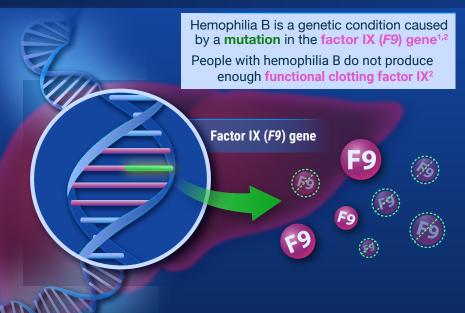
Investigational CRISPR-Based Targeted Gene Insertion for Hemophilia B

For Study Investigator Use Only

CRISPR-based targeted gene insertion for hemophilia B is investigational and the efficacy and safety has not been evaluated by any regulatory authority



Gene insertion aims to permanently restore the body's ability to independently produce factor IX without the need for routine factor replacement therapy³

What is Gene Insertion?

Gene insertion is a type of gene editing where a therapeutic gene can be precisely added to specific sections of DNA to restore the body's ability to work as it should³



Liver

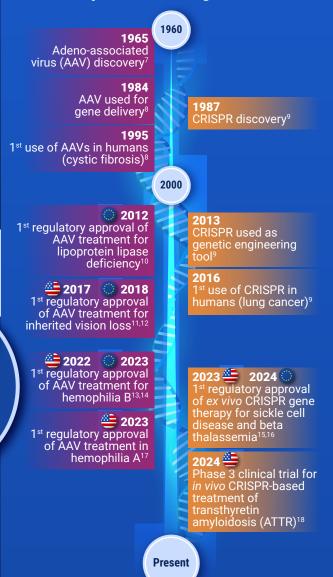
In vivo CRISPR-based targeted gene insertion is a type of gene editing being investigated in hemophilia B. By adding a therapeutic F9 gene, the body can make functional clotting factor IX on its own³⁻⁵



In other words...

Genes are like the body's instruction manual. Sometimes, typos in the manual ("mutations") cause the body to miss one of the instructions it needs to produce functional product, such as factor IX in patients with hemophilia B. The goal of gene editing is to carefully correct those typos or insert the right instructions into the manual, so the body can function as it should, and factor IX can be produced⁶

Technological advances leading up to in vivo CRISPR-based targeted gene insertion for hemophilia B investigational studies



Investigational in vivo CRISPR-based targeted gene insertion for hemophilia B

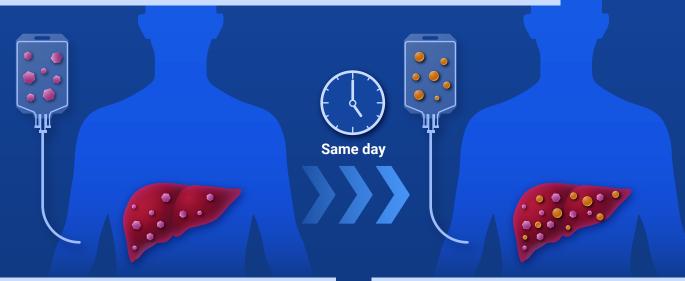


CRISPR is a versatile tool. CRISPR-based targeted gene insertion for hemophilia B is an investigational **in vivo** therapy, which means gene insertion takes place in liver cells inside the body. With **ex vivo** gene therapies, patients' cells are removed and modified outside in a lab before they are reintroduced back to the body^{4,5,19,20}

Investigational CRISPR-Based Targeted Gene Insertion is a Two-Step Process:4,5

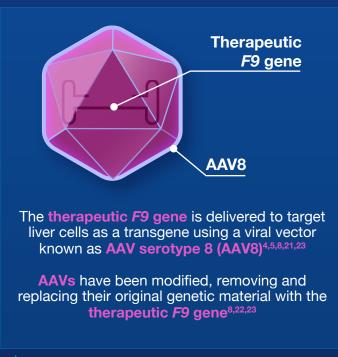
Step 1: Delivery of Therapeutic F9 Gene and CRISPR

CRISPR-based targeted gene insertion for hemophilia B is an *in vivo* therapy given by intravenous infusion, which includes two components that are delivered to target liver cells^{4,5}



First, the investigational **therapeutic** *F9* **gene** is delivered to liver cells to provide instructions for making **clotting factor IX**^{4,5,8,22}

