpha-1 Antitrypsin (Inhaled AAT) product, which is being developed for the treatment of Alpha-1 Antitrypsin Deficiency (AATD)[[31]](#footnote-31).

# 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.*

* + Bluebird Bio has opened a manufacturing facility in Durham, North Carolina where it will make its cell and gene therapy treatments*.*
  + uniQure gave six data presentations[[32]](#footnote-32), at the American Society of Gene and Cell Therapy (ASGCT) 21st Annual Meeting held in Washington D.C., April 29 - May 2, 2019. Sander van Deventer, chief scientific officer at uniQure, said: "We are very pleased to have such a strong showing at ASGCT, and to have new preclinical data featured in Huntington's disease, haemophilia A and Fabry disease."
  + ADMA Biologics announced that the US Patent and Trademark Office issued to it US Patent No. 10,259,865 related to methods of treatment and prevention of *S. pneumonia* infection. The patent claims encompass methods of preparing immune globulin via harvesting plasma from *S. pneumonia* vaccinated, healthy adult human donors and pooling the harvested plasma as the source for manufacturing a hyperimmune anti-pneumococcal immune globulin containing elevated opsonic antibodies to a plurality of *S. pneumonia* serotypes. The issued claims also encompass hyperimmune anti-pneumococcal immune globulin so prepared, methods of treating *S. pneumonia* infection and methods of providing immunotherapy using the hyperimmune anti-pneumococcal immune globulin.
  + Roche launched Emicizumab under the brand name Hemlibra in India for preventive treatment of haemophilia A.

# Specific country events

* + In the US, Bayer and its partner Johnson & Johnson have agreed to pay $US 775 million to settle thousands of lawsuits related to their blood thinner, Xarelto. There are around 25,000 claimants. The companies are not admitting liability in their settlement.
  + A US study[[33]](#footnote-33) found that the chances of finding an unrelated bone marrow donor are higher for US patients of European descent than for those of non-European descent. Researchers included over 1,300 blood cancer patients at Memorial Sloan Kettering Cancer Center, in New York City, who sought a fully matched bone marrow donor between 2005 and 2017. While 67 per cent of patients with European ancestry received a matched transplant from an unrelated donor[[34]](#footnote-34), the rate for non-Europeans was only 33 per cent, including Asians, white Hispanics and Africans. Those of African descent had the lowest rate. Most who did not have a full match either received a partial match (17 per cent of all patients) or a cord blood transplant (24 per cent). Four per cent of patients did not receive a transplant – most of these patients were of African descent. Joint author Juliet Barker said in a news release: "We have identified tremendous racial and ethnic disparity in transplant access. What's more, it has been thought by some that if you just increase the number of registered adult donors that it would resolve this problem, but it hasn't." Barker, director of the Cord Blood Transplant Program at Memorial Sloan Kettering, said the findings underline the importance of efforts to improve outcomes of alternative donor transplantation, including the use of unrelated donor cord blood. Barker also said that the difficulty for patients with origins in southern Europe hasn't been widely appreciated. She explained that transplant centres can quickly gauge a patient's chances for a matched donor and should abandon futile adult donor searches if chances are poor; she emphasised that this becomes more and more important as the population becomes more diverse.
  + The Australian Government has granted $A 80 million funding to Peter MacCallum Cancer Centre in Melbourne to kick-start it as a potential CAR T-cell manufacturing hub. That amount will be supplemented with $A 25 million from the Centre’s majority-owned [Cell Therapies](http://www.celltherapies.com.au/) to create the Peter Mac Centre of Excellence in Cellular Immunotherapy.
  + Research has found[[35]](#footnote-35) that for Queensland patients with secondary immunodeficiency, home‐based subcutaneous immunoglobulin treatment offers better health outcomes and cost savings compared with hospital‐based intravenous immunoglobulin treatment.
  + A study[[36]](#footnote-36) has found that haemophilia care providers in the UK have insufficient knowledge on how to assess the risk of prolonged bleeding associated with dental procedures. Earlier studies [revealed](https://hemophilianewstoday.com/2018/12/21/hemophilia-patients-show-worse-oral-hygiene-than-healthy-controls-study/) that children and adults with severe [haemophilia](https://hemophilianewstoday.com/what-is-hemophilia/) have poorer oral hygiene than the healthy population and may require more invasive dental treatments. International guidelines advise that these patients may need to take prophylactic therapies prior to dental treatments. Less invasive dental techniques have decreased the risk of bleeds. More recent guidelines specifically identify which treatment approaches should be accompanied by clotting factor replacement therapies. UK researchers conducted a questionnaire-based study to assess if haemophilia clinical teams were aware of the current guidelines. There were forty-one participants. Most (85 per cent) said they usually followed the [United Kingdom Doctors’ Haemophilia Organization](http://www.ukhcdo.org/) (UKHCDO) [guidelines](https://www.nature.com/articles/sj.bdj.2013.1097.pdf), while 4 per cent followed the [World Federation of Hemophilia](https://www.wfh.org/) (WFH) 2006 [guidelines](http://www1.wfh.org/publication/files/pdf-1190.pdf). The rest said they used “local” guidelines, based on either UKHCDO or WFH recommendations. However, only two respondents were able to answer all questions and 50 per cent of participants answered fewer than half of the questions correctly. The respondents showed a tendency to overprescribe bleeding management therapies. The researchers suggested: “Education initiatives and algorithms aimed at implementing updates on recommendations about the risk of bleeding are indicated to reverse this trend.”
  + Doctors in Canada proposed a set of measures to judge the degree of the success of programs helping teen-age [haemophilia](https://hemophilianewstoday.com/what-is-hemophilia/) patients transition to adult care, especially for those with more severe disease. They also enumerated 15 “key elements” of a successful paediatric-to-adult transition program, including eight the doctors saw as feasible to implement within five years[[37]](#footnote-37).
  + In Nigeria, the Anambra State House of Assembly, keen to reduce the number of new sickle cell patients in the state, passed a bill that makes genotype testing compulsory before marriage. Parents, guardians, priests, pastors and marriage registries, that permit or perform a marriage without a genotype test, risk a fine of N200,000 or imprisonment for a term of three years or both.

