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Hemgenix as First Gene Therapy for Treatment of Haemophilia B

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Abstract: *We know about haemophilia B is an inheritable bleeding complaint performing from missing or inadequate situations of blood clotting Factor IX, a protein demanded to produce blood clots to stop bleeding. Haemophilia B is a rare, lifelong bleeding complaint caused by a single gene disfigurement, performing an inadequate product of factor IX, a protein primarily produced by the liver that helps blood clots form. Treatments for moderate to severe haemophilia B include precautionary infusions of factor IX relief remedy to temporarily replace or condense low situations of blood- clotting factor and, while these curatives are effective, those with haemophilia B must cleave to strict, lifelong infusion schedules. But lately US FDA authorize hemegenix for haemophilia. the first and only one- time gene remedy for applicable grown-ups with haemophilia. Hemgenix is approved for the treatment of grown-ups with haemophilia B who presently use factor IX Prophylaxis remedy.*

Keywords: Haemophilia B, Prophylaxis, X chromosome, Etranacogene dezaparvovec

I. INTRODUCTION

Haemophilia B is the alternate most common type of haemophilia. It is also known as factor IX insufficiency, or Christmas. It was firstly named "Christmas'' after the first person diagnosed with the complaint back in 1952. numerous cases still die before majority due to shy treatment.[1] With proper treatment, life expectation is only about 10 times less than healthy men. Overall, the death rate for people with haemophilia is about doubly that of the rate for healthy men. For severe haemophilia, the rate is four to six times advanced. haemophilia B is the result of the body not making enough factor IX. haemophilia B is caused by an inherited X-linked sheepish particularity, with the imperfect gene located on the X chromosome. Ladies have two clones of the X chromosome.[2]

1.1 Etranacogene Dezaparvove

Etranacogene dezaparvovec (Hemgenix, CSL Behring) is an adeno-associated virus vector-based gene therapy that carries a gene for clotting factor IX and is given as a one-time IV infusion. The therapy causes the patient's liver to produce factor IX protein, thereby increasing levels of factor IX in the blood and limiting bleeding episodes.[3]Etranacogene dezaparvovec, sold under the brand name hemogenic is a gene therapy used for the treatment of hemophilia B. Etranacogene dezaparvovec is an adeno-associated virus vector-based gene therapy which consists of a viral vector carrying a gene for clotting Factor IX. The gene is expressed in the liver to produce factor IX protein, to increase blood levels of factor IX, and thereby limit bleeding episodes. hemophilia B is a genetic bleeding disorder resulting from missing or insufficient levels of blood clotting factor IX, a protein needed to produce blood clots to stop bleeding. [4]

The safety and effectiveness of etranacogene dezaparvovec were evaluated by the US Food and Drug Administration (FDA) in two studies of 57 adult men 18 to 75 years of age with severe or moderately severe Hemophilia B. Effectiveness was established based on decreases in the men's annualized bleeding rate (ABR).[5] one study, which had 54 participants, the subjects had increases in Factor IX activity levels, a decreased need for routine Factor IX replacement prophylaxis, and a 54% reduction in ABR compared to baseline. The FDA granted the application for etranacogene dezaparvovec priority review, orphan drug, and breakthrough therapy.

designations. The FDA approved Hemgenix to CSL Behring LLC.Etranacogene dezaparvovec was approved for medical use in the United States.[6]

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1.2 Haemophilia B

Haemophilia B Haemophilia B is a life-changing rare complaint. People with the condition are particularly vulnerable to bleeds in their joints, muscles, and internal organs, leading to pain, swelling, and common damage. Current treatments for moderate to severe hemophilia B include life-long precautionary infusions of factor IX to temporarily replace or condense low situations of the blood-clotting factor. hemophilia B is a lifelong bleeding complaint caused by a single gene disfigurement, performing an inadequate product of factor IX, a protein primarily produced by the liver that helps blood clots form.[7] [***Figure No 1 & 2***]

