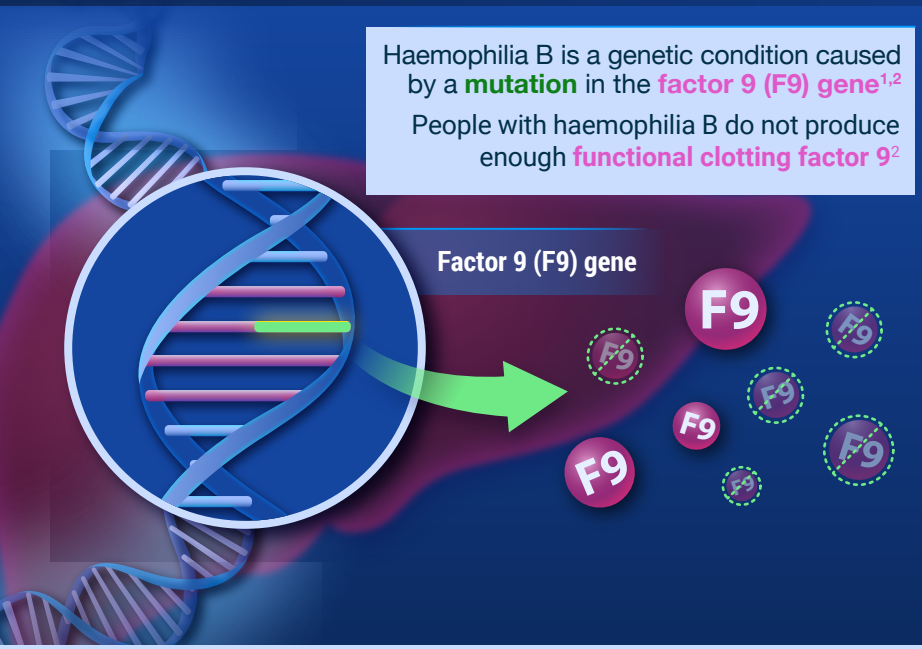
CRISPR-Based Targeted Gene Insertion for Haemophilia B

For Haemophilia B Community

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



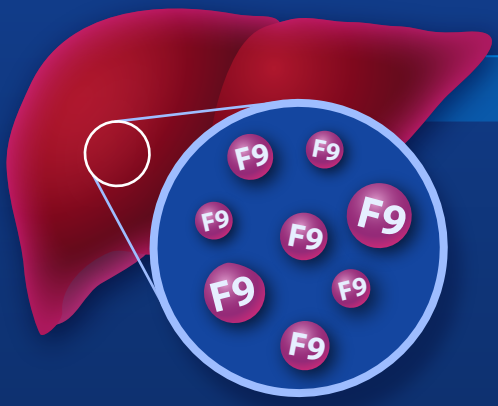
Haemophilia B is a genetic condition caused by a **mutation** in the **factor 9 (F9) gene**[1,2]

People with haemophilia B do not produce enough **functional clotting factor 9**[2]

Gene insertion aims to permanently teach the body how to produce clotting factor long-term, without the need for routine factor replacement therapy[3]

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 should[3]



CRISPR-based targeted gene insertion is a type of gene editing being investigated in haemophilia B. By adding a therapeutic factor 9 gene, the body can make functional clotting factor 9 on its own[3-5]

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 9 in people with haemophilia 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 9 can be produced[6]

Technological advances leading up to CRISPR-based targeted gene insertion for haemophilia B investigational studies

1960

1965 Adeno-associated virus (AAV) discovery[7]

1984 AAV used for gene delivery[8]

1987 CRISPR discovery[9]

1995 1st use of AAVs in humans (cystic fibrosis)[8]

2000

2012 1st regulatory approval of AAV treatment for lipoprotein lipase deficiency[10]

2013 CRISPR used as genetic engineering tool[9]

2016 1st use of CRISPR in humans (lung cancer)[9]

2017 (US) **2018** (EU) 1st regulatory approval of AAV treatment for inherited vision loss[11,12]

2022 (US) **2023** (EU) 1st regulatory approval of AAV treatment for haemophilia B[13,14]

2023 (US) 1st regulatory approval of AAV treatment in haemophilia A[17]

2023 (US) **2024** (EU) 1st regulatory approval of CRISPR gene therapy for sickle cell disease and beta thalassaemia[15,16]