# Research not included elsewhere

*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 study[[38]](#footnote-38) has found that alterations in the lungs’ network of blood vessels, caused by [sickle cell disease](https://sicklecellanemianews.com/what-is-sickle-cell-anemia/) (SCD), reflect disease burden and should be carefully monitored over time.
  + A brain-mapping study[[39]](#footnote-39) shows that [sickle cell disease](https://sicklecellanemianews.com/what-is-sickle-cell-anemia/) patients experience silent strokes in the deep white matter of the brain that is prone to low oxygen supply.
  + A study in mice[[40]](#footnote-40) has found that when blood platelets are activated during exercise, they release factors that increase the number of newborn neurons in the hippocampus.
  + A new study[[41]](#footnote-41) aims to provide a thorough accounting of blood cell production from hematopoietic stem cells. The findings are significant for understanding anaemia, diseases of the immune system, and blood cancers such as leukemias and lymphomas. Camilla Forsberg, professor of biomolecular engineering in the Baskin School of Engineering at UC Santa Cruz, said: "We're trying to understand the balance of production of blood cells and immune cells, which goes wrong in many kinds of disorders".
  + Reduced blood flow to the heart (myocardial ischemia) was the subject of a recent pilot study[[42]](#footnote-42) at Duke University. The proof-of-concept study aimed to demonstrate the feasibility of using specific metabolites that show distinct changes in their levels (in individuals suffering from myocardial ischemia or blocked arteries) induced by a stress-test. Dr Limkakeng, lead author of the study commented in a press release[[43]](#footnote-43): “Augmenting the imaging of a stress test with metabolite biomarkers could make that process more accurate or more efficient.”
  + In a breakthrough study[[44]](#footnote-44)**,** biomedical engineers in the University of Minnesota found that the building blocks of sickle cell disease are much less efficient at organizing than previously thought. They suggest that developing new medicines that are effective at lower doses and cause fewer side effects might be easier than had been thought.
  + Research on the mechanics of blood clotting has shown[[45]](#footnote-45) how proteins called “integrins” — receptors in the outer membranes of cells that facilitate how cells bind to one another and interact with their environment — form an intermediate state between their active and inactive forms that promotes the aggregation of platelets.