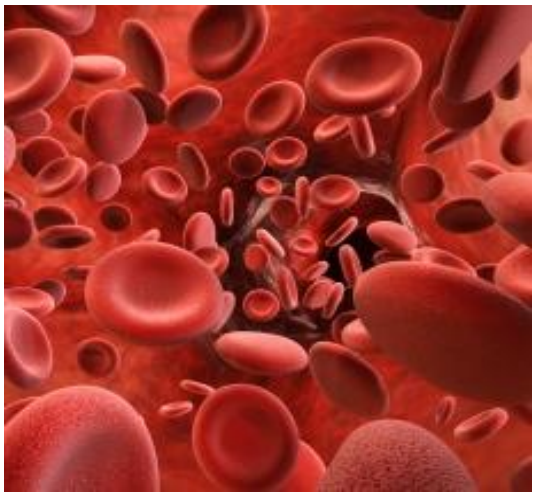

Figure No 1

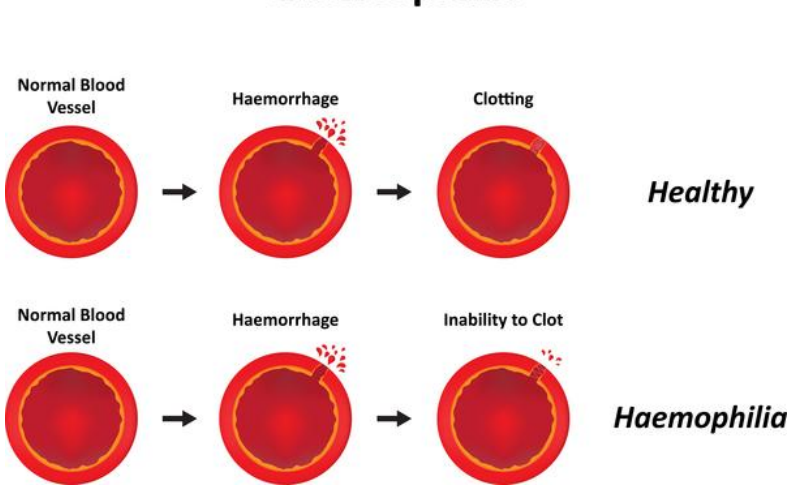

Figure No 2

1.3 Causes of Hemophilia B

The F9 gene is located on the X chromosome and thus is inherited as anX- linked recessive particularity. In about 30 new cases of hemophilia B, the altered gene occurs spontaneously without a former family history. utmost people inherit it from their mother, who carries an amiss gene. But it can also be when a Hemophilia B isa heritable bleeding disorder. However, it means you inherited an abnormal gene that affects the amount of clotting factor 9 in your body, if you have hemophilia B. generally, a gene called F9 carries instructions on how to produce factor 9. Men or people with DMAB inherit hemophilia B if their natural mothers carry the condition.[8]

If a woman or person has an abnormal F9 gene on one of their X chromosomes, they carry hemophilia B, but they will not have symptoms. That is because there is a normal F9 gene on their alternate X chromosome. This person can pass the chromosome carrying the abnormal F9 gene on to their natural mannish child. As men and people have just one chromosome, they will develop hemophilia B. Hemophilia B may be without passing from mother to son through a

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process called spontaneous mutation. In spontaneous mutation, the embryo is created when an egg and sperm combine thresholds to divide and produce farther cells. The new cells contain duplicates of the genes in the single cell, and sometimes, misapprehensions or mutations be during the gene copying process.still, your child may have hemophilia B or carry hemophilia B.[9] **[Figure No 3]**