2024 (US) Phase 3 clinical trial for CRISPR-based treatment of transthyretin amyloidosis (ATTR)[18]

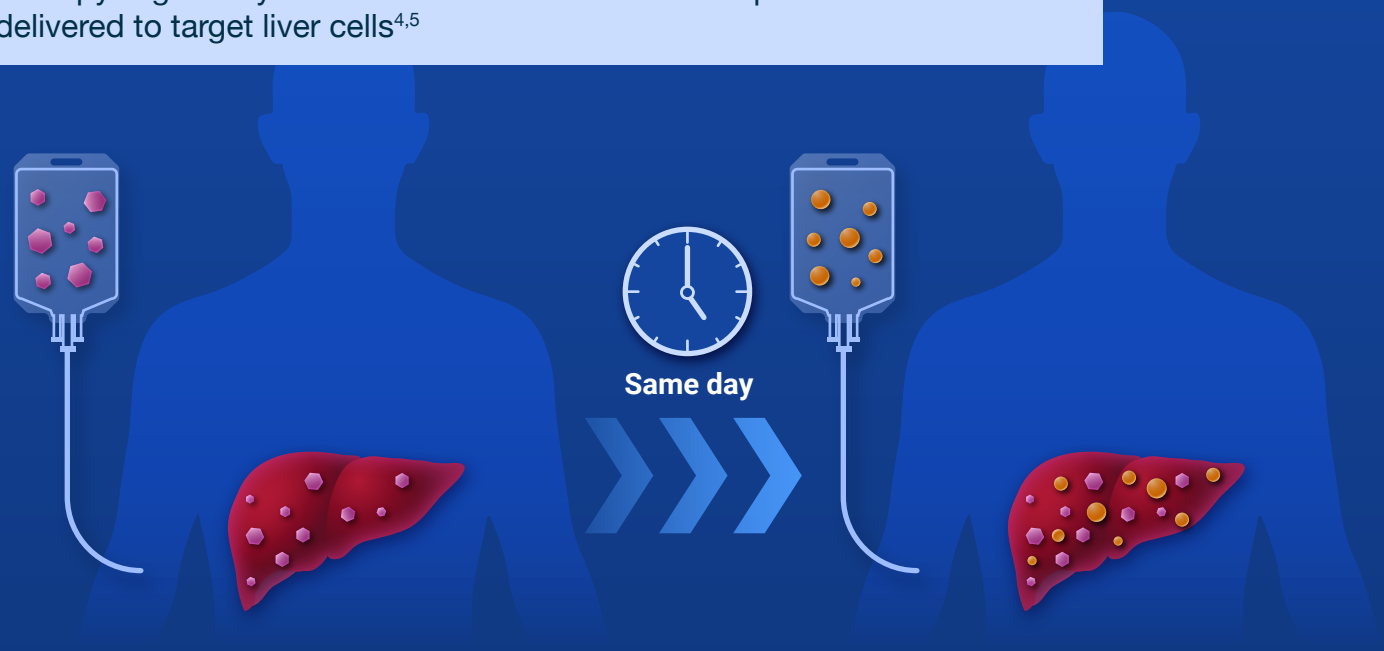
Present

Investigational CRISPR-based targeted gene insertion for haemophilia B

Investigational CRISPR-based Targeted Gene Insertion is a Two-step Process:[4,5]

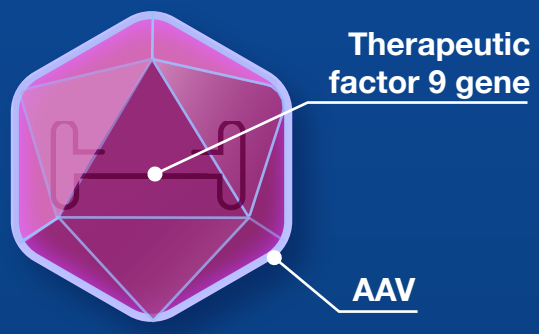
Step 1: Delivery of Therapeutic Factor 9 Gene and CRISPR

Therapy is given by IV infusion and includes two components that are delivered to target liver cells[4,5]