# 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

* + On 28 March 2019 the US Centers for Disease Control and Prevention (CDC) switched its recommendation for first-line treatment for severe malaria to a drug not approved by the FDA, because the previously recommended drug will no longer be produced by the manufacturer. The new recommendation is for artesunate, which the World Health Organization (WHO) already recommends as first-line treatment for severe malaria. Quinidine gluconate, no longer to be made by Eli Lilly, is the only intravenous malaria drug approved by the FDA for use in the US. US clinicians will now need to call the CDC's malaria hotline to obtain intravenous artesunate. It will be made available under the FDA’s expanded use investigational new drug (IND) protocol.
  + The FDA approved the use of Sanofi’s dengue vaccine, Dengvaxia, subject to the condition that it can be used to treat people aged 9 to 16 with a laboratory-confirmed prior infection and living in areas where the disease is endemic. In the US, the disease is particularly prevalent in Puerto Rico and several other offshore territories and protectorates such as the US Virgin Islands and American Samoa. In December, Dengvaxia won European approval for people aged 9 to 45 living in endemic areas who have a documented prior infection.
  + Scientists at [QUT](https://www.qut.edu.au/) and the [QIMR Berghofer Medical Research Institute](https://www.qimrberghofer.edu.au/) have found[[46]](#footnote-46) that it is the dengue fever mosquito common to north and central Queensland which poses the greatest danger of spreading the Zika virus in Australia. They showed that not only was the dengue mosquito effective at transmitting Zika, but also that the virus was in the mosquitoes' reproductive organs. Zika could therefore persist in mosquito populations by females passing it to their young.
  + Emergent BioSolutions announced promising initial results for a Phase II clinical study of its experimental chikungunya vaccine, a virus-like particle (VLP) product called CHIKV-VLP[[47]](#footnote-47).

## Influenza

* + Vytenis Andriukaitis, the EC's commissioner for health and food safety, announced in a statement[[48]](#footnote-48) that the European Commission and 15 member states had signed framework contracts with Seqirus to produce and supply pandemic influenza vaccine. Similar negotiations were under way with a second pharmaceutical company. He said: " Member States signing the contracts can rest assured that their citizens will have access to vaccines in case of an influenza pandemic at the best price available. This is one additional example where acting together we get stronger and achieve more."
  + UK company Enesi Pharma has partnered with the US Department of Health and Human Services Biomedical Advanced Research and Development Authority (BARDA) on needle- free flu vaccines using its ImplaVax technology. This allows solid-dose vaccine to be delivered quickly under the skin. One aim is that patients will be able to self- administer the vaccine. Enesi says the system could boost immune responses and reduce storage and distribution costs. The project with BARDA will involve evaluating solid-dose formulations of marketed flu vaccines. *In vitro* tests will determine titre generation, mechanical strength, and certainty of implantation. *In vivo* tests will compare efficacy and dosing regimens, including a comparison of solid-dose implants with placebo and vaccine delivered by syringe.
  + Seqirus will manufacture its cell-based influenza vaccine (Flucelvax Quadrivalent) for the 2019/2020 flu season. The vaccine will use a cell-based candidate vaccine virus (CVV) for 4 influenza strains identified by WHO for the upcoming northern hemisphere flu season[[49]](#footnote-49).