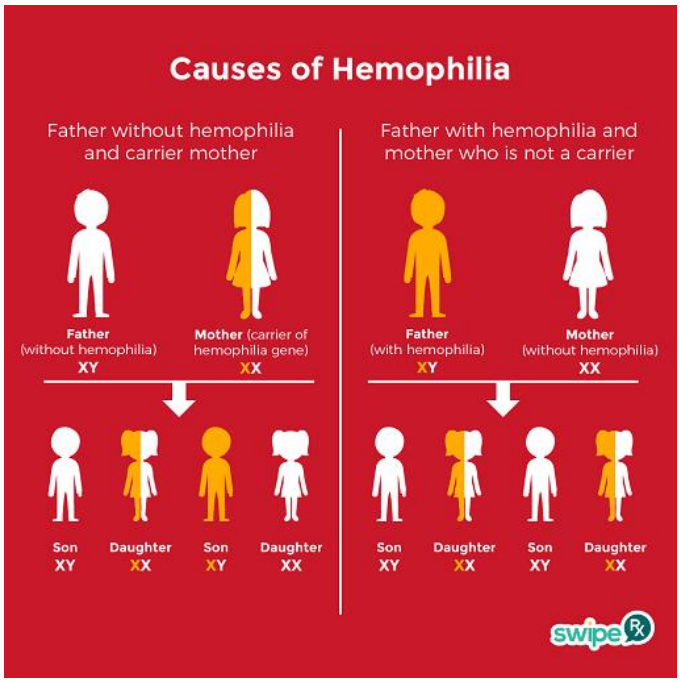

Figure No 3

1.4 Hemegenix

Hemegenix is a gene therapy that reduces the rate of abnormal bleeding in eligible people with hemophilia B by enabling the body to continuously produce factor IX, the deficient protein in hemophilia B. It uses AAV5, a non-infectious viral vector, called an adeno-associated virus (AAV). These genetic instructions remain in the target cells, but generally do not become a part of a person's DNA. Once delivered, the new genetic instructions allow the cellular machinery to produce stable levels of factor IXHemgenix is a one-time gene therapy product given as a single dose by IV infusion. The gene is expressed in the liver to produce Factor IX protein, to increase blood levels of Factor IX and thereby limit bleeding episodes. [10]

1.5 Gene Therapy

Over the years we have seen a variety of advancements for the hemophilia community, but gene therapy is the first treatment option to offer those living with hemophilia B–and caregivers–the possibility of freedom from the need for regular, ongoing infusions.hemogenic is a gene therapy that reduces the rate of abnormal bleeding in eligible people with hemophilia B by enabling the body to continuously produce factor IX, the deficient protein in haemophilia B. The therapy also has the potential to prevent further damage to joints, which could enable these patients to avert joint disease later in life.[11]

It uses AAV5, a non-infectious viral vector, called an adeno-associated virus (AAV). The AAV5 vector carries the Padua gene variant of Factor IX (FIX-Padua) to the target cells in the liver, generating factor IX proteins that are 5x-8x more active than normal. These genetic instructions remain in the target cells, but generally do not become a part of a person's own DNA. Once delivered, the new genetic instructions allow the cellular machinery to produce stable levels of factor IX.[12]

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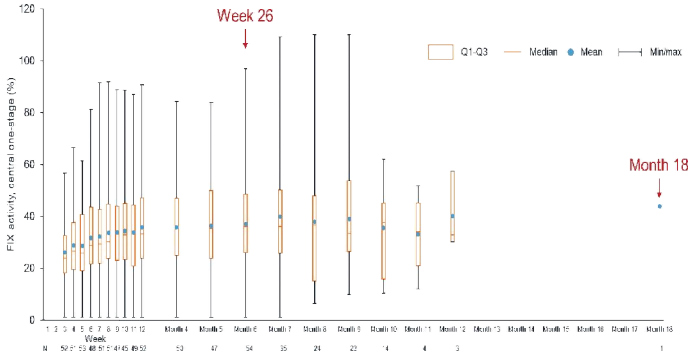
1.6 About the Pivotal HOPE-B Trial

The pivotal Phase III HOPE-B trial is an ongoing, multinational, open-label, single-arm study to evaluate the safety and efficacy of Hemgenix. Fifty-four adult haemophilia B patients classified as having moderately severe to severe haemophilia B and requiring prophylactic factor IX replacement therapy were enrolled in a prospective, six-month, or longer observational period during which time they continued to use their current standard of care therapy to establish a baseline Annual Bleeding Rate (ABR). After the six-month lead-in period, patients received a single intravenous administration of hemgenix at the 2x10^13 gc/kg dose. Patients were not excluded from the trial based on pre-existing neutralizing antibodies (NAbs) to AAV5.[13]

A total of 54 patients received a single dose of hemgenix in the pivotal trial, with 53 patients completing at least 18 months of follow-up. The primary endpoint in the pivotal HOPE-B study was ABR 52 weeks after achievement of stable factor IX expression (months 7 to 18) compared with the six-month lead-in period. For this endpoint, ABR was measured from month seven to month 18 after infusion, ensuring the observation period represented a steady-state factor IX transgene expression. Secondary endpoints included assessment of factor IX activity.[14]