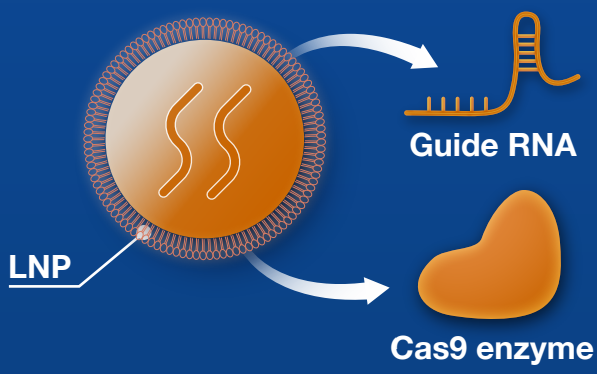
First, the **therapeutic factor 9 gene** is delivered to liver cells to provide the instructions for making **clotting factor 9**[4,5,8,19]

Then, **CRISPR** is delivered. CRISPR is a precise tool that enables targeted gene insertion at a specific location in DNA[4,5,9]



The **therapeutic factor 9 gene** is delivered to the target liver cells using a viral vector known as **adeno-associated virus (AAV)**, which are naturally good at delivering DNA[4,5,8,20,21]

AAVs have been modified, removing and replacing their original genetic material with the **therapeutic factor 9 gene**[8,19,21]



CRISPR technology has two parts which work together for gene insertion: a **guide RNA** strand and a **Cas9 enzyme**[3,9,22]

Specially designed packages, known as **lipid nanoparticles (LNPs),** are fat-based molecules that help carry CRISPR technology to a precise location in the liver[23]