## Ebola virus disease

* + On 25 March 2019 it was reported that the number of Ebola cases in the Democratic Republic of Congo had passed 1000 in the eighth month of the outbreak, with 58 recorded in the previous week. By then 634 deaths had been recorded. Over 91,000 people had been vaccinated with Merck's VSV-EBOV vaccine. A preliminary estimate published by WHO suggests that the vaccine has been more than 97 per cent effective in a ring trial where contacts — and contacts of contacts — of confirmed cases have been offered vaccination[[50]](#footnote-50).

## MERS-CoV

* + By 28 March, Saudi Arabia had recorded 111 confirmed MRS-CoV cases so far this year.

## Other diseases

* + Scientists at the Task Force for Global Health[[51]](#footnote-51) have described what needs to be done to achieve the WHO goal of eliminating [hepatitis B and C virus](https://www.mdmag.com/conditions/hepatitis-c) infections as public health threats by 2030 and preventing over 7 million deaths. The WHO goal targets a 90 per cent reduction of 2015 levels in new chronic infections, to fewer than 1 million new infections per year, and a 65 per cent reduction in deaths to fewer than half a million deaths annually. The report, “[What is Needed to Eliminate Hepatitis B Virus and Hepatitis C Virus as Global Health Threats](https://www.gastrojournal.org/article/S0016-5085(18)35205-3/pdf),” was published in Gastroenterology.
  + A new study[[52]](#footnote-52) supported by the National Institute of Allergy and Infectious Diseases (NIAID) found that an experimental antibody may suppress HIV levels for up to 4 months in people on a short-term pause from anti-retroviral therapy (ART).
  + Emergent BioSolutions has initiated a Phase III trial[[53]](#footnote-53) to evaluate the lot consistency, immunogenicity, and safety of AV7909 (anthrax vaccine adsorbed with CPG 7909 adjuvant) following a two-dose schedule administered intramuscularly in healthy adults. AV7909 is being developed for post-exposure prophylaxis of disease resulting from suspected or confirmed Bacillus anthracis exposure. The study will use three consecutively manufactured lots of the vaccine. The trial will be a randomized, double-blind, parallel-group study with 3,850 adults across 35 US states. It will take about 20 months.
  + Measles cases in the US have already exceeded the [highest number](https://www.washingtonpost.com/health/2019/04/22/us-measles-cases-surge-officials-scramble-stop-near-record-outbreak/?utm_term=.c611183a8393) on record in a single year since the disease was declared eliminated in 2000. Officials say most people who have fallen ill were unvaccinated.
  + Less than a year after WHO verified elimination of rubella in Australia (meaning there was no ongoing local transmission) cases have returned. To 23 April, 13 had been reported, over half in NSW. The disease was recorded 10 times each in 2018 and 2017.

