Gene therapy for haemophilia B – everything you need to know

How many people have haemophilia B in the UK?

About 2,000 people in the UK live with haemophilia B, of which 242 adults are categorised to have a severe form of the condition and 271 are classed as moderate. Severe haemophilia is when factor levels are less than 1% of normal. Moderate haemophilia is when people have factor levels of 1-5% of normal. Moderately severe is a subset of moderate haemophilia defined as people with 1-2% of normal clotting levels.

How does gene therapy work?

People with haemophilia B are born with a version of the factor IX gene that does not work properly. This means the liver cannot make enough of its own factor IX. Gene therapy works by creating a working version of the factor IX gene.

The gene is put inside a viral vector, which is an inactivated virus, meaning it cannot spread in the body and does not cause illness in humans. The virus' purpose is to get the factor IX gene to the liver. Once that is done, the viral vector is broken down and removed by the body.

Once the gene therapy is delivered, through an infusion, the liver can start making its own factor IX, without the gene becoming part of the person's DNA.

Gene therapy cannot be reversed.

Who is eligible for gene therapy?

Adults with severe or moderately severe haemophilia B who do not have an inhibitor or a history of inhibitors. In England this is estimated by NICE to be around 250 people. Some people have antibodies against the viral vector used in gene therapy which may stop the FIX gene from getting to the liver. This can be established using a blood test. If large amounts of antibodies are detected, this may mean that gene therapy is not suitable for that person.

People with severe liver damage will not be eligible.

What about gene therapy for haemophilia A?

There are ongoing trials, but gene therapy for haemophilia A is not currently being considered for use in the NHS.

How is gene therapy given?

Gene therapy is given by a single infusion. At present it can only be given once. The infusion usually takes between one and two hours, but you will be at the centre for the entire day to complete paperwork and to be monitored.

How do you know gene therapy has worked?

Factor levels usually rise within two to three weeks of the infusion and will be monitored by your healthcare team. Treatment will be adjusted accordingly. Once certain levels are reached, usually 5%, prophylaxis is stopped. Stable levels are seen within six to 12 months.

Gene therapy may not work in a minority of patients. Also, in clinical trials there were examples of people who found that gene therapy raised their clotting levels higher than the normal range which increased the risk of excessive clotting.

Does gene therapy mean I won't need any treatment in the future?

The hope is that people who have gene therapy will experience at least three years of near-normal factor IX levels, but this is not guaranteed. The factor levels you achieve may last for decades or they could decline over time.

There may be situations where you need an extra boost of factor IX, such as in the event of surgery or trauma. If your factor levels decline below a certain level you may need to return to factor prophylaxis. It is important to stay in touch with your local haemophilia centre.

If you have pre-existing joint damage you will still need regular access to your specialist physiotherapist.

How long will gene therapy last?

Recent trials for gene therapies for haemophilia B have shown that sustained factor levels for most people last for at least three years. Earlier trials for gene therapies have shown that people can have sustained factor levels for a decade or more. The factor levels you achieve may last for decades or they could decline over time.

What are the risks of gene therapy?

Gene therapy will not work for everyone and, at present, there is no way of knowing who gene therapy will or won't work for.

The short term side effects most commonly seen in clinical trials are:

- Headaches
- Flu-like symptoms
- Allergic reactions
- Dizziness
- Eye itching
- Stomach discomfort
- Chest discomfort
- A rash
- A fever
- Feeling sick
- Feeling tired
- Feeling unwell

The medium and long-term risks are:

- An inflamed liver which requires treatment using a corticosteroid.
- Blood clots, the risks, after gene therapy, become closer to the general population. The risk may be higher in older people or those who have certain medical conditions, such as heart problems and strokes.
- Fragments of the virus vectors used to get the gene therapy to the liver might be in the blood, semen and bodily waste. This means a person who has had gene therapy can't donate blood or semen or be an organ donor. There is also a chance that these fragments could be transmitted during sex which means condoms or other barrier contraception should be used for up to a year after the gene therapy infusion.
- It is theoretically possible that gene therapy could get into your DNA. If this happened, the person might be at increased risk of cancer.

What's involved before having gene therapy?