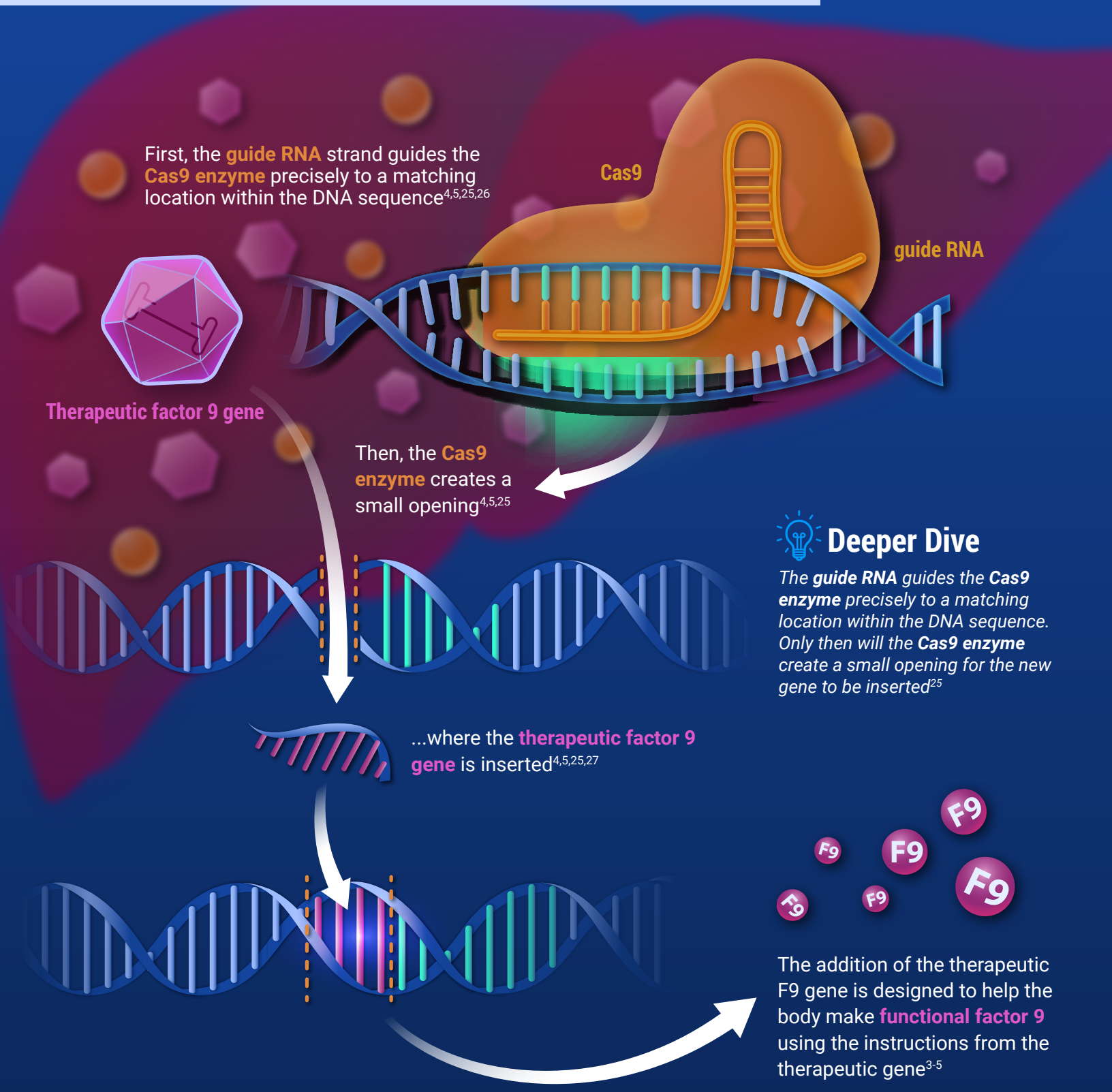
Deeper Dive

CRISPR is a versatile tool. CRISPR-based targeted gene insertion for haemophilia B is an 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 the lab before they are reintroduced back to the body[4,5,24,25]

Investigational CRISPR-based Targeted Gene Insertion is a Two-step Process:[4,5]

Step 2: Targeted Insertion of Therapeutic Factor 9 Gene

Once inside liver cells, **CRISPR** is designed to create an opening in the DNA at a precise location where the **therapeutic factor 9 gene** can be inserted[4,5,25]



Deeper Dive

*The **guide RNA** guides the **Cas9 enzyme** precisely to a matching location within the DNA sequence. Only then will the **Cas9 enzyme** create a small opening for the new gene to be inserted*[25]

The addition of the therapeutic F9 gene is designed to help the body make **functional factor 9** using the instructions from the therapeutic gene[3-5]

What You Need to Know

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

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

... builds on a strong foundation of genetic research that continues to grow and is being investigated in pre-clinical studies and clinical trials[26]

...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 again[24]

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

...is hoping for paediatric use[4,5]

...aims to be a lifelong treatment, after a single dose for haemophilia B without the need for routine factor replacement therapy[4,5,24,26]

Deeper Dive

If treatment is not successful, patients can discuss with their healthcare practitioners about safely returning to their previous treatment routine or other treatment options that do not use AAVs[4,5,26]