1. Bradley KE, et al. Abstract 594. Presented at: the American Academy of Orthopaedic Surgeons Annual Meeting; March 12-16, 2019; Las Vegas. [↑](#footnote-ref-1)
2. Nicole P Juffermans, et al., “Towards patient‐specific management of trauma hemorrhage: the effect of resuscitation therapy on parameters of thromboelastometry”, Journal of Thrombosis and Haemostasis, 2019 <https://doi.org/10.1111/jth.14378>. [↑](#footnote-ref-2)
3. Henriquez DDCA et al., “Fluid resuscitation during persistent postpartum haemorrhage and maternal outcome: A nationwide cohort study”, *European Journal of Obstetrics & Gynecology and Reproductive Biology, 22 March 2019* [European Journal of Obstetrics & Gynecology and Reproductive Biology](https://www.mdlinx.com/ct.cfm?cid=7561409&typ=js&rdr=https://www.ejog.org/article/S0301-2115(19)30054-5/fulltext?rss=yes&mor=1) [↑](#footnote-ref-3)
4. Markus M Mueller, et al., “Recommendations From the 2018 Frankfurt Consensus Conference”, 12 March 2019. *JAMA.* 2019;321(10):983-997. doi:10.1001/jama.2019.0554. See also the JAMA [editorial](https://jamanetwork.com/journals/jama/fullarticle/2727432) [↑](#footnote-ref-4)
5. Professor Wood is head of the Transfusion Research Unit at Monash University and president-elect of the International Society of Blood Transfusion. [↑](#footnote-ref-5)
6. To the limbic [↑](#footnote-ref-6)
7. A G Radhika et al., “Parenteral Versus Oral Iron for Treatment of Iron Deficiency Anaemia During Pregnancy and post-partum: A Systematic Review”, *Journal of Obstetrics and Gynaecology of India.* February 2019, Volume 69, [Issue 1](https://link.springer.com/journal/13224/69/1/page/1), pp 13–24 <https://doi.org/10.1007/s13224-018-1191-8> [↑](#footnote-ref-7)
8. Julia Bohlius et al., “Management of Cancer-Associated Anemia With Erythropoiesis-Stimulating Agents: ASCO/ASH Clinical Practice Guideline Update”, [Journal of Clinical Oncology](https://ascopubs.org/doi/full/10.1200/JCO.18.02142) 20 May 2019, vol.37 no.15. Pp 1336-1351. Online 10 April. Also in [Blood Advances](http://www.bloodadvances.org/content/3/8/1197?sso-checked=true), 2019 3: 1197-1210 doi: <https://doi.org/10.1182/bloodadvances.2018030387> [↑](#footnote-ref-8)
9. Jordan K Schaefer, et al., “Association of Adding Aspirin to Warfarin Therapy, Without an Apparent Indication, With Bleeding and Other Adverse Events”. *JAMA Intern Med.* 4 March 2019;179(4):533-541. doi:10.1001/jamainternmed.2018.7816 [*JAMA Internal Medicine*](https://jamanetwork.com/journals/jamainternalmedicine/fullarticle/2726050) [↑](#footnote-ref-9)
10. David J Graham et al., “Comparative Stroke, Bleeding, and Mortality Risks in Older Medicare Patients Treated with Oral Anticoagulants for Nonvalvular Atrial Fibrillation”, [American Journal of Medicine,](https://eur01.safelinks.protection.outlook.com/?url=https%3A%2F%2Fwww.amjmed.com%2Farticle%2FS0002-9343(19)30051-8%2Ffulltext&data=02%7C01%7C%7C1859172531994a98a60908d6c52ed3db%7C84df9e7fe9f640afb435aaaaaaaaaaaa%7C1%7C0%7C636913202260920859&sdata=fPs1YnDr8kVqpYAnQBE7eWh4pQiqTFTqAcxKSihoKi0%3D&reserved=0) May 2019, Volume 132, Issue 5, Pages 596–604.e11