No serious adverse reactions were reported. One death resulting from urosepsis and cardiogenic shock in a 77-year-old patient at 65 weeks following dosing was considered unrelated to treatment by investigators and the company sponsor. A serious adverse event of hepatocellular carcinoma was determined to be unrelated to treatment with HEMGENIX by independent molecular tumour characterization and vector integration analysis. No inhibitors to factor IX were reported.[15] **[Figure No 3&4]**



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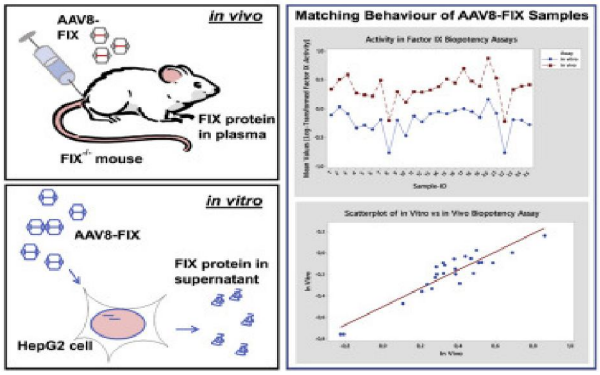

Figure No 4

1.7 Side Effects of Hemgenix in Clinical Trials

In clinical trials for hemgenix the most common side effects reported in more than 5% of patients were liver enzyme elevations, headache, elevated levels of a certain blood enzyme, flu-like symptoms, infusion-related reactions, fatigue, nausea, and feeling unwell. These are not the only side effects possible. haemophilia B is a genetic bleeding disorder resulting from missing or insufficient levels of blood clotting Factor IX, a protein needed to produce blood clots to stop bleeding. [16]

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1.8 Symptoms

Symptoms can include prolonged or heavy bleeding after an injury, surgery, or dental procedure; in severe cases, bleeding episodes can occur spontaneously without a clear cause. Prolonged bleeding episodes can lead to serious complications, such as bleeding into joints, muscles, or internal organs, including the brain. Most individuals who have haemophilia B and experience symptoms are men. The prevalence of haemophilia B in the population is about one in 40,000; haemophilia B represents about 15% of patients with haemophilia. Many women carriers of the disease have no symptoms. However, an estimated 10-25% of women carriers have mild symptoms; in rare cases, women may have moderate or severe symptoms. The most common adverse reactions associated with Hemgenix included liver enzyme elevations, headache, mild infusion-related reactions, and flu-like symptoms. Patients should be monitored for adverse infusion reactions and liver enzyme elevations (transaminitis) in their blood. [17]

1.9 Treatment

Treatment typically involves replacing the missing or deficient clotting factor to improve the body's ability to stop bleeding and promote healing. Patients with severe haemophilia B typically require a routine treatment regimen of intravenous (IV) infusions of Factor IX replacement products to maintain sufficient levels of clotting factor to prevent bleeding episodes.This historic approval provides a new treatment option that reduces the rate of annual bleeds, reduces, or eliminates the need for prophylactic therapy and generates elevated and sustained factor IX levels for years after a one-time infusion the largest gene therapy trial in haemophilia B. 7 to 18 months post-infusion, the mean adjusted annualized bleeding rate (ABR) for all bleeds was reduced by 54 percent compared to the six-month lead-in period on factor IX prophylactic replacement therapy (4.1 to 1.9). In addition, 94 percent (51 out of 54) of patients treated with hemegenix discontinued use of prophylaxis and remained free of previous continuous routine prophylaxis therapy.

While these therapies are effective, those with haemophilia B must follow lifelong infusion schedules. They may also still experience spontaneous bleeding episodes as well as limited mobility, joint damage, or severe pain as a result of the disease. For appropriate patients, hemgenix allows people living with haemophilia B to produce their own factor IX, which can lower the risk of bleeding. [18]

II. RESULTS

From the study demonstrated that hemgenix allowed cases to produce mean factor IX exertion of 39 percent at six months and36.7 percent at 24 months post infusion. The FDA blessing is supported by results from the ongoing Stopgap- B trial, the largest gene remedy trial in haemophilia B to date. Results from the study demonstrated that hemgenix allowed cases to produce mean factor IX exertion of 39 at six months and36.7 at 24 months post infusion.

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