If gene therapy seems right for you, you should discuss this with your consultant. You'll then be referred to your nearest gene therapy treatment centre, if this isn't offered at your centre, where you will receive comprehensive information about gene therapy from your medical team. There will be a step-by-step discussion process so you know what to expect at each stage.

You will be screened for anti-AAV antibodies and there will be a review of your general health and liver health. If eligible, you will be referred to a psychologist to ensure you are fully prepared for all aspects of the impact of gene therapy.

You will be asked for written consent for the gene therapy infusion and for your data to be included in the national registry.

Expect to spend a considerable amount of time in clinic for numerous tests before and immediately after gene therapy.

What's involved after having gene therapy?

After gene therapy you will need blood tests between one to three times a week to check whether gene therapy is working and to look for any side effects. The blood tests will check if the liver enzymes are healthy. If your liver is inflamed, you may be prescribed a corticosteroid tablet and will need to have regular tests until it returns to normal. You may be referred to a liver specialist during this time.

You will be asked not to drink alcohol for up to six months following gene therapy. As gene therapy involves the liver and monitoring is being done to look for immune response, any alcohol can mimic the immune response. This could lead to the wrong treatment being given.

I think I'm eligible for gene therapy – what do I do now?

Talk to your haemophilia consultant, who will put you in touch with your nearest gene therapy centre for detailed discussions about what's involved and the potential risks and benefits of treatment.

Where can I receive gene therapy?

NHS England has commissioned eight centres in England to give gene therapy. These centres will work with local haemophilia centres to ensure the right information is available to make an informed decision about this treatment.

The centres are:

- Haemostasis and Thrombosis Centre, St Thomas' Hospital, Guys and St Thomas' NHS Foundation Trust
- Katharine Dormandy Haemophilia and Thrombosis Centre, Royal Free Hospital, Royal Free London NHS Foundation Trust
- Manchester Adult's Haemophilia Comprehensive Care Centre, Manchester Royal Infirmary, Manchester University Foundation Trust
- Oxford Haemophilia & Thrombosis Centre, Nuffield Orthopaedic Centre, Oxford University Hospitals NHS Foundation Trust
- Leeds Haemophilia Centre, St James's University Hospital, Leeds Teaching Hospitals NHS Trust
- Bristol Haemophilia Comprehensive Care Centre, Bristol Haematology and Oncology Centre, University Hospitals Bristol and Weston NHS Foundation Trust

- West Midlands Adult Comprehensive Care Haemophilia & Thrombosis Centre, Old Queen Elizabeth Hospital, University Hospitals Birmingham NHS Foundation Trust
- The Haemophilia Comprehensive Care Centre, Addenbrooke's Hospital, Cambridge University Hospitals NHS Foundation Trust

Is gene therapy a cure for haemophilia?

Gene therapy provides long term relief from disease symptoms but does not currently remove the abnormal gene from the body. Undergoing gene therapy will not prevent you from passing on the haemophilia gene to your daughters.

What about Wales, Scotland and Northern Ireland?

As health is a devolved issue, this decision by NICE and NHS England applies to England only. Decisions in Wales and Northern Ireland consider NICE and NHS England's decisions, but a separate process would have to be followed before it is available in these countries. In Scotland, it is already under consideration by the Scottish Medicines Consortium (SMC) for it to be made available through the NHS in Scotland.

Who's behind gene therapy research?

Gene therapy for haemophilia was pioneered by Professor Ted Tuddenham and Professor Amit Nathwani at the Royal Free Hospital in London and the first successful trials in gene therapy for haemophilia B were published in 2011. The discovery of the Padua variant of the FIX gene, which has five- to 10-fold higher activity, allowed Dr Lindsey George and colleagues to lower the gene therapy dose required while increasing factor levels achieved. This work laid the foundations for the latest trials which saw the licensing of the first two gene therapies for haemophilia B.

When will gene therapy be available on the NHS?

Under the agreement reached with NHS England, funding is available immediately. However, because of the lengthy consent, information and testing process involved with gene therapy we would expect the first people to receive gene therapy through the NHS in autumn 2024.

Who makes this product?

The National Institute for Health and Care Excellence (NICE) has approved CSL Behring's gene therapy etranacogene dezaparvovec, known as Hemgenix. There are other gene therapy products for haemophilia B in the pipeline, including Pfizer's gene therapy fidanacogene elaparvovec, which may be available through the NHS by the end of 2024.