    DOI: <https://doi.org/10.1016/j.amjmed.2018.12.023> [↑](#footnote-ref-10)
11. Christine Voors-Pette et al., “Safety and Tolerability, Pharmacokinetics, and Pharmacodynamics of ACT017, an Antiplatelet GPVI (Glycoprotein VI) Fab**”,** *Arteriosclerosis, Thrombosis, and Vascular Biology,* Vol. 39 no. 5 Originally published1 May 2019 <https://doi.org/10.1161/ATVBAHA.118.312314> [↑](#footnote-ref-11)
12. Jason P Swindle et al., “[Healthcare costs among patients with hemophilia A treated with factor replacement or bypassing agents](https://www.tandfonline.com/doi/abs/10.1080/03007995.2019.1596437?journalCode=icmo20),” published online 3 May 2019 in the journal [*Current Medical Research and Opinion*](https://www.tandfonline.com/loi/icmo20). <https://doi.org/10.1080/03007995.2019.1596437> [↑](#footnote-ref-12)
13. AAVs are viruses that can produce an immune response in patients, so not all patients are eligible for this gene therapy [↑](#footnote-ref-13)
14. [phase III HOPE-B pivotal study of AMT-061](https://clinicaltrials.gov/ct2/show/NCT03569891) [↑](#footnote-ref-14)
15. This generates a “hyperactive” form of factor IX [↑](#footnote-ref-15)
16. Children's Hospital of Philadelphia [↑](#footnote-ref-16)
17. <https://www.medpagetoday.com/recent-developments/hemophilia/78500> . George is also the principle investigator for Spark's SPK-8011 phase I/ II trial for haemophilia A, for which [preliminary data](https://ash.confex.com/ash/2018/webprogram/Paper115495.html) was reported at the 2018 ASH (American Society of Haematology) meeting. [↑](#footnote-ref-17)
18. The study, “[Combined use of antifibrinolytics and activated prothrombin complex concentrate (aPCC) is not related to thromboembolic events in patients with acquired haemophilia A: data from FAIR Registry](https://link.springer.com/article/10.1007%2Fs11239-018-1750-y),” was published in the [*Journal of Thrombosis and Thrombolysis*](https://link.springer.com/journal/11239). [↑](#footnote-ref-18)
19. E Mauro et al., “[Acquired Haemophilia A. Which is the best therapeutic choice in older adults? Single center study of 4 cases](https://www.reumatismo.org/index.php/reuma/article/view/1041),” 1 April 2019, [Reumatismo](https://www.reumatismo.org/index.php/reuma/index). Vol 71, no 1, pp 37-41 [↑](#footnote-ref-19)
20. at Dana-Farber/ Boston Children's Cancer and Blood Disorders Center and the University of Massachusetts Medical School [↑](#footnote-ref-20)
21. # Yuxuan Wu, et al., “Highly efficient therapeutic gene editing of human hematopoietic stem cells”, *Nature Medicine* volume 25, pages776–783 (2019) <https://www.nature.com/articles/s41591-019-0401-y> and Shuqian Xu et al, ”Editing aberrant splice sites efficiently restores β-globin expression in β-thalassemia” *Blood* 2019; doi: <https://doi.org/10.1182/blood-2019-01-895094>

    [↑](#footnote-ref-21)
22. Giulia Schiroli et al., “Precise Gene Editing Preserves Hematopoietic Stem Cell Function following Transient p53-Mediated DNA Damage Response”, 21 March, Cell Stem Cell. <https://www.cell.com/cell-stem-cell/fulltext/S1934-5909(19)30071-2> [↑](#footnote-ref-22)
23. TDT is a severe, progressive type of beta thalassemia characterized by severe anaemia, unavoidable iron overload, serious comorbidities, and a shorter lifespan compared with the general population. Patients with TDT need lifelong care and must have blood transfusions every few weeks to alleviate anaemia and keep them alive. Currently, allogeneic hematopoietic stem cell transplant is the sole treatment option with the potential to correct the genetic deficiency. In February 2019, the first patient was treated with CTX001 in a Phase I/ II trial in patients with TDT. The open-label trial is designed to assess the safety and efficacy of a single dose of CTX001 in patients aged 18 to 35 years who have TDT, non-beta zero/beta zero subtypes. [↑](#footnote-ref-23)
24. Robert D Kirkton et al., “Bioengineered human acellular vessels recellularize and evolve into living blood vessels after human implantation”, [*Science Translational Medicine,*](https://cts.businesswire.com/ct/CT?id=smartlink&url=http%3A%2F%2Fstm.sciencemag.org%2Flookup%2Fdoi%2F10.1126%2Fscitranslmed.aau6934&esheet=51960552&newsitemid=20190327005673&lan=en-US&anchor=Science+Translational+Medicine%2C&index=2&md5=4a99938ae36011c5f84d82a4740cb9f4) 27 Mar 2019:  
    Vol. 11, Issue 485, eaau6934 DOI: 10.1126/scitranslmed.aau6934 Correction published 1 May 2019 [↑](#footnote-ref-24)
25. Bussell JB, Arnold DM, Boxer MA, et al. [Long-term fostamatinib treatment of adults with immune thrombocytopenia (ITP) during the phase 3 clinical trial program](https://onlinelibrary.wiley.com/doi/full/10.1002/ajh.25444) [published online February 19, 2019]. Am J Hematol. doi: 10.1002/ajh.25444 [↑](#footnote-ref-25)
26. Michael D Tarantino et al., “Long-term treatment with romiplostim and treatment-free platelet responses in children with chronic immune thrombocytopenia”, March 2019 : *Haematologica* doi:10.3324/haematol.2018.202283 <http://www.haematologica.org/content/early/2019/03/01/haematol.2018.202283.long> [↑](#footnote-ref-26)
27. Ewelina Mamcarz, et al., “Lentiviral Gene Therapy Combined with Low-Dose Busulfan in Infants with SCID-X1”, [April 18, 2019](https://www.nejm.org/toc/nejm/380/16?query=article_issue_link) N Engl J Med 2019; 380:1525-1534  
    DOI: 10.1056/NEJMoa1815408