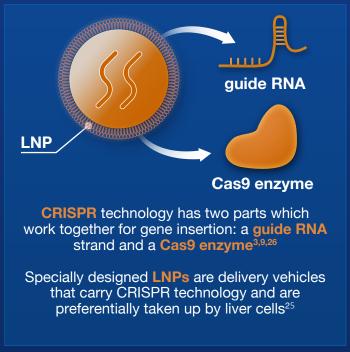
Then, a lipid nanoparticle (LNP) delivers CRISPR, a precise tool that is designed to enable targeted gene insertion at a specific location in the DNA^{4,5,9,25}



Deeper dive

A **transgene** is a DNA sequence or combination of sequences that can produce functional protein²⁴

 In CRISPR-based targeted gene insertion, the transgene, which consists only of the F9 gene and does not carry a promoter, is integrated into the patient's genome^{4,5}



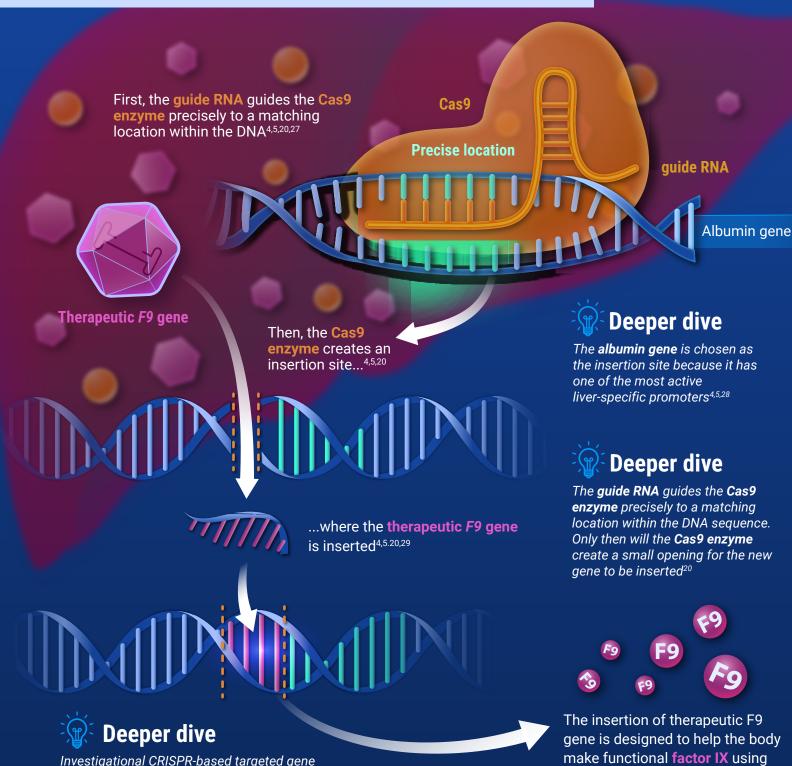
Deeper dive

LNPs are used to package the gRNA and the mRNA to encode the Cas9 enzyme, because they are the preferred method for delivering RNA to the liver^{8,25}

Investigational CRISPR-Based Targeted Gene Insertion is a Two-Step Process:4,5

Step 2: Targeted Insertion of Therapeutic *F9* **Gene**

Once inside target liver cells, **CRISPR** is designed to precisely target a specific location in the DNA to enable targeted insertion of the **therapeutic** *F9* **gene**^{4,5,20}



the instructions from the

therapeutic gene³⁻⁵

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insertion generates factor IX protein that is

the same as naturally occurring, functional

human factor IX protein^{4,5}

Investigational CRISPR-Based Targeted Gene Insertion for Hemophilia B...



...builds on a strong foundation of genetic research that continues to grow and is being investigated in pre-clinical studies and clinical trials²⁷



Deeper dive

If treatment is not successful,



...currently can only be given once. Today, the viral vectors used in treatment can only be introduced to the body once because the body's immune response may prevent them from being delivered again¹⁹

patients can discuss with their healthcare practitioners about safely returning to their previous treatment routine or other treatment options that do not use AAVs4,5,27



...targets liver cells (non reproductive cells), so the therapeutic gene and its effects are not aimed to be passed down to offspring^{4,5}





...hoping for pediatric use^{4,5}





...aims to be a lifelong treatment after a single dose for hemophilia B, hopefully without the need for routine factor replacement therapy^{4,5,19,29}

CRISPR-based targeted gene insertion may be suitable for pediatric use because translational research suggests that the treatment is durable even as the liver continues to grow^{4,5}

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