Deeper Dive

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

1. National Bleeding Disorder Foundation. Hemophilia B. https://www.hemophilia.org/bleeding-disorders-a-z/types/hemophilia-b. Accessed March 11, 2024.
2. National Organization for Rare Disorders. Hemophilia B. https://rarediseases.org/rare-diseases/hemophilia-b/. Accessed March 11, 2024.
3. American Society of Gene and Cell Therapy. Gene Editing. https://patienteducation.asgct.org/gene-therapy-101/gene-editing. Accessed March 11, 2024.
4. Regeneron. Data on file.
5. Sabin L. Novel approaches for gene-based therapies: Targeted gene insertion of Factor 9 as a potential durable treatment for hemophilia B. Lecture presented a: American Society of Hematology; 2023; San Diego, CA.
6. American Society of Gene and Cell Therapy. Hemophilia. https://patienteducation.asgct.org/disease-treatments/hemophilia. Accessed April 11, 2024.
7. Hastie E et al. *Hum Gene Ther*. 2015;26:257-265.
8. Wang D et al. *Nat Rev Drug Discov*. 2019;18(5):258-378.
9. Guo N et al. *J Adv Res*. 2022;40:135-152.
10. Glybera. Summary of Product Characteristics. UniQure biopharma; 2012.
11. US Food and Drug Administration. FDA approves novel gene therapy to treat patients with a rare form of inherited vision loss. https://www.fda.gov/news-events/press-announcements/fda-approves-novel-gene-therapy-treat-patients-rare-form-inherited-vision-loss. Accessed March 13, 2024.
12. Luxterna. Summary of Product Characteristics. Novartis Europharm Limited; 2018.
13. National Bleeding Disorder Foundation. FDA approves first gene therapy to treat adults with hemophilia B. https://www.hemophilia.org/news/first-hemophilia-b-gene-therapy-approved-by-fda. Accessed March 13, 2024.
14. Hemgenix. Summary of Product Characteristics. CSL Behring GmbH; 2023.
15. US Food and Drug Administration. FDA approves first gene therapy for patients with sickle cell disease. https://www.fda.gov/news-events/press-announcements/fda-approves-first-gene-therapies-treat-patients-sickle-cell-disease. Accessed March 13, 2024.
16. Casgevy. Summary of Product Characteristics. Vertex Pharmaceuticals Limited; 2024.
17. US Food and Drug Administration. FDA approves first gene therapy for adults with severe hemophilia A. https://www.fda.gov/news-events/press-announcements/fda-approves-first-gene-therapy-adults-severe-hemophilia. Accessed March 13, 2024.
18. Intellia Therapeutics. Intellia Therapeutics Announces First Patient Dosed in the Phase 3 MAGNITUDE Study of NTLA-2001 as a Single-Dose CRISPR-Based Treatment for Transthyretin Amyloidosis with Cardiomyopathy. https://ir.intelliatx.com/news-releases/news-release-details/intellia-therapeutics-announces-first-patient-dosed-phase-3. Accessed March 20, 2024.
19. American Society of Gene & Cell Therapy. Viral vector overview. https://asgct.org/global/documents/patient-ed-infographics/sept-launch-website-material/viral_vector_overview-(7).aspx?_ga=2.48894181.291594531.1716920733-636341200.1705006481&_gl=1*1hml908*_ga*NjM2MzQxMjAwLjE3MDUwMDY0ODE.*_ga_6FB6X4L6XF*MTcxNjkyMDczMy4yNS4wLjE3MTY5MjA3MzMuNjAuMC4w*_ga_Q37QKR6TCJ*MTcxNjkyMDczMy4yNS4wLjE3MTY5MjA3MzMuMC4wLjA. Accessed March 13, 2024.
20. American Society of Gene & Cell Therapy. What is gene therapy? https://asgct.org/global/documents/patient-ed-infographics/what-is-gene-therapy.aspx?_gl=1*mfgd0r*_ga*NjM2MzQxMjAwLjE3MDUwMDY0ODE.*_ga_Q37QKR6TCJ*MTcxNjkyMDczMy4yNS4xLjE3MTY5MjA4NTUuMC4wLjA.*_ga_6FB6X4L6XF*MTcxNjkyMDczMy4yNS4xLjE3MTY5MjA4NTUuNTMuMC4w&_ga=2.48290405.291594531.1716920733-636341200.1705006481. Accessed March 13, 2024.
21. Mietzsch M, Agbandje-McKenna M. *Ann Rev Virol*. 2017;4(1):iii-v.
22. Uddin F, et al. *Front Oncol*. 2020;10:1387.
23. Kazemian P, et al. *Mol Pharmaceutics*. 2022;19(6):1669-1686.
24. American Society of Gene and Cell Therapy. Vectors 101. https://patienteducation.asgct.org/gene-therapy-101/vectors-101. Accessed March 13, 2024.
25. Asmamaw M, Zawdie B. Biologics: *Targets and Therapy*. 2021;15:353-361.
26. American Society of Gene and Cell Therapy. How does gene editing work? https://asgct.org/global/documents/patient-ed-infographics/gene-editing-infographic-(1).aspx?_gl=1*whqa23*_ga*NjM2MzQxMjAwLjE3MDUwMDY0ODE.*_ga_Q37QKR6TCJ*MTcxNjkyMDczMy4yNS4xLjE3MTY5MjEzNjguMC4wLjA.*_ga_6FB6X4L6XF*MTcxNjkyMDczMy4yNS4xLjE3MTY5MjEzNjguNjAuMC4w&_ga=2.54655592.291594531.1716920733-636341200.170500648. Accessed March 13, 2024.
27. American Society of Gene and Cell Therapy. Gene Therapy Approaches. https://patienteducation.asgct.org/gene-therapy-101/gene-therapy-approaches. Accessed March 11, 2024.

777 Old Saw Mill River Road, Tarrytown, NY 10591

06-2024 US-REGNV131-POS-24-05-0001

REGENERON®