    The study concluded that: *Lentiviral vector gene therapy combined with low-exposure, targeted busulfan conditioning in infants with newly diagnosed SCID-X1 had low-grade acute toxic effects and resulted in multilineage engraftment of transduced cells, reconstitution of functional T cells and B cells, and normalization of NK-cell counts during a median follow-up of 16 months.* (ClinicalTrials.gov number, [NCT01512888](http://clinicaltrials.gov/show/NCT01512888).) [↑](#footnote-ref-27)
28. Other participating sites and key collaborators are at UCSF Benioff Children’s Hospital, the National Institutes of Health (NIH) and Seattle Children’s Hospital. [↑](#footnote-ref-28)
29. Investigational new drug [↑](#footnote-ref-29)
30. frozen in liquid nitrogen [↑](#footnote-ref-30)
31. In 2016, Kamada's Phase II study in the US met the primary endpoint; but the FDA expressed concerns about data from the European Phase II/ III study on the candidate. In 2017, the FDA provided guidance for further development and requested a complete proposed study protocol for moving on to the phase III development. In April 2018 the FDA issued a response letter, giving further direction on the proposed phase III study protocol for inhaled AAT product. Now the FDA has said that all the grey areas have been addressed. [↑](#footnote-ref-31)
32. uniQure's presentations at ASGCT were:

    1. **Sustained Mutant Huntingtin Lowering in the Brain and Cerebrospinal Fluid of Huntington's Disease Minipigs Mediated by AAV5-miHTT Gene Therapy (Abstract #672)** Oral Session Title: Neurological and Neurosensory Gene Therapy
    2. **Towards AAV5-mediated Gene Therapy for Hemophilia A with a Factor IX Variant that functions independently of FVIII (Abstract #959)** Oral Session Title: AAV Vectors and Disease Targets II
    3. **Development of an AAV5-based Gene Therapy for Fabry Disease (Abstract #960)** Oral session title: AAV Vectors and Disease Targets II
    4. **Pre-Existing Anti-Adeno-Associated Virus (AAV) Serotype 5 Neutralizing Antibodies (NABs) Titers in Minipig Serum Do Not Reflect Levels of Anti-AAV5 NABs Titers in Their Cerebrospinal Fluid (CSF) (Abstract #291)** Poster Session Title: Immunological Aspects of Gene Therapy and Vaccines
    5. **Improving AAV Quality Attributes and Process Robustness Through Molecular Redesign (Abstract #343)** Poster Session Title: Vector and Cell Engineering, Production or Manufacturing
    6. **Transfer of Therapeutic miRNAs within Extracellular Vesicles Secreted from Huntington's Disease iPSC-Derived Neurons (Abstract #228)** Poster Session Title: Neurological Diseases

    [↑](#footnote-ref-32)
33. Juliet N Barker et al., “Racial disparities in access to HLA-matched unrelated donor transplants: a prospective 1312-patient analysis”, published online 27 March 2019, *Blood Advances* 2019 3:939-944; doi: <https://doi.org/10.1182/bloodadvances.2018028662> [↑](#footnote-ref-33)
34. Not all Europeans had the same success: 41 per cent from southern Europe had a fully matched donor, compared with between 64 per cent and 77 percent of others. [↑](#footnote-ref-34)
35. ## Tanja M Windegger et al., “Cost–utility analysis comparing hospital‐based intravenous immunoglobulin with home‐based subcutaneous immunoglobulin in patients with secondary immunodeficiency”, 18 March 2019, *Vox Sanguinis*

    [https://doi.org/10.1111/vox.12760](https://eur04.safelinks.protection.outlook.com/?url=https%3A%2F%2Fdoi.org%2F10.1111%2Fvox.12760&data=02%7C01%7C%7C7a513b77689f48230e1608d6c2d32cb7%7C84df9e7fe9f640afb435aaaaaaaaaaaa%7C1%7C0%7C636910609783076575&sdata=LCtV6dqqkooBfx%2FYR%2F8iKbWpbLs66L%2FJp8smkPzJ5ls%3D&reserved=0) [↑](#footnote-ref-35)
36. Aza Rahman et al., “[U.K. hemophilia treaters’ knowledge of risk assessment for prolonged bleeding associated with dental procedures](https://doi.org/10.1111/scd.12359),” first published 17 February 2019, [Special Care in Dentistry](https://onlinelibrary.wiley.com/journal/17544505). [Volume39, Issue2](https://onlinelibrary.wiley.com/toc/17544505/2019/39/2) March/April 2019, Pages 173-179 <https://doi.org/10.1111/scd.12359> [↑](#footnote-ref-36)
37. Findings of the study, “[Outcomes indicators and processes in transitional care in adolescents with haemophilia: A Delphi survey of Canadian haemophilia care providers](https://onlinelibrary.wiley.com/doi/abs/10.1111/hae.13699),” were published in [Haemophilia](https://onlinelibrary.wiley.com/journal/13652516). [↑](#footnote-ref-37)
38. German R Carstens et al., “[Clinical relevance of pulmonary vasculature involvement in sickle cell disease](https://onlinelibrary.wiley.com/doi/abs/10.1111/bjh.15795),” [British Journal of Haematology](https://onlinelibrary.wiley.com/journal/13652141). 10 February 2019, <https://doi.org/10.1111/bjh.15795> [↑](#footnote-ref-38)
39. Andria L Ford et al., “[Silent infarcts in sickle cell disease occur in the border zone region and are associated with low cerebral blood flow](http://www.bloodjournal.org/content/132/16/1714?sso-checked=true),” [*Blood*](http://www.bloodjournal.org/) 2018 132:1714-1723;

    doi: <https://doi.org/10.1182/blood-2018-04-841247> [↑](#footnote-ref-39)
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50. Between 1 August 2018, and 25 March 2019, 71 cases of Ebola occurred among 93,965 at-risk contacts who were vaccinated in 679 rings. During the same time period, 880 cases occurred among at-risk individuals who were not vaccinated. Of the 71 cases in the first group, 15 experienced onset of symptoms 10 or more days after vaccination — the length of time after which vaccinated people are assumed to be protected. Only 8.8 per cent of the vaccinated rings reported Ebola cases and only 2.2 per cent reported them 10 days or more after vaccination. According to the report, 76 per cent of cases among vaccinated people occurred among high-risk contacts, and only two out of 68,279 vaccinated contacts of contacts developed Ebola, indicating to researchers that ring vaccination is effective. WHO, “Preliminary results on the efficacy of rVSV-ZEBOV-GP Ebola vaccine using the ring vaccination strategy in the control of an Ebola outbreak in the Democratic Republic of the Congo” <https://www.who.int/csr/resources/publications/ebola/ebola-ring-vaccination-results-12-april-2019.pdf>. [↑](#footnote-ref-50)
51. The Task Force for Global Health is an international, nonprofit organization dedicated to improving the health of people in need, particularly in developing countries. Authors of the report were John Ward, a Senior Scientist at the US Centers for Disease Control and Prevention (CDC) assigned to the task force, and Alan Hinman, a Consulting Adviser for the Center for Vaccine Equity (CVE) program at the task force. [↑](#footnote-ref-